Niosomes: A Future Of Targeted Drug Delivery Systems As Promising Nanocarrier Through Blood-Brain Barrier For Natural Drug Delivery

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Abstract

In recent years, the treatment of infectious diseases and immunisation has undergone a revolutionary change. Not only were a large number of biological disease-specific species established, but emphasis was also put on the efficient delivery of these biological species. Niosomes are an evolving class of new structures of vesicles. Niosomes are vesicles that are self-assembled and consist mainly of synthetic surfactants and cholesterol. In niosome surfactant vesicles, various drugs are enlisted and attempted. Niosomes have proven to be a promising drug carrier and have the ability to decrease drug side effects and increase therapeutic efficacy in different ways.

Keywords: Niosomes, Drug carrier, Multilamellar vesicles, Drug targeting, Peptide Drugs.

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INTRODUCTION

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[1]. 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 or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. Niosomes are promising vehicle for drug delivery and being non-ionic, Niosomes are unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. They are very similar to the liposomes. Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Niosomes have shown promise in the release studies and serve as a better option for drug delivery system. The drug is incorporated into niosomes for a better targeting of the drug at appropriate tissue destination[2-3].

➢ Salient Features of Niosomes[4]

- ✓ Osmotically active and stable.
- ✓ Niosomes increases the stability of entrapped drug.
- ✓ They can be made to reach the site of action by oral, parenteral as well as topical routes.
- ✓ Surfactant used in niosomes does not require special conditions.
- ✓ Surfactants used in niosomes are biodegradable, biocompatible, and non-immunogenic.
- ✓ They improve the therapeutic

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- ✓ performance of the drug molecules by delayed clearance from the circulation.
- ✓ Niosomes exhibit flexibility in their structural characteristics (composition, fluidity, size) and can be designed to desired situation.

➢ Structure of Niosome[5]

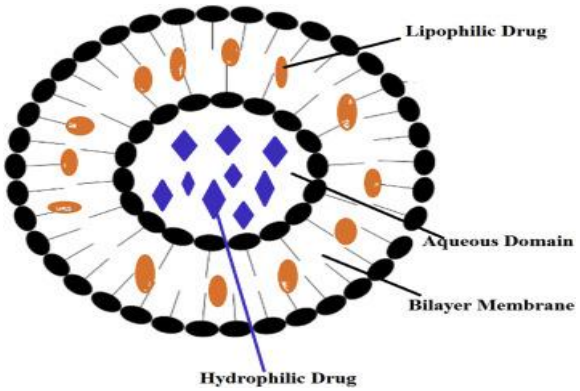


Fig 1. Structure of Niosomes

In Fig.1 shows structure of niosomes. A typical niosomes vesicle would consist of a vesicle forming amphiphilic i.e. a non-ionic surfactant such as Span-60, which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate, which also helps in stabilizing the vesicle.

➢ Compositions of Niosomes

The two major components used for the preparation of niosomes are,

1. Cholesterol
2. Nonionic surfactants

1. Cholesterol

Cholesterol is a steroid derivative, which is used to provide rigidity and proper shape, conformation to the niosomes preparations.

2. Nonionic surfactants

The following non-ionic surfactants are generally used for the preparation of niosomes. e.g. Spans (span 60, 40, 20, 85, 80), Tweens (tween 20, 40, 60, 80), Brijs (brij 30, 35, 52, 58, 72, 76). The non-ionic surfactants possess a hydrophilic head and a hydrophobic tail.

Surfactants used in formulation of niosomes[6]

Niosomes are non-ionic surfactant unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. The surfactants that are reported to form niosomes are as follows:

1. Ether linked surfactant

These are surfactants in which the hydrophilic hydrophobic moieties are ether linked, polyoxyethylene alkyl ethers with the general formula, where n, i.e. number of carbon atoms varies between 12 and 18 and m, i.e. number of oxyethylene unit varies between 3 and 7.

2. Di-alkyl chain surfactant

Surfactant was used as a principal component of niosomal preparation of stibogluconate and its potential in delivering sodium stibogluconate in experimental marine visceral leishmaniasis has been explored.

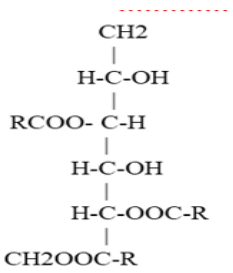
3. Ester linked

These are the surfactants in which hydrophilic and hydrophobic moieties are ester linked. Ester linked surfactant,

This surfactant was also studied for its use in the preparation of stibogluconate bearing niosomes and in delivery of sodium stibogluconate to the experimental marine visceral leishmaniasis following administration of niosomal system.

4. Sorbitan Esters:

The typical structural formula of sorbitan ester is,

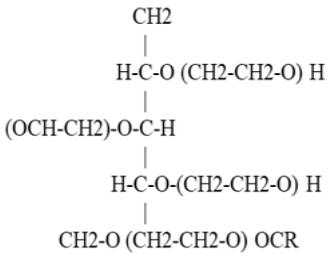


Where, R is H or an alkyl chain

The formula of a representative component is shown above. Sorbitan esters based niosomes bearing methotrexate were prepared and evaluated for pharmacokinetics of the entrapped methotrexate in tumor bearing mice.

5. Poly-sorbates

The typical structural formula of polysorbates is -



It is an alkyl chain this series of surfactants has been used to study the pharmacokinetics of niosomal entrapped methotrexate.

➢ Types of Niosomes

1. Small unilamellar vesicles (SUV)

SUV are commonly produced by sonication, and French Press procedures. Ultrasonic electro capillary emulsification or solvent dilution techniques can be used to prepare SUV (size 0.1-1 µm).

2. Multilamellar vesicles (MUV)

Exhibit increased-trapped volume and equilibrium solute distribution and require hand-shaking method. They show variations in lipid compositions (0.5-10 µm).

3. Large unilamellar vesicles (LUV)

The injections of lipids solubilised in an organic solvent into an aqueous buffer, can result in spontaneous formation of LUV, but the better method of preparation of LUV is Reverse phase evaporation or by Detergent solubilisation method. (1-30 µm).

➢ Advantages of Niosomes[7-9]

- ✓ Niosomal 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 solubility.
- ✓ The vesicles may act as a depot, releasing the drug in a controlled manner.
- ✓ 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
- ✓ 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.

➢ Factors Affecting Formation of Niosomes[11-13]

i) Nature of surfactants

Surfactants used for preparation of niosomes must contain a hydrophilic head and hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or in some cases a single steroidal group. 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 esterase to triglycerides and fatty acid in vivo. The surfactants with alkyl chain length from C_{12}-C_{18} are suitable for preparation of niosome.

ii) 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 (Critical Packing Parameters) = $\frac{v}{lc \times a0}$

Where, v = hydrophobic group volume,
lc = the critical hydrophobic group length,
a^0 = the area of hydrophilic head group.

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

If CPP < ½ then formation of spherical micelles,
If ½ < CPP < 1 formation of bilayer micelles,
If CPP > 1 formation of inverted micelles.

iii) Membrane composition

The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by different additives.

iv) Nature of encapsulated drug

The physico-chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The drug interacts with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers and hence increases vesicle size.

v) 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.

➢ Characterization of Niosomes[14]

i) Size Shape of niosome

Vesicles assumed to be spherical, their mean diameter can be determined by using laser light scattering method. Also diameter can be determined by using electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy and optical microscopy.

ii) Bilayer formation

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

iii) Number of lamellae

It can be determined by using NMR spectroscopy, small angle X-ray scattering and electron microscopy.

iv) Membrane rigidity

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

v) % Entrapment efficiency (EE)

The entrapment efficiency (EE) is expressed as

$$\% EE = \frac{\text{Amount of entrapped drug}}{\text{Total amount added}} \times 100$$

It is determined after separation of unentrapped drug, on complete vesicle disruption by using about 1ml of 2.5% sodium lauryl sulfate, briefly homogenized and centrifuged and supernatant assayed for drug after suitable dilution. Entrapment efficiency is affected by following factors.

a) Surfactants

The chain length and hydrophilic head of non-ionic surfactants affect entrapment efficiency, such as stearyl chain C_{18} non-ionic surfactant vesicles show higher entrapment efficiency than lauryl chain C_{12} non-ionic surfactant vesicles. The tween series surfactants bearing a long alkyl chain and a large hydrophilic moiety in the combination with cholesterol at 1:1 ratio have highest entrapment efficiency for water soluble drugs. HLB value of surfactants affects entrapment efficiency, such as HLB value of 14 to 17 is not suitable for niosomes, but HLB value of 8.6 has highest entrapment efficiency and entrapment efficiency decreases with decrease in HLB value from 8.6 to 1.7. The entrapment efficiency is affected by phase transition temperature of surfactants, i.e. span 60 exhibits highest entrapment efficiency in series having highest transition temperature.

b) Cholesterol content

The incorporation of cholesterol into bilayer composition of niosome induces membrane-stabilizing activity and decreases the leakiness of membrane. Hence, incorporation of cholesterol into bilayer increases entrapment efficiency.

➢ Methods of Preparation of Niosomes[15]

i. Ether injection method

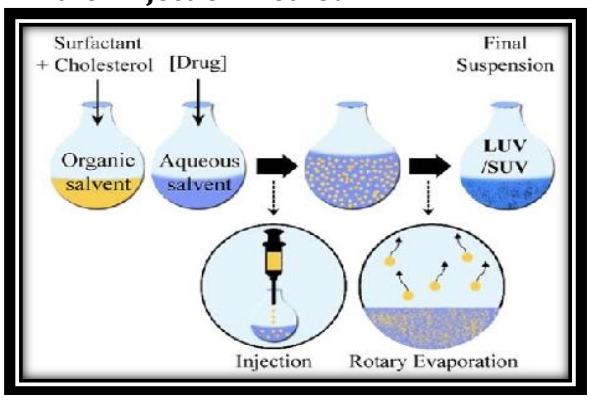


Fig 2: Ether injection method

In Fig 2 Shows Ether injection method. This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether (volatile organic solvent) into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether (volatile organic solvent) leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm.

ii. Thin film hydration technique

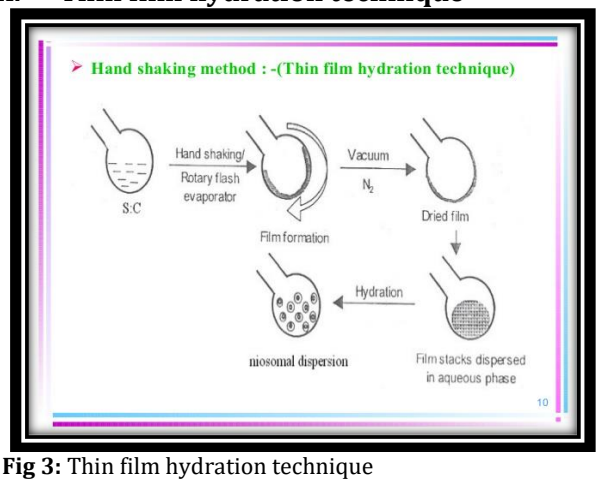


Fig 3: Thin film hydration technique

In fig 3 shows 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 multilamella niosomes.

iii. Sonication method

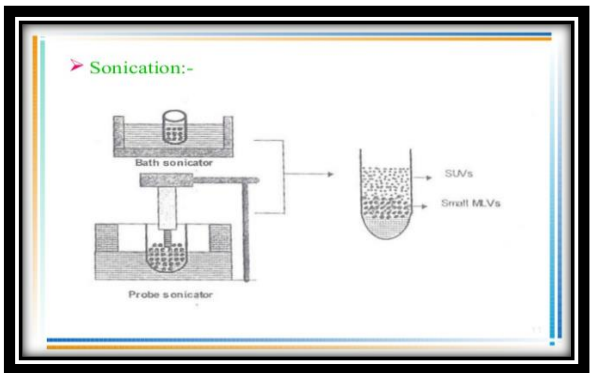


Fig 4: Sonication method

In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10ml glass vial. The mixture is probe sonicated at 60^{0}C for 3 minutes using a sonicator with a titanium probe to yield niosomes.

iv. Reverse phase evaporation technique (REV)

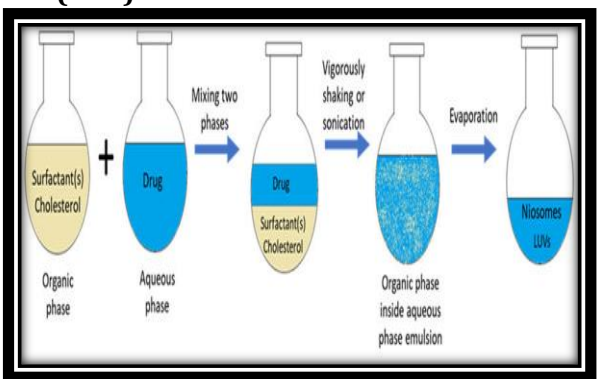


Fig 5: Reverse phase evaporation technique (REV)

In fig 5 shows Reverse phase evaporation technique. Cholesterol and surfactant (1:1)are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5^{0}C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffer saline (PBS).The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.

v) Micro fluidization

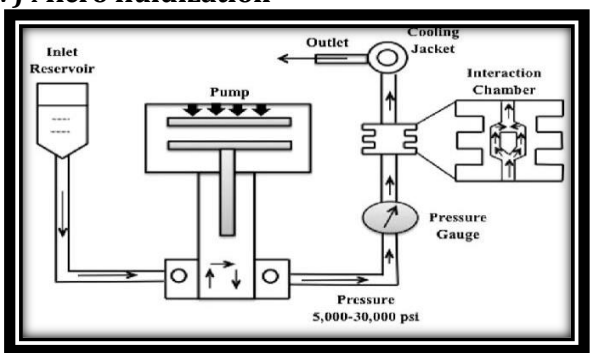


Fig 6: Micro fluidization

It is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra-high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a smaller size, greater uniformity, and better reproducibility of niosomes formed.

vi) Multiple membrane extrusion method

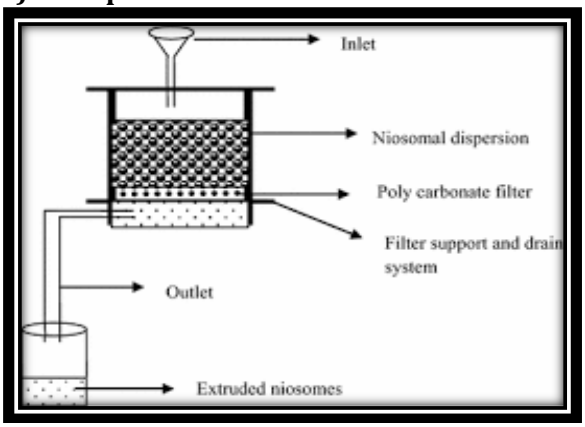


Fig 7: Multiple membrane extrusion method

In fig 7 shows 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.

vii) 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 µM 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.

viii) 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.

ix) Formation of niosomes from proniosom es

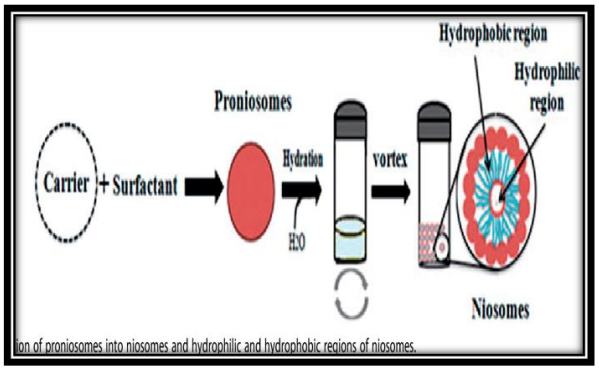


Fig 8: Formation of niosomes from proniosomes

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 as proniosomes shown in fig 8. The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation. T=Temperature. Tm = mean phase transition temperature.

➢ Methods of Separation of Unentrapped Drug from Niosomes[16]

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

i) Dialysis

The aqueous niosomal dispersion is dialyzed in dialysis tubing against suitable dissolution medium at room temperature. The samples are withdrawn from the medium at suitable time intervals, centrifuged and analysed for drug content using suitable method (U.V spectroscopy, HPLC etc).

ii) Gel filtration

The unentrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex- G-50 column and eluted with suitable mobile phase and analyzed with suitable analytical techniques.

iii) Centrifugation

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

➢ Stability of Niosomes[17]

a) Physical stability

The niosomes can change their physical characteristics in several ways.

- ✓ The particle size may change because of aggregate formation and fusion.
- ✓ Occurrence of phase separation of bilayer components, upon storage.
- ✓ Leakage of encapsulated material from niosomes.

The changes in particle upon storage of phosphatidyl choline containing niosomes over pharmaceutically relevant time intervals can be minimized by the selection of proper charge inducing agents. Mostly, negatively charged phospholipids (phosphatidyl glycerol) are used to stabilize the niosomes.

b) Chemical stability

The stability of niosomes depends on the chemical stability of the lipid components and the bilayer components of niosomes, designed for carrying a drug or phospholipids.Many investigators choose the formation of lysophosphatidyl choline as a standard measure for the chemical stability to

phospholipids. Since, the presence of lysophosphatidyl choline in lipid bilayer greatly enhances the permeability of niosomes, the most important method for minimizing this problem is the proper sourcing of the phospholipid to be used. They should be essentially free from any lyso-phosphatidyl choline to start with and free of any peroxidation of phospholipids produces the formation of cyclic peroxides and hydro peroxides. Peroxidation of the phospholipids may be minimized by a number of ways such as,

- ✓ Minimum use of unsaturated phospholipids.
- ✓ Use of nitrogen or argon to minimize exposure to oxygen.
- ✓ Use of light resistant container.
- ✓ Removal of heavy metals.

c) Stability in biological fluids

The inability of niosomes to retain entrapped substances when incubated in blood or plasma has been known for a decade. The instability of niosomes in plasma appears to be the result of transfer of bilayer lipids to albumin and high-density lipoproteins. Both lecithin and cholesterol also exchange with the membrane of red blood corpuscle. Niosomes are most susceptible to high density lipoprotein attack at their gel to liquid crystalline phase transition temperature. The susceptibility of niosomal phospholipids to lipoprotein and phospholipase attack is strongly dependent on niosome size and type. Generally, multilamellar vesicles are most stable whereas small lamellar vesicles are least stable. The bile salts also destabilize the bilayer membrane structure, thereby, leading to release of the entrapped material.

➢ Application of Niosomes[18]

1) Drug targeting:

One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticulo-endothelial system. A carrier system can be attached to niosomes to target them to specific organs. Many cells also possess the intrinsic ability recognize and bind specific carbohydrate determinants, and this can be exploited by niosomes to direct carrier system to cells.

2) 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. Niosomal entrapment of Doxorubicin and Methotrexate (in two separate studies) showed beneficial effects over the unentrapped drugs, such as decreased rate of proliferation of the tumor and higher plasma levels accompanied by slower elimination.

3) 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.

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.

5) 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.

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.

7) Transdermal Drug Delivery Systems utilizing Niosomes:

Transdermal drug delivery utilizing niosomal technology is widely used in cosmetics; in fact, it was one of the first uses of the niosomes. Topical use of niosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to unentrapped drug.

Other Applications:

a) Sustained Release:

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

b) Localized Drug Action:

Drug delivery through niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through

epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects.

CONCLUSION

Niosomes are osmotically active, less toxic, and chemically stable as a method of drug delivery. Due to the functional groups that can be added on their hydrophilic heads, surface modification is comparatively simple on them. As the ligand of the distinctive receptor, niosomes active targeting to the desire tissue are arbitrated with many therapeutic means. As a revolutionary and capable approach to natural drug delivery, nonionic surfactant vesicles have been introduced. They are primarily composed of non-ionic surfactants and cholesterol, and typically contain a buffer solution at the correct pH within them. Various approaches that affect the establishment and properties of the drug, the amount of cholesterol, composition, form, and quantities of surfactant can be used. In pharmaceutical uses, this method has an optimistic future, mainly with the growing availability of new schemes to resolve BBB and target the niosomes to the CNS.

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