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Niosomes: An Emerging Drug Delivery System

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ABSTRACT: Niosomes are a novel drug delivery system, in which the medication is encapsulated in a vesicle. Niosomes are formations of vesicles by hydrating mixture of cholesterol and nonionic surfactants. Different novel approaches used for delivering these drugs include liposomes, microspheres, nanotechnology, micro emulsions, antibody loaded drug delivery, magnetic microcapsules, implantable pumps and niosomes. Niosomes and liposomes are equiactive in drug delivery potential and both increase drug efficacy as compared with that of free drug. Niosomes are now widely studied as an alternative to liposomes. 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. The application of niosomal technology is widely used to treat a number of diseases. Niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, antiinfective agents. Drug delivery potential of niosome can enhance by using novel concepts like proniosomes, discomes and aspasome. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Thus these areas need further exploration and research so as to bring out commercially available niosomal preparation.

KEY WORDS: Niosomes, Vesicles, Target cells, Biological environment.

1. INTRODUCTION: [1,2,3]

The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localisation of drug, leading to get maximum efficacy of the medication. Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic non-ionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Niosomes are one of the best among these carriers. Structurally, niosomes are similar to liposomes and also areequiactive in drug delivery potential but high chemical stability and economy makes niosomes superior than liposomes. Both consist of bilayer, which is made up of non-ionic surfactant in the case of niosomes and phospholipids in case of liposomes. Niosomes are microscopic lamellar structures of size range between 10 to1000 nm and consists of biodegradable, non immunogenic and biocompatible surfactants.

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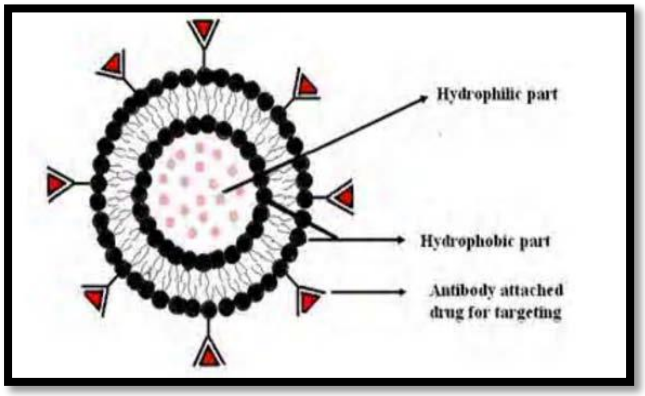

Figure 1: Niosome Structure

2. ADVANTAGES OF NIOSOMES:[2]

- The vesicles may act as a depot, releasing the drug in a controlled manner.
- They are osmotically active and stable, and also they increase the stability of entrapped drug.
- 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.
- The surfactants used are biodegradable, biocompatible and non-immunogenic.
- 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.

- The vesicles may act as a depot, releasing the drug in a controlled manner.
- Handling and storage of surfactants requires no special conditions.
- Due to the unique infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together they, as a result can accommodate drug molecules with a wide range of solubilities.
- Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate thedelivery rate of drug and administer normal vesicle in external non-aqueous phase.

2. TYPES OF NIOSOMES [8]

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

i) Multi lamellar vesicles (MLV)(MLV, Size=>0.05 µm)
ii) Large unilamellar vesicles (LUV),(LUV, Size=>0.10 µm).
iii) Small unilamellar vesicles (SUV).(SUV, Size=0.025-0.05 µm)

i. Multilamellar vesicles (mlv):
It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes.these vesicles are highly suited as drug carrier for lipophilic compounds.

ii. Large unilamellar vesicles (luv):
Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

iii. Small unilamellar vesicles (suv):
These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.

4. METHODS OF PREPERATION: [1,2,3,5]

A. Ether injection method
This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether 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 leads to formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000 nm.

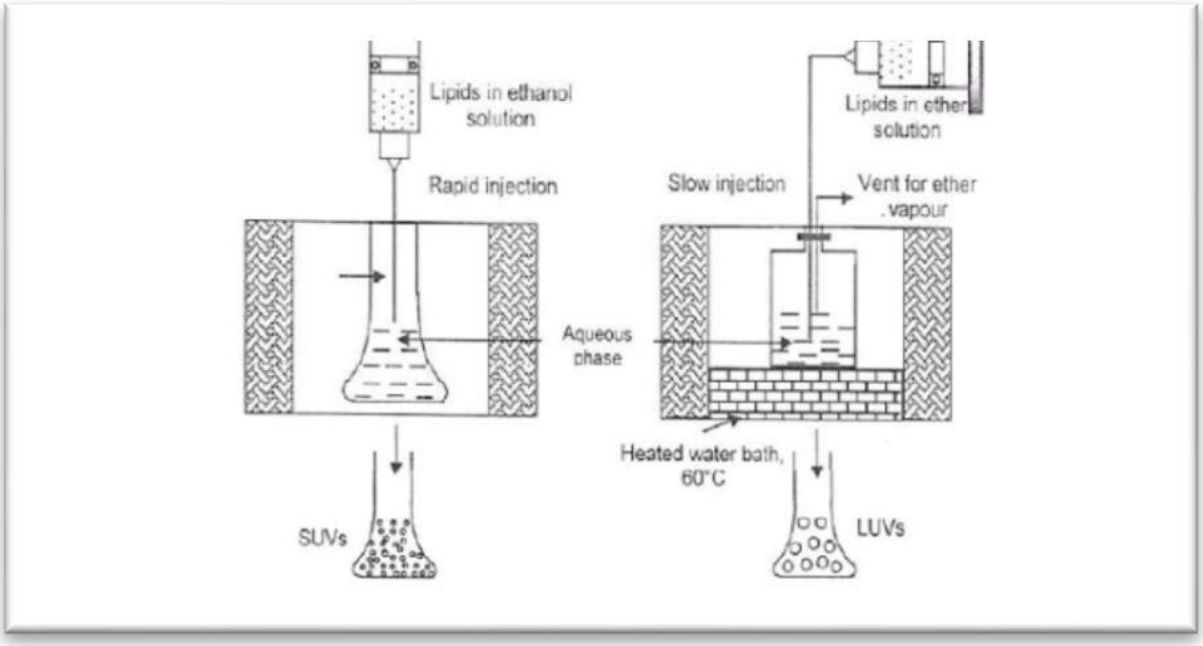

Fig.2: Ether injection method

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 niosomes film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.

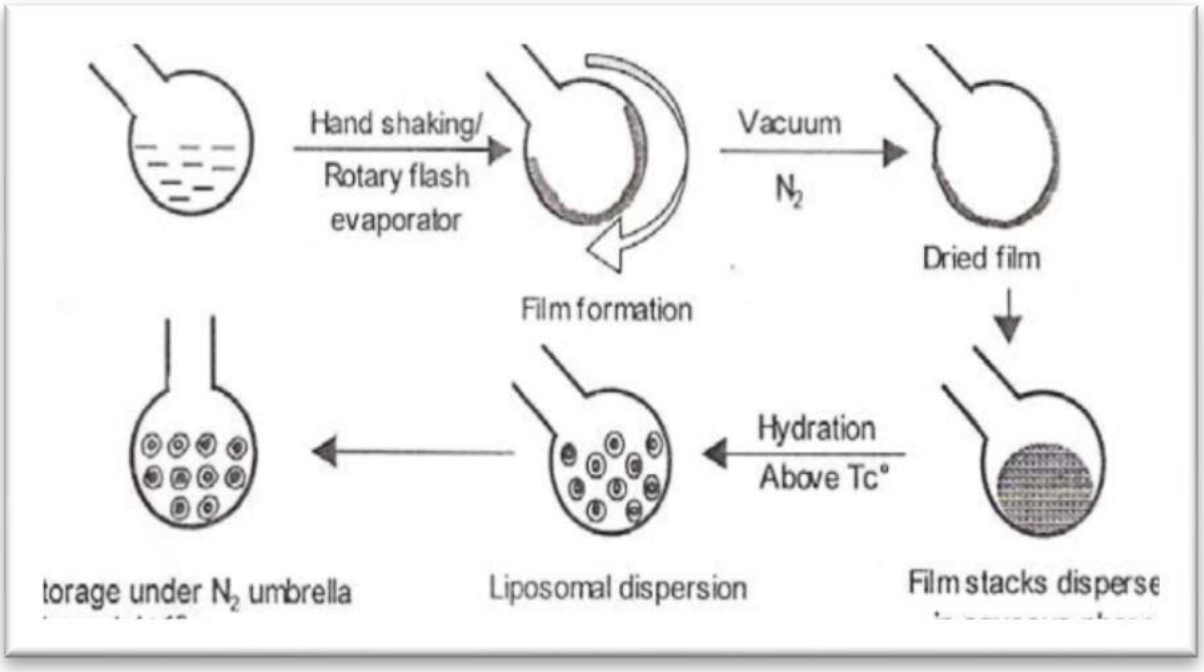

Fig 3: Hand Shaking Method of Niosomes Preparation

C. Sonication

A typical method of production of the vesicles is by sonication of solution as described by Cable. 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.

D. Micro fluidization

Micro fluidization 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 greater uniformity, smaller size and better reproducibility of niosomes formed.

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

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

niosomes. Raja Naresh et al have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

5. NIOSOMES IN COMPARISON WITH LIPOSOMES [11,26]

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. Niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from double chain phospholipids (neutral or charged). Niosomes behave in-vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. Encapsulation of various anti neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, increasing the anti-tumor efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. They can be expected to target the drug to its desired site of action and/or to control its release.

6. COMPONENTS OF NIOSOMES:[9]

Niosomes mainly contains following types of components:

I. Non-ionic surfactants:

Selection of surfactant should be done on the basis of HLB value. As Hydrophilic Lipophilic Balance (HLB) is a goodindicator of the vesicle forming ability of any surfactant, HLB number in between 4 and 8 was found to be compatible with vesicle formation. It is also reported that the hydrophilic surfactant owing to high aqueous solubility. on hydration do not reach a state of concentrated systems in order to allow free hydrated units to exist aggregates and coalesced to form lamellar structure.

a) Alkyl ethers: some surfactants for the preparation of niosomes containing drugs/chemicals.

1) Surfactant-I (Mol.Wt.473) is C16 monoalkyl glycerol ether with average of three glycerol units.

2) Surfactant-II (Mol.Wt.972) is diglycerol ether with average of the seven glycerol units.

3) Surfactant III (Mol.Wt.393) is ester linked surfactant.

b) Alkyl esters: Sorbitan esters are most preferred surfactant used for the preparation of niosomes amongst this category of surfactants. Vesicles prepared by the polyoxyethylene sorbitan monolaurate are relatively soluble than other surfactant vesicles]. For example polyoxyethylene (polysorbate 60) has been utilized for encapsulation of diclofenac sodium.

c) Alkyl amides: Alkyl amide (e.g. galactosides and glucosides) have been utilized to produce niosomal vesicles

d) Fatty acid and amino acid compounds: Long chain fatty acids and amino acid moieties have also been used in some niosomes preparation.

II. Cholesterol:

Steroids are important components of the cell membrane and their presence in membrane affect the bilayer fluidity and permeability. Cholesterol is a steroid derivative, which is mainly used for the formulation of niosomes. Although it may not show any role in the formation of bilayer, its importance in formation of niosomes and manipulation of layer characteristics can not be discarded. In general, incorporation of cholesterol affect properties of niosomes like membrane permeability, rigidity, encapsulation efficiency, ease of rehydration of freeze dried niosomes and their toxicity.As a result of this, the niosome become less leaky in nature.

III. Charged molecule:

Some charged molecules are added to niosomes to increase stability of niosomes by electrostatic repulsion which prevents coalescence. The negatively charged molecules used are diacetyl phosphate (DCP) and phosphotidic acid. Similarly, stearylamine (STR) and stearyl pyridinium chloride are the well known positively charged molecules used in niosomal preparations.These charged moleculesare used mainly to prevent aggregation of niosomes.Maltodextrin is a polysaccharide. It has minimal solubility in organic solvent. Thus it is possible to coat maltodextrin particles by simply adding surfactant in organic solvent.

7. EVALUATION

1. Entrapment efficiency [8,9]

After preparing niosomal dispersion, unentrapped drug is separated by dialysis centrifugation and gel filtration. The drug remain entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzed resultant solution by appropriate assay method using following equation.

2. Particle size analysis [8,10]

Particle size analysis was done by scanning electronic microscopy (SEM) using JEOL JSM-T330A scanning microscope brass stab. The stabs were placed briefly in a

drier and then coated with gold in an ion sputter. Pictures of niosomes were taken by random scanning of the stub and count. The diameter is about 30 niosomes was measured from the photomicrographs of each batch. Finally, average mean diameters were taken into consideration.

3. In-vitro release study [11,12]

Human cadaver skin (HCS) was obtained from ventral part of forearm of 35 years old male corpse and was stored at 4°C. HCS membrane was spread and punches it at approximately 3 cm2 area. Trimmed away the excessfat and sliced to 500 □m thickness using a Daw's derma tone. These slices were hydrated in pH 7.4 PBS for 24 hrs prior to use. The HCS were attached to Khesary cell (K.C., filled with 100 ml of PBS) and add 10 mg niosomal suspension on it. Finally, cell was immersed into the receptor compartment. The dermal surface was just flush to the surface of permeation fluid (PBS), which was maintain at 37°C □□0.50°C and stirred magnetically at 50 r.p.m., aliquots were withdraw and replaced with the same volume of fresh buffer, at every sampling points and analyzed by U. V. Spectrophotometer method at 294 nm.

4. Stability study [13]

All niosomal formulations were subjected to stability studies by storering at 4°C, 25°C and 37°C in thermostatic oven for the period of three months. After one month, drug content of all the formulations were checked by method discussed previously in entrapped efficiency parameter. *In-vitro* release studies of selected formulations were also carried out.[13]

8. APPLICATIONS

Targeting of bioactive agents[10]

a) To reticulo-endothelial system (RES)

The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is
also by circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver.

b) To organs other than RES

It has been suggested that carrier system can be directed to specific sites in the body by use
of antibodies50. Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier.Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells.

Diagnostic imaging with niosomes[17]

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

Ophthalmic drug delivery[17]

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 marketedformulation (Dorzolamide) The chitosancoated niosomal formulation timolol maleate (0.25%) exhibits more effect for reduction intraocular pressure as compared to a
marketed formulation with less chance of cardiovascular side effects.

Delivery of peptide drugs

Yoshida *et al*51 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.

Neoplasia[19,26]

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 sarcoma58. 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 elimination.

Immunological application of niosomes[17]

Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander60 have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

Transdermal delivery of drugs by niosomes[19]

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 niosomes. Jayraman *et al*61 has studied the topical delivery of erythromycin from

various formulations including niosomes or hairless mouse. From the studies, and confocal microscopy, it was seen that non-ionic vesicles could be formulated to target pilosebaceous glands.

9. CONCLUSION:-

The concept of incorporating the drug into liposomes or niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers. Niosomes have great drug delivery potential for targeted delivery of anti-cancer, antiinfective agents. Drug delivery
potential of niosome can enhance by using novel concepts like proniosomes. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Niosomes are thoughts to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parentral.

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