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Review Article

NIOSOMES: AS ATARGETED DRUG DELIVERY SYSTEM

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ABSTRACT

Over the past several years, with the advancement of biotechnology and genetic engineering, the treatment of infectious diseases and immunization has undergone a revolutionary shift. Niosomes are a novel vesicular drug delivery system in which the medication is encapsulated in a closed bilayer structure, consisting of cholesterol, one or more non-ionic surface active agents and a charge inducing molecules. Niosomes are structurally similar to the liposomes and consider as better carrier for drugs delivery due to various factors like stability, cost, storage condition etc. This article reviews the current deepening and widening of interest of niosomes in many scientific disciplines and particularly its application in medicine. This article also presents an overview of the technique of preparation of niosomes, types of niosomes, its characterization and their applications.

Keywords: Bilayer, surfactants, carrier, novel vesicles.

INTRODUCTION

Niosomes are a novel vesicular drug delivery system, in which the medication is encapsulated in a closed bilayer structure, composed of a non-ionic surface active agents and hence the name niosomes('Nios' – Non ionic surfactant and 'Somes' – Vesicles).These are synthetic microscopic vesicles consisting of cholesterol, one or more non-ionic surface active agents and charge inducing molecules. Most surface active agents when added in water gives micelles however some surface active agents gives bilayer structure know as niosomes. This may be unilamellar vesicles or multilamellar vesicles depending on method of preparations. The design of dosage form is an important parameter in targeting the drug at specific site of action. Drugtargeting(smart drug delivery) is increase the concentration of drug relative to others. The aim of targeted drug delivery system is to prolong, localized, target, and have a protected drug interaction with diseased tissue. Targeted drug delivery system release the medicament at the site of actionwhere as in conventional drug delivery system, drug is absorbed across the biological membrane. This helps to maintain the desired plasma and tissueconcentration in the body, therefore by preventing any damage to the healthy tissue due to drug.Number of carriers are used to deliver the drug at targeted site which includes the niosomes, liposomes, immunoglobulin, serum proteins, polymers, microspheres, erythrocytes, nanoparticles etc.

SALIENT FEATURES AND ADVANTAGES OF NIOSOMES

- Niosomes are biocompatible, biodegradable and non-immunogenic in nature.
- Niosomes can improve the performance of drug by protecting the drug from biological membrane, delayed clearance of drug from the circulation and show the desired effect at the site of action.
- They are resistance to hydrolytic degradation.
- No specific handling and storage condition is required.
- Niosomes improve the oral bioavailability of poorly absorbed drugs.
- Niosomes can be designed according to the desired situation.
- Niosomes can accommodate the drug molecules with wide range of solubility due to its hydrophilic as well as hydrophobic part.

- The ability of non-ionic surfactant to form bilayer depends on the HLB values of surfactant, chemical structure of components and critical packing parameter.

DISADVANTAGES OF NIOSOMES

- Leaking of entrapped drug
- Inefficient drug loading
- Hydrolysis of entrapped drug may occur which limits the shelf life of niosomes dispersion.
- Aggregation may occur

STRUCTURE OF NIOSOMES

Niosomes and liposomes are structurally similar to each other,both are made up from the bilayer. In niosomes bilayer is made up from the non-ionic surface active agents while in liposomes it ismade up from phospholipids. Both niosomes and liposomes show same functions in vivo and increase the bioavailability of drug by reducing the clearance.(See fig.no 1)

Basic structural components of niosomes

a.Non-ionic surfactant
b.Cholesterol
c.Chargeinducing molecules

A. Non-ionic surfactant

Eg: polyglycerol, alkylethes, glucosyldialkylethers, crown ethers, polyoxyethylene alkyl ethers and esters.
The surfactant molecules orients themselves in such a way that thehydrophilic ends of non-ionic surfactant point outwards, while the hydrophobic ends face each other to form a bilayer. Most surfactant when added in water gives micellar structure, however some surfactant can yield bilayer vesicles known as niosomes, which is depends on critical packing parameter.

B.Cholesterol(sterols)

Niosomes are formed when a mixture of surfactant and cholesterol are hydrated. This is added in preparation of vesicles to minimize the leaching of bilayer. The ratio of surfactant/lipid used for preparation of niosomes is 10-30mM (1-25% w/w). cholesterol stabilizes niosomestowards the destabilizing effect of plasma and serum compounds.

C.Charge inducing molecules

i. Negatively charged molecules

Eg.Diacetyl phosphate (DCP), phoshotidic acid etc

ii.Positively charged molecules

Eg.Stearylamine (STR), stearylpyridium chloride etc
charge inducing molecules increase the stability of niosomes by electrostatic repulsion which prevents the aggregation of vesicles. This is to be added in the ratio of 2.5 - 5 mol %. High concentration of these molecules inhibit the niosomes formation.

VARIOUS TYPES OF NIOSOMES

On the basis of size and number of bilayers

A. Multi-lamellar vesicles (MLV)(0.5-10 um)

MLV are most widely used. It is simple to make and stable upon storage. It consists of a number of bilayers surrounding theaqueous lipid compartment separately.

B. Largeunilamellar vesicles (LUV)(1-30 um)

Large amount of material can entrapped due to a high aqueous/lipid ratio.

C. Smallunilamellar vesicles (SUV)(0.1-1um)

SUV mostly prepare from MLV by sonication and other suitable methods.

Other types of niosomes

A. Aspasomes

It is the combination of acorbylpalmitate, cholesterol and highly charged lipid diacetyl phosphate. This mixture is hydrated with aqueous solution to give niosomes. It is used to increase transdermal penetration.

B. Proniosomes

Proniosomes is a dry product which may be hydrated immediately before use to yield aqueous Niosome dispersion.It is used to minimize the problem of Niosome such as physical stability,aggregation, fusion and leaking.

C. Ethosomes

High concentration of ethanol and isopropyl alcohol is used to prepare ethosomes which have high permeation to deeper skin.

D. Elastic niosomes

Elastic nature of niosomes allows it to pass through channels that are less than one tenth of their own diameter.

E. Discomes

It has a large discoid structure. It exists under the certain phase transition diagram of non-ionic surfactant.

METHOD OF PREPARATION

1. Ether injection method

Surfactant and cholesterol is dissolved in diethyl ether and injected into an warm (60°C) aqueous phase containing drug. Ether is evaporated and gives LUVs.

2. Hand shaking method (Thin flim hydration method)

Surfactant and lipid is dissolved in organic solvents. The evaporation of organic solventsat room temperatures gives thin dryflim, which is then rehydrated with drug solution with intermittent shaking of flask. This process gives MLVs.

3. Transdermal pH gradient drug uptake process (Remote loading)

Solution of surfactant and lipid is made in chloroform. Solvent is evaporated under reduced pressure to get a thin film. This thin flimis rehydrated, then the solution is treated to three freeze thaw cycles and sonicated. The aquose solution of drug is added to the above mixture and pH is adjusted to 7-7.2 using 1M disodium phosphate. Finally mixture is heated at 60°C for 10 min gives niosomes.

4. Reverse phase evaporation techniques

Surfactant and cholesterol are dissolved in the chloroform ether mixture and sonicated at 4-5°C. In clear solution add Phosphate buffer solution(PBS) and again sonicated. Organic solvents are removed at 40°C under the reduced pressure. The viscous niosomes suspension is diluted with PBS and heated at 60°C for 10 min to get niosomes.

5. Micro fluidization

This method is based on submerged jet principle in which two fluidized streams interact in a precisely defined micro channels at ultra high velocities to get uniform size SUVs.

6. Multiple membrane extrusion method

Solution of surfactant, cholesterol and diacetyl phosphate is made in chloroform. Solvent is evaporated to get dry thin flim, Which is rehydrated with aqueous drug solution. This suspension is extruded through polycarbonate membrane which is placed in series upto 8 passage. This is also used for size reduction of niosomes.

7. Bubble method

This is the new method for the preparation of niosomes and liposomes in one step without the use of organic solvents. Surfactant and cholesterol is dispersed in buffer (pH7.4) at 70°C. This resultant mixture is homogenized for 15 min and immediately afterwards bubbled nitrogen gas at 70° C.

8. Sonication
This method is primarily used for conversion of MLVs into SUVs.

9. Formation of niosomes from:proniosomes
A dry product of niosomes is hydrated immediately before use to yield niosomes suspension. In this method the niosomes is coated with water soluble material.

SEPARATION OF UNENTRAPPED DRUG
The removal of unentrapped solutes from the vesicles can be done by dialysis, gel filtration and centrifugation method.

FACTORS AFFECTING FORMATION OF NIOSOMES
1. Nature of surfactant
Ester type of non-ionic surfactant are less stable and less toxic than ether type. HLB value of surfactant is more important for niosomes preparation (see table no 2). The geometry of vesicles formed is depend on the critical packing parameter of the surfactant(Fig no 2). It is calculated from the following equation,

$$CPP = v/lc \times a0$$

Where,
CPP = Critical packing parameter
V = hydrophobic group volume
lc = Critical hydrophobic group length
a0 =Area of hydrophilic head group
As the hydrophilic chain of surfactant is increased, it results into lowering the phase transition temperature, increase the leakage of low molecular weight drug from the aqueous compartment hence stability of niosomes suspension is decreased.
As the hydrophobic chain length of surfactant is increased, it results in increase of transition temperature, decreased the leakage of low molecular weight drug fromthe aqueous compartment, increased encapsulation of drug hence increased the stability of niosomes suspension.

2. Nature of encapsulated drug
The physicochemical properties of drug influence charge and rigidity of niosomes bilayer. Leakage of hydrophobic drugs from the bilayer is less as compare to hydrophilic drugs.Hydrophobic drugs improve transdermal penetration of drugs and increase the stability of formulation. On the other hand hydrophilic drugs are prone to leakage from bilayer hence stability of preparation is decreased. Amphiphilic drugs are well encapsulated in the niosomes.

3. Cholesterol contents
The concentration of cholesterol is depends on HLB values of surfactant. The surfactant/lipid ratio is in the range of 10-30 mM (1-2.5% w/w). it may influence the physical properties and structure of niosomes. Appropriate quantity of cholesterol increase the hydrodynamic diameter and entrapment efficiency. High concentration of cholesterol decrease the release rate of the drugs due to increase in the rigidity of bilayer.

4. Temperature of hydration
It should be above the gel to liquid phase transition temperature of system. It may influence the shape and size of niosomes.

5. Method of preparation
Different methods are used to prepare the niosomes suspension such as, reverse phase evaporation method gives small size vesicles, hand shaking method give larger vesicles than ether injection method. Niosomes prepared by transmembrane pHgradient method gives niosomes with greater entrapment efficiency and better retention of entrapped drug.

CHARACTERISATION OF NIOSOMES
1. Size, Shape and Morphology
Structure of Niosomes has been visualized and established by using freeze fracture microscopy while photon correlation spectroscopy used to determine size of the vesicles. Electron microscopy used for morphological studies of vesicles. Laser diffraction is used to determine particle size distribution, mean surface diameter.Niosomes diameter can be determined by using light microscopy, photon correlation microscopy and freeze fracture electron microscopy.

2. Niosomal drug loading and Entrapment efficiency
Drug entrapped in vesicles is determine by the complete disruption of niosomes using 50% n-propanol or 0.1% triton X-100 and resultant solution is analyzed for drug content by using appropriate method.

% Niosomal Recovery = (Amount of niosomesrecoverd/ Amount of polymer + Drug + Excipient) x 100

% Entrapment Efficiency (% EF) = (Amount of drug entraped/ Total amount of drug) x 100

% Drug Loading = (Amount of drug in niosomes/ Amount of niosomes recovered) x 100

3. Vesicles charge
Vesicle charge is more important as charged vesicles are more stable against aggregation and fusion than uncharged vesicles. To know the surface charge (potential) zeta potential of individual niosomes can be determined by microelectrophoresis or pH sensitive flurophores or dynamic light scattering. The surface charge is an important parameter for in vivo behavior of niosomes.

4. Bilayer Rigidity and Homogeneity
The bilayer rigidity and homogeneity is an important parameter for biodegradation and biodistribution of niosomes. It is determined by NMR, DSC and FT-IR (Fourier transform-infra red spectroscopy) techniques.

5. Niosomal drug release
Drug release from the niosomesis determined by incubating aknow quantity of drug loaded niosomes in a suitable buffer at 37°C with intermittent stirring. Withdraw the samples periodically and analyze the drug content with suitable method.

6. In-vitro drug release
It uses dialysis tubing which is washed and soaked in distilled water. The niosomes suspension is pipetted into a tube and sealed. The bag containing the suspension is placed in 200 ml of buffer solution in a 250 ml beaker with constant stirring at 25° C or 37° C. at various time intervals the buffer solution is analyzed for the drug content by suitable method.

7. Biological characterization
Sterility, pyrogenicity and animal toxicity studies are performed.

APPLICATIONS OF NIOSOMES
Drug Targeting
One of the most useful application of niosomes is drug targeting. Niosomes can target to the reticulo-endothelial system (RES) as well as to other organs. RES cells take up the niosomesvesicles. The uptake of vesicles is controlled by serum factor know as opsonin, which mark them for clearance. This result into accumulation of the drug at the target site and which is used for treating tumor in animals, parasitic infections of liver.
A carrier system such as antibodies, immunoglobulin etc can be attached to niosomes for targeting specific organs.
Anti-neoplastic Treatment
Most anti cancer drug causes serious side effect, which can be minimized by use of the niosomes. Niosomes can alter the metabolism, prolong circulation and half life of the drug, thus decreasing the side effects of drug. It decrease the rate of proliferation of tumor and higher plasma concentration accomplished by slower elimination.

Niosomes as Drug Carriers
Niosomes is used as drug carriers for the number of drugs. Niosomes containing anti-cancer drugs which are suitably designed are taken up by the tumors cells due to enhanced permeation rate of tumor cells. The niosomes is permeable to oxygen hence used as carrier for hemoglobin within the blood so used in anaemic patients.

Leishmaniasis
In this the parasite of leishmaniasis invades in the cells of the liver and spleen. Smaller size of niosomes can be taken up passively by liver and spleen and accumulated in the sinusoidal space of epithelium.

Delivery of Peptide Drugs
Orally administered peptide drug faces the challenge of bypassing the enzymes which would breakdown the peptide drug. Use of niosomes with peptide drug protects the peptide from the destructing enzymes.

Studying Immunological Response
Niosomes are less toxic, immunoselective and stable, hence used to study nature of the immune response provoked by the antigens.

Transdermal Drug Delivery
The major drawback of transdermal drug delivery is poor penetration of drug across the skin membrane. Niosomes of drug have the better penetration rate across the skin.

Use in Diagnosis
Conjugation of niosomes with a suitable agents used for diagnosis. PEG 4400 and PEG & NCP exhibits significant improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging.

Localized Drug Delivery
Drug delivery through niosomes is one of the approach to achieve localized drug action. Small size of liposomes with their low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration.

Sustained Release
Drugs with low therapeutic effects index and poor water solubility when encapsulated in niosomes, it is maintained in the circulation. This results intothe increase of sustained action of drug.

CONCLUSION

Recent improvements in the field of biotechnology and pharmaceuticals research have resulted in the affirmation of small molecules such as proteins and vaccines as a major class of therapeutic agents .These, however, constitute numerous drug-associated challenges such as poor bioavailability, suitable route of drug delivery ,physical and chemical instability and potentially serious side effects.Niosomes provides all signs of a successful carrier for such drugs .A view point of the usefulness of niosomes in the delivery of proteins and vaccines can be unsubstantiated with a wide scope in encapsulating toxic drugs such as anti-AIDS drugs, anti-cancer drugs and anti-viral drugs.Niosomes may be prepared by various methods, which affect their formations along with the properties of the drug, cholesterol content and amount, structure and type of surfactant. As a drug delivery device, niosomes are stable and also improves the stability of the entrapped drug. However the technology utilized in niosomes is still in its infancy. Hence, researchers are going on to develop a suitable technology for large scale production because it is a promising targeted drug delivery system.

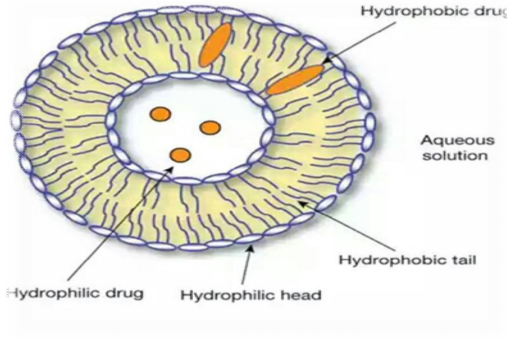

Fig. 1:

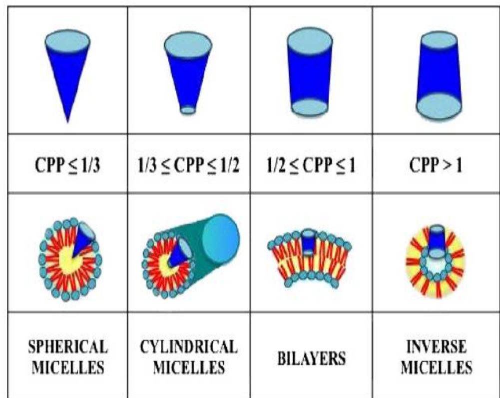

Fig. 2:

Table 1: Difference between Liposomes and Niosomes

LIPOSOMES	NIOSOMES
Requires special storage and handling condition	No special condition is require for storage and handling
Phospholipids are prone to Oxidative Degradation	Non-ionic surfactants are stable towards this
Phospholipids may be neutral or charged	Non-ionic surfactants are uncharged
More expensive	Less expensive

Table 2: HLB Value of surfactant and their impact in niosomes formation

HLB Value	Impact on formulation
14-16	Does not produce niosomes
8.6	Increase entrapment efficiency of niosomes
1.7-8.6	Decrease entrapment efficiency
>6	Need to add cholesterol in formation of bilayer vesicle
Lower value	Need to add cholesterol to increase stability

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