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NIOSOMES: A PROMINENT THERAPEUTIC CARRIER MOLECULES TOWARDS TARGETED SITE

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ABSTRACT

During the treatment of several infectious diseases there is a huge revolutionary change in the treatment of diseases from past few decades. As there is an advancement in pharmaceutical field, biotechnology not only drugs towards target site have been developed but also advancement in delivering drug towards target site has developed i.e., carriers. Drug targeting is a process in which on administration of drug substance the drug gets distributed in the body and therapeutic agents interact with targeted site without affecting the surrounding of target site. For targeted drug release there is a requirement of carriers for delivering of the drug, the novel drug delivery system plays an important role especially niosomes plays a prominent role as carriers it consists of two components mainly cholesterol and non-ionic surfactants. The niosomes are capable of delivering both hydrophilic and lipophilic drugs in a controlled manner. And it is used in treatment of several diseases like cancer, leishmaniasis, skin fungal infections, eye diseases, acne treatment, brain and CNS diseases.

KEYWORDS: Niosomes, Drug carrier, Targeted site, Hydrophilic and Lipophilic drugs, Factors, Applications.

INTRODUCTION

The release of therapeutic molecules in a controlled manner towards targeted site by a carrier is known as targeted drug delivery system. A German scientist Paul Ehrlich in 1909, had

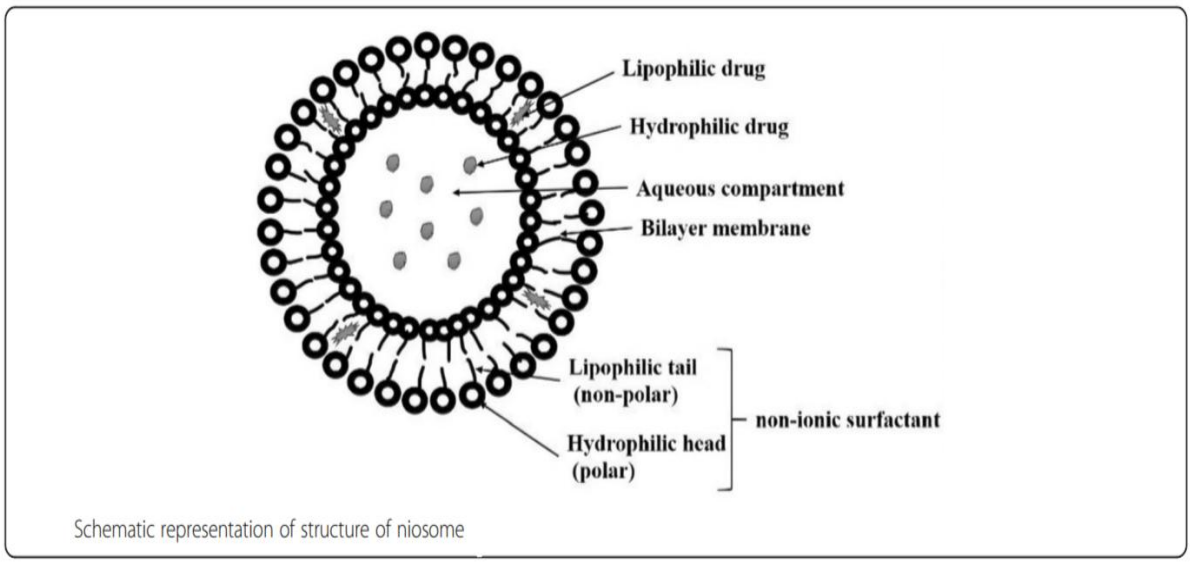
started his research on drug delivery system which mainly described about targeted action of drug molecule towards target site.[4] Niosomes are considered as 2nd generation carrier systems.[5] Niosomes are considered as drug carrier they are made of non-ionic surfactants and cholesterol they form in to bilayer on self -association in aqueous phase in which interfacial tension is developed between the hydrophobic tail and aqueous phase it contains a hydrophilic head towards outside and inside of bilayer whereas the hydrophobic tail is directed toward inside of bilayer so it forms like amphiphile.[9,10]

There is an advantage of niosomes compared to liposomes the niosomes are chemically more stable, low production cost, high loading capacity.[4] when drug is targeted towards targeted site it does not affects the surrounding of targeted site which leads to increase in efficacy of the drug product.[7] They have ability to load both hydrophilic and lipophilic drugs it is another advantage of niosomes. usually, niosomes exits in in a size range from 10 to 1000nm.[3] Based on the concentration of cholesterol and nonionic surfactant the size of niosomes is varied. The surfactants that are used mostly are biodegradable, non-immunogenic, biocompatible.[3]

Components of niosomes[4]

1.Cholesterol: It provides support and it has grater rigidity capacity which prevent leakage of drug and it also provides structure and shape to niosomes.

2.Non-Ionic surfactants: They mainly help in solubility of poorly soluble drugs and improve their bioavailability. examples like tween, spans, polyoxy ethylene alkyl esters, polyglycerol alkyl ethers are used.



Schematic representation of structure of niosome

Advantages[1,3,4]

- Niosomes es are suitable to deliver the therapeutic agents through various routes such as topical, oral, parenteral.
- As niosomes are oily based preparations they are easily accepted by the patients for administration called patient compliance.
- The niosomes release of drug in a controlled manner towards a target site.
- In topical preparations they have occlusive property which causes hydration of the skin which leads to increase in the penetration of the drug in skin
- There is no requirement of special conditions to handle nonionic surfactants.
- Poorly soluble drugs have increased their bio availability.[15]
- They have good protection property for drug from enzyme metabolism.
- They are biodegradable, non -toxic and able to large amount of drug in niosomes.[23]

Disadvantages[16]

- There is a leakage of entrapped drug.
- During the storage of niosomal preparation there may be an aggregation and fusion.
- It has physical instability
- And it is a time-consuming process.
- The membrane filtration and sterilization are not suitable for niosomes.
- Sometimes brust release may take place.

Different types of niosomes[18]

1. Multilamellar (MLV)
2. Unilamellar. (LUV)
3. Small unilamellar (SUV)

To prepare the above one there are different types of methods are involved and they vary in size[24]

Type of niosomal vesicle	Vesicle size	Method of preparation
Multilamellar vesicles	Greater than 0.05 µm	Hand shaking method
Small unilamellar vesciles	0.025-0.5 µm	Sonication, extrusion method, solvent dilution technique.
Large unilamellar vesicles	Greater than 0.10 µm	Revers phase evaporation method.

Methods of preparation

1. Sonication[3]

i. In the sonication mediated process, Baillie etal's method is used in niosomes.
ii. Mixture of drug solution in the buffer along with surfactant and cholesterol is added.
iii. And the above mixture is sonicated with titanium probe sonicator at 60°C for 3 min to yield niosomes.

2. Ether injection method[6,11,12,13]

i. In this type the mixture of surfactant, cholesterol, and drug are dissolved in the diethyl ether.
ii. The above mixture with the help of 14- gauze needle it is inserted in go the aqueous phase.
iii. The ether solution is evaporated by using rotatory evaporator which leads to the formation of single layer vesicle

3. Bubble method[3]

i. Basically, in this type of method the usage of round bottom flask with three neck position is kept in water bath to control the temperature.
ii. The cholesterol and surfactant is added to the buffer at pH7.4 at 70°C. In the first neck the water reflux is kept and in second neck thermometer and in last neck the supply of nitrogen gas is arranged.
iii. The above mixture is kept in above flasks and it is mixed for 15sec with high shear speed by using homogenizer. And nitrogen gas is passed at 70°C at third neck the formation of unilamellar vesicles take place [29].

4. Ethanol injection method[3]

i. The surfactant is added to ethanol solution with the help of needle it is added to the saline or water.
ii. In the next step the vaporization of ethanol take place which leads to the formation of vesicles.

5. Reverse phase evaporation method[3,4]

i. In this method the mixture of cholesterol and surfactant (1:1ratio) is added to the chloroform.

ii. To the above mixture if the addition of the water or aqueous phase may lead to the formation of the oil in water type of emulsion.
iii. Which are sonicated then the emulsion is dried at 40°C to obtain a large vesicles semisolid gel then on addition of PBS (phosphate buffer saline) it gives clear gel.
iv. The clear gel is again sonicated and the organic phase is removed at low pressure and temperature.
v. And in next step the suspension is further mixed with [phosphate buffered saline at heated at 60°C leads to the formation of niosomal vesciles.

6. Transmembrane pH gradient drug uptake process[3,6]

i. The surfactants and cholesterol are mixed with chloroform and the chloroform is evaporated which leads to the formation of the thin film around the round bottom flask.
ii. And in next step the film hydration is done by using the 300 mM citric acid by vortex mixing that causes formation of the multilamellar vesicles formation they are frozen and thawed 3 times and sonicated.
iii. For niosomal solution an aqueous solution containing drug is added and mixed pH is raised to 7.0 to 7.2 with 1M disodium phosphate and heated to 60°C for 10 min to obtain niosomes.

7. Multiple membrane extrusion method[3]

i. The mixture of surfactant, cholesterol and dicetyl phosphate are added to chloroform forms thin layer on evoparation.the film is hydrated by using the aqueous drug polycarbonate membrane.
ii. The solution is passed through membrane and placed in series of 8 passages and it is best method to obtain niosomal size as per requirement. It mainly controls size of niosomes.

8. Micro fluidizations[3]

i. In this technique the submerged jet principle is used in which two fluidized streams interacts at high velocities through microchannels in the interaction chamber.
ii. The thin impingement sheet is arranged at front so that the energy remains constant at niosomes formation site and smaller size niosomes are formed.

Factors influencing the niosomal formation

1. The drug[27]

i. The drug is encapsulated in niosomes causes increase in the size of the vesicle.

ii. The chemical and physical nature of the drug has been greatly affected by drug and the hydrophilic head of surfactant which leads to increase in the charge that leads to the mutual repulsion surfactant bilayer causes an increase in vesicle size.
iii. The entrapment of drug mainly depends on the HLB value of the drug.

2. Surfactant

i. The HLB value is proportional to the size of the niosomes i.e. an increase in the value of the HLB leads to increase in the size of the niosomes and causes decrease in the surface free energy and increase in surface hydrophobicity of the surfactants.
ii. The HLB value of span 85 is 1.8 to span 20 HLB Value is 8.6 are used at HLB 1.8 it shows greater entrapment of the drug.
iii. The bilayer exists in the gel or liquid that totally depends on the temperature surfactants and cholesterol. In the gel alkyl chains are very well ordered and in liquid it is disordered.

3. Hydration temperature

i. The hydration temperature of niosomes mainly affect the size and shape of niosomes.
ii. The temperature should always lie above the gel, liquid phase transition temperature.
iii. If there is change in hydration temperature it may lead to the modification of arrangement of surfactant in to vesciles and vesciles shape modification take place. If it is cooled or heated the size may vary so, while preparing we need to keep in mind regarding selection of hydration temperature.

4. Cholesterol content

i. Addition of cholesterol cause increase in hydrodynamic diameter and entrapment efficiency.
ii. The cholesterol mainly acts by two possible ways i.e.;

1. Increase in the chain order of liquid state bilayer
2. Decrease in chain order of gel state bilayer

iii. The gel state converted to liquid ordered phase by addition of high concentration cholesterol. As the concentration of cholesterol increased it produces the increase in rigidity of bilayers and slow release of encapsulated drug towards site.

5. Charge

In the presence of charges, it may lead to increase in inter lamellar distance between successive bilayer in multilamellar vesicle structure and that causes increase in overall entrapped volume.

6. Ressistance to osmotic stress

i. The reduction of vesicle diameter is caused by addition of hypertonic solution to a suspension of niosomes.
ii. In addition of hypotonic solution, the vesicle swells and initially slow release take place due to inhibition of eluting fluid from vesicle and followed by faster release due to mechanical loosening of vesicle structure under osmotic stress.

7. Membrane composition

i. The stable niosomes can be prepared by addition of drugs, surfactants, and other additives like cholesterol.
ii. The characteristics of niosomal bilayer and stability permeability can be modified by addition of different additives.

Characterization of niosomes[17-22]

1. Number of lamellae[7]

In this method the lamellae count can be determined by using nuclear magnetic resonance (NMR) spectroscopy, small angle x-ray scattering and electron microscopy.

2. Bilayer formation[7]

Non-ionic surfactants form a bilayer vesicle by an x-cross formation under light polarization microscopy.

3. Bilayer Rigidity and Homogeneity[3]

The bio distribution and biodegradation of niosomes are influenced by rigidity of bilayer. The niosomal size and dispersion can be detected by NMR, differential scanning calorimetry (DSC) and FTIR technique.

4. Entrapment efficiency[4]

In this type of technique in which unentrapped drug content can be determined by gel filtration technique and entrapped drug by vesicle disruption using 50% n-propanol and examining the solution by proper assay method.

$$EE = \frac{entrapped\ drug\%}{entrapped\ drug + drug\ in\ supernatant} \times 100$$

5. Invitro release study[6]

This study is performed by using dialysis tubing method. The suspension is combined in open end dialysis membrane and it is receptor cell containing buffer solution. It is now continuously shake. Samples are collected and further procedures are followed.

6. Zeta potential analysis[4]

The colloidal properties of niosomes can be determined by zeta potential. By using zeta potential analyzer works on electrophoretic light scattering and laser doppler velocimetry method is used the niosomes derived from proniosomes are determined by above technique temperature is maintained at 25°C the charge on vesicle and mean zeta potential values are compared with standard deviation of measurements.

7. Osmotic shock[4]

In this technique the change in the vesicle size can be observed easily the niosomal suspension is incubated with hypertonic, hypotonic, isotonic solutions for 3hours then their will a change in their size of vesicles can be viewed under the optical microscopy.

8. Scanning electron microscopy[3]

The niosomes are observed under SEM (JSM 6100 JEOL, Tokyo, Japan) they are placed on the SEM sample stub using double sided sticking tape and it is coated with gold film under low pressure. With suitable magnification and by adjusting it the proper images are taken.

Marketed products of niosomes

S.no	Brand Name	Delivery System	Generic Name	Daily Dose	Manufacturer
1.	Acnebenz	Gel	Clindamycin	Once or twice a day	Sanstuti pharmaceutocals pvt. Ltd.
2.	Britney spears –Curious	Liquid spray	Fragrance	2gms daily	Britney spears
3.	Acenttab	Tablet	Aceclofe-nac	One tablet in the morning and one in the evening	Bindlysh biotech LTD
4.	Voltaren	Capsule	Diclofenac sodium	Daily 2 to 3 times	Elam pharma pvt. LTD.
5.	Menarini	Gel	Ketofrofen2-[3-benzoylphenyl]	3 times per day	Nicholas Piramal India LTD

			Proponic acid		
6.	Linoresal	Liquid	Baclofen	3 times per day	La Renon Health care pvt. LTD
7.	Capsian-p	Cream	Capsaicin-Topical	3 or 4 times a day	Sun pharmaceutical industries. LTD
8.	Cis-revertrol, Phytoalexin	Semisolid	Resveratrol	Daily up to 3 months	Alchemax Pharma pvt. LTD
9..	Aquasol-E	Capsule	Vitamin-E	Swallow capsules whole do not crush for 1-3 years	Capsulation and Pharmaceutical pvt. LTD
10.	Turmeric Root	Capsule	Turmeric	500-2000mg turmeric per day	Bioprex labs or Biomed ingredient pvt. LTD

Lancome has turned out with an assortment of anti-ageing agents which are niosome based. L'Oreal is also conducting research on anti-ageing cosmetic products.[8,24]

Applications[2,3,4]

1. Niosomes as drug carriers

Niosomes carries a drug towards a targeted site and release the drug in controlled manner example in 5-florouracil is mainly used in the treatment of skin cancer it is called as chemotherapy 5FU loaded polyethylene glycolcoated and uncoated niosomes are used in the treatment of breast cancer.

2. Niosomes are used in the treatment of few diseases like,

1) Antineoplastic treatment

i. The antineoplastic drugs are used in the treatment of cancer called as chemotherapy and mostly these drugs have poor penetration power in to tumour cells so it causes few side effects.

ii. But the usage of antineoplastic loaded niosomes can prevent the side effects and increase their metabolism, half-life of the drug in the body. And this helps to maintain the plasma concentration of blood. And it is used in various types of cancer like Breast cancer, ovarian cancer, lung cancer.[14,30]

2) Leishmaniasis

i. It is a type of disease where the causative organism belong s to genus leishmania effects the cells of liver and spleen called visceral leishmaniasis or kala Azar.

ii. To treat leishmaniasis the niosomes are capable of high loading of drugs without giving any side effects and it gives better efficacy.

3. Delivering of peptide drugs

The main purpose to use niosomes it to protect the peptides from the gastrointestinal enzymes action on the peptides, after oral administration of drugs the drug should be protected from pH, proteolytic enzymes trypsin, pepsin chymotrypsin etc [25,26]. Mainly those enzymes cause breakdown of peptides. So, the niosomes protects peptides as well as it acts as good carriers.

4. In the study of Immune response

i. The immune response mainly occurs when the any foreign substance or any mostly harmful substance enters it to body, the body tries to fight against it and destroys. Foreign particles like protein or antigens.
ii. While studying the niosomes are seem to be more stable and show less toxicity so it used in the study of immune response against antigens.

5. Niosomes are also used in the treatment of eye diseases through ocular drug delivery system. example: cyclopentolate it is used in mydriasis (pupil dilation) and cycloplegia (paralysis of ciliary muscle in the eye)

6. Cyclopentolate belongs to the medication class called ad mydriatics. Delivering of anti-inflammatory and antibiotic agents:

i. The antibiotics are suitable to carry in niosomes which shows good penetration and retention in skin when it applied to the skin and it shows a targeted action. In few invitro studies of rifampicin the release of rifampicin from niosomes are in controlled and prolonged.
ii. The anti-inflammatory drugs encapsulated in niosomes had undergone several studies like cytotoxicity, drug entrapment efficiency, skin tolerability in a mice have shown greater action compared to the non-loaded niosomes which causes mucosa irritation ad main adverse effect on topical application.

7. Antiviral drugs

The antiviral drugs loaded in niosomes have undergone few studies especially zidovudine undergone some studies like entrapment efficiency and sustain release of drug. they have

shown release of drug in for a longer period of time in a controlled manner. zidovudine is first anti-HIV drug.

8. Cosmetics

During 1970's and 80's the usage of niosomes in cosmetics had done by L'Oreal. And the first product of niosomes is introduced by Lancome in 1987. They have shown greater stability, penetrability when applied to the skin and good bioavailability. Lancome is a niosomal cream for antiaging used as foundation cream.

9. Other applications

The usage of niosomes in sustained release and localized drug action has shown greater stability and efficacy and increase in skin penetration and retention and shows localized action and site of administration. Niosomes are used in the treatment of acne and other dermatological diseases where as in acne in penetrates in to pilosebaceous unit to treat acne.[23]

Different routes of application of niosomal drugs and examples[3,4]

1. Ocular route: Timolol and Cyclopentolate
2. Nasal route: Influenza viral vaccine and Sumatriptan.
3. Trandermal route: levonorgestrel and estradiol.
4. Intravenous route: Insulin and Cisplatin.
5. Inhalation: All Trans Retinoic acids.

CONCLUSION

In the advancement of pharmaceutical field especially in novel drug delivery system by usage of niosomes they have shown a promising delivery of drugs towards a targeted site. The niosomes are capable of encapsulating both hydrophilic and lipophilic drugs. The niosomes are studied as alternative to liposomes due to their stability, low cost, biocompatible etc. And they are used in treatment of several diseases related to ocular, CNS, cancer, and in acne treatment, skin fungal infections. At present scenario the niosomes plays a great role in treatment of various diseases as targeted drug delivery.

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