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NIOSOMES-A NOVEL DRUG DELIVERY SYSTEM

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Abstract:
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. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. The method of preparation of niosome is based on liposome technology. The basic process of preparation is the same i.e. hydration by aqueous phase of the lipid phase which may be either a pure surfactant or a mixture of surfactant with cholesterol. After preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation or gel filtration. A method of in-vitro release rate study includes the use of dialysis tubing. Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. 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.

Keywords: *Niosomes, Vesicular systems, Drug Delivery*

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1.INTRODUCTION:

Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic non-ionic surfactants, with or without incorporation of cholesterol or other lipids. This class of vesicles was introduced. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. One of the reasons for preparing niosomes is the assumed higher chemical stability of the surfactants than that of phospholipids, which are used in the preparation of liposomes. Due to the presence of ester bond, phospholipids are easily hydrolysed. Unreliable reproducibility arising from the use of lecithin in liposomes leads to additional problems and has led scientist to search for vesicles prepared from other material, such as non-ionic surfactants. Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. 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. In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as diacetyl phosphate

- Niosomes are the drug delivery system, in which the medication is encapsulated in avesicle.
- The vesicle is composed of lipid bilayer nonionic surface-active agents and hence name asniosomes.
- The niosomes are very small, microscopic in size. The size lies in nanometric scale.
- Niosomes are unilamellar and multilamellar vesicles.
- A diverse range of materials have been used to form niosomes such as sucrose, ester, surfactants and polyethylene alkyl ether surfactants. alkyl ether surfactants, alkyl ester, alkyl amides, fatty acids and amino acid compound.

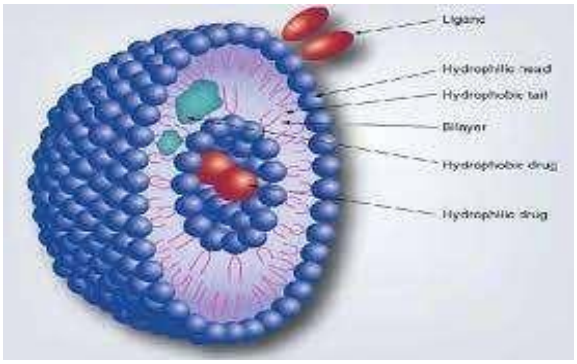
Definition of noisome:

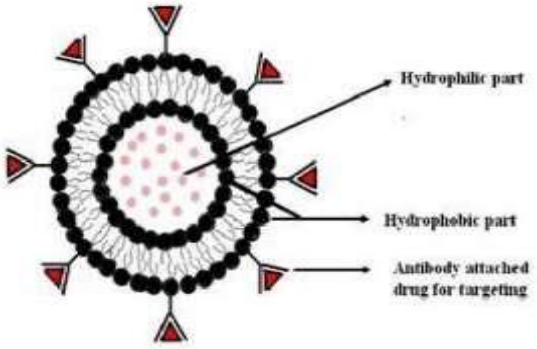
A niosome is a non-ionic surfactant-based vesicle. Niosome**s** are formed mostly by non- ionic surfactant and cholesterol incorporation as an excipient. Other excipients can also be used. They are structurally similar to liposomes in having a bilayer, however, the materials used to prepare noisome make them more stable.

*Structure of niosomes***:**

The structure of noisome is similar to that of liposomes in which both are made up of lipid bilayer. However, the bilayer in the case of Niosomes is made up of cholesterol and non-ionic surface- active agents rather than phospholipids.

Niosomes are made up of a surfactant bilayer with its hydrophilic ends exposed on the outside and inside of the vesicle, while the hydrophobic chains face each other within the bilayer





*Advantages of niosomes***:**

The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages: -

- 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 nonaqueous phase. ·
- The vesicle suspension is water–based vehicle. This offers high patient compliance in comparison with oily dosage forms. ·
- Niosomes 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.
- 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 surfactants are biodegradable, biocompatible and non-immunogenic hence can be used safely in preparation of niosomes. ·
- They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment restricting· Handling and storage of surfactants requires no special condition

Disadvantages:

- Production cost is high.
- Leakage and fusion of encapsulated drug/molecules.
- Sometimes phospholipids undergo oxidation and hydrolysis like reaction.
- Short half-life.
- Low solubility.

2.TYPES OF NIOSOMES:

Small unilamellar vesicles- (SUV, size -0.025-0.05nanometers) are commonly produced by sonication, and French press procedures. Ultra-sonic electrocapillary emulsification or solvent dilution techniques can be used to prepare SUVs

Multilamellar vesicle-(MLV, size >0.05 nanometers) exhibit increased trapped volume and equilibrium solute distribution. And require hand-shaking method. They show variations in liquid composition.

Large unilamellar vesicle-(LUV, 100-250 nanometers) the injections of lipids solubilized in an organic solvent into aqueous buffer can result in spontaneous formation of LUV. But the better method of preparation of luv is reverse phase evaporation, or by detergent solubilization method.

3.PREPARATION METHODS OF NIOSOMES:

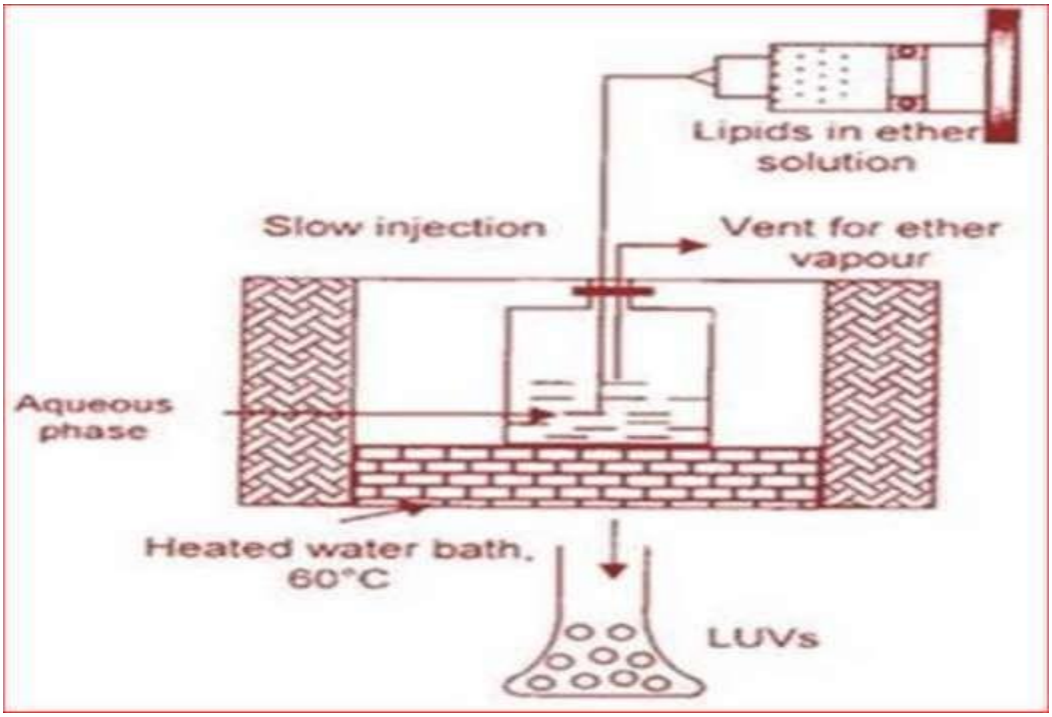
The preparation methods should be chosen according to the use of the niosomes, since the preparation methods influence the number of bilayers, size, size distribution, and entrapment efficiency of the aqueous phase and the membrane permeability of the vesicles.

- Ether injection method.
- Handshaking method.
- Sonication method.
- Micro fluidization method.
- The bubble method.
- Reverse phase evaporation technique.
- Multiple membrane extrusion method.
- Trans membrane pH gradient uptake process.
- Formation of niosome from proniosomes.

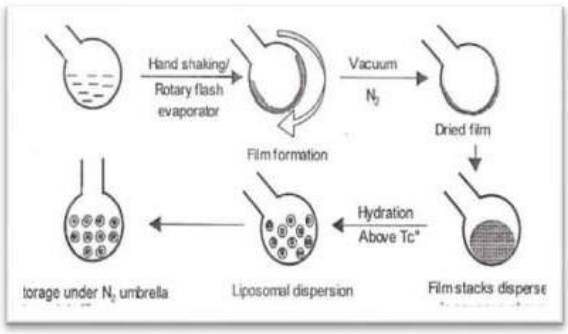
By all these methods niosomes are prepared. Niosomes may be unilamellar and multi lamellar depend on the method used to prepare them.

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. The disadvantage of this method is that a small amount of ether is often still present in the vesicle suspension and is often difficult to remove.

Niosomes prepared by ether injection technique were found to be discrete and through SEM analysis. The drug content containing drug: polymer in various ratios of 1:1, 1:2, 1:3, 1:4 and 1:5 were found. Thus, there was a steady increase in the drug content on increasing the polymer concentration in the formulation.



Hand shaking method (thin film hydration method):
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. Thermosensitive niosomes were prepared by evaporating the organic solvent at 60°C and leaving a thin 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. Large multilamellar vesicles are prepared. entrapped methotrexate in niosomes prepared by Hand shaking method using lipophilic surfactants like span 40, span 60 and span 80, cholesterol. and di-cetyl phosphate in ratio of 47.5: 47.5: 5. The tissue distribution of methotrexate was improved after entrapping with niosomes. the prepared doxorubicin entrapped niosomes using pure surfactant or a mixture of surfactants and cholesterol. It is modified this method for preparation of methotrexate entrapped niosomes.



Sonication:

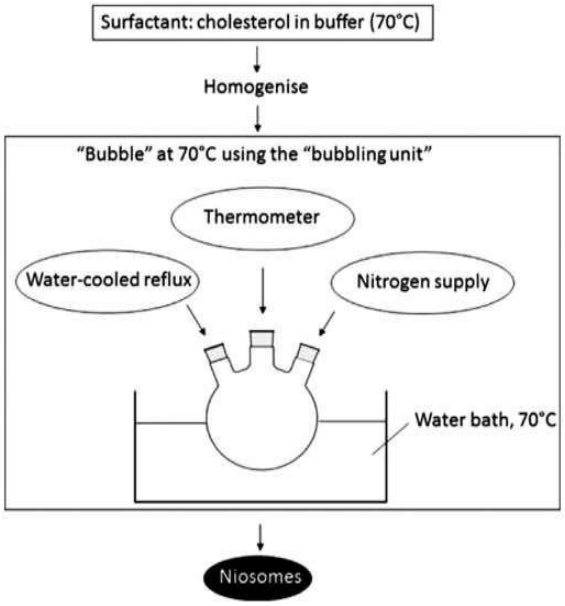
A typical method of production of the vesicles is by sonication of solution as described by Cable. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes. The resulting vesicles are small and unilamellar. In the case of niosomes the resulting vesicle sizes are in general larger than liposomes, niosomes being no smaller than 100 nm in diameter. Baillie et al prepared 5,6 carboxy fluorescein in entrapped niosomes by sonication method. Prepared sonicated niosomes by sonication of multilamellar niosomes being prepared by Ether injection method, modified this method for entrapment of 9- desglycinamide 8-arginine vasopressin. prepared niosomes by sonication of transdermal delivery of estradiol by niosomes in vitro.

Microfludization:

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.

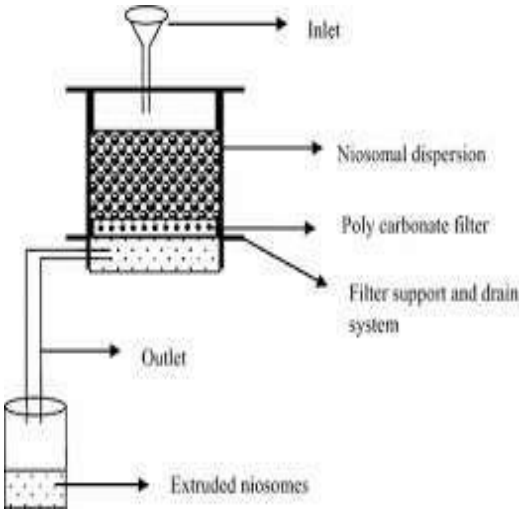
Bubble method **:**

In this method organic solvents are not used. surfactants, additives, and phosphate buffer solution transferred to a three necked glass reactor. To control the temperature. The reactor is placed in a water bath. Nitrogen gas enters the first neck the thermometer is positioned in the second neck and water reflux in the third neck. These components are mixed for 15s with high shear homogenizer and immediately afterward bubbled with nitrogen gas at 70 c to yield niosomes.



Multiple membrane extrusion method:

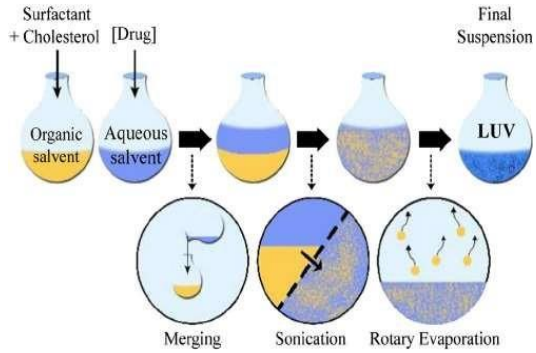
Mixture of surfactant, cholesterol and diacetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug polycarbonate membranes, solution and a good method for controlling niosome size. the resultant suspension extruded through which are placed in series for up to 8 passages. It is good method for controlling noisome size.



Reverse phase evaporation technique:

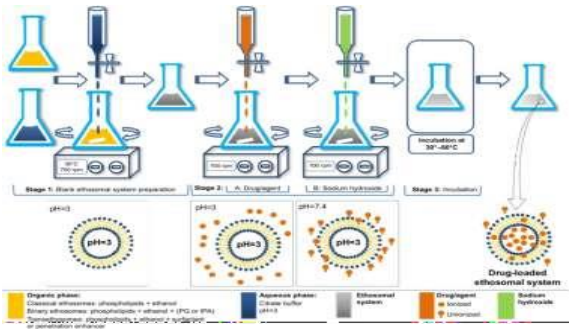
The novel key in this method is the removal of solvent from an emulsion by evaporation. Water in oil emulsion is formed by bath sonication of a mixture of two phases, and then the emulsion is dried to a semi-solid gel in a rotary evaporator under reduced pressure. The next step is to bring about the collapse

of certain portion of water droplets by vigorous mechanical shaking with a vortex mixture. In these circumstances, the lipid monolayer, which encloses the collapse vesicles, is contributed to adjacent intact vesicles to form the outer leaflet of the bilayer of large unilamellar niosomes. 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 40c under low pressure. The resulting viscous niosomes suspension is diluted with Phosphate buffer saline and heated on water bath at 60c for 10 minutes to yield niosomes.



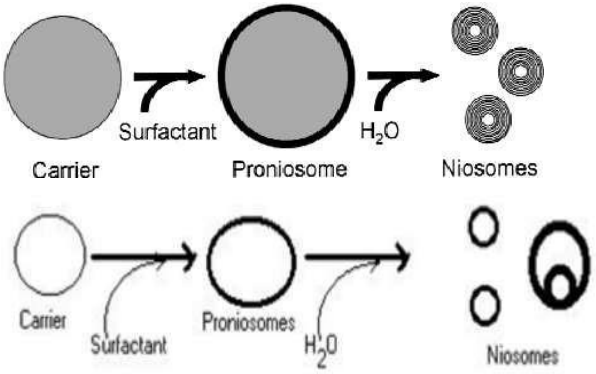
***Transmembrane p^H gradient drug uptake process* : (inside acidic)**

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 mixture is later heated at 60°C for 10 minutes to give niosomes.



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 "Proniosomes". The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation. T=Temperature. Tm = mean phase transition temperature.



The formulation of niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free-flowing powder, which could be rehydrated by addition of warm water.

10. The size and number of bilayers of vesicles consisting of polyoxyethylene alkyl ethers and cholesterol can be changed in alternative way. A temperature rise above 600 C transform a small unilamellar vesicles to large multilamellar vesicles while vigorous shaking at room temperature results in the opposite effect by changing multilamellar vesicles into unilamellar ones. The transformation from unilamellar to multilamellar vesicles at higher temperature might be characteristics for the polyethylene alkyl ether surfactants since it is known that polyethylene glycol (PEG) and water demixes at higher temperature due to a breakdown of hydrogen bondings between water and PEG moieties. Generally free drug is removed from the encapsulated drug by gel permeation chromatography dialysis methods or by centrifugation. Often weight density differences between niosomes and the external phase are smaller than in the case of liposomes which make separation by centrifugation very difficult. A possibility is to add protamine to the vesicle suspension in order to facilitate separation during centrifugation

4. Characterisation of Niosomes

Entrapment Efficiency:

After preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation, or gel filtration 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. Where, Entrapment efficiency (EF) = (Amount entrapped total amount) x 100 Entrapment efficacies of hydrophilic and lipophilic compounds depend on the preparation method. concluded that niosomes prepared by ether injection method resulted in entrapment efficacies of carboxy fluorescein that were significantly higher than those of vesicles prepared by hand shaking. used glycerol surfactants and reported that the entrapment efficacy decreased as the amount of cholesterol added in the non-ionic surfactant vesicle increased.

*Vesicle Diameter***:**

Niosomes, similar to liposomes, assume spherical shape and so their diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy. Freeze thawing (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.

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 analysed for the drug content by an appropriate assay method.

Stability and Toxicity Studies:

Compared to liposomes, niosomes are relatively stable structures some concern has been expressed regarding the stability of niosomes in vitro and their toxicity in vivo. Surfactants are used in the preparation of niosomes, which may be a cause of toxicity. However, there are virtually no reports available on the in vivo toxicity of niosomes linked with the concentration of ether or esters surfactants used in the preparation of vesicles. toxicity of These include:

1.1 the ciliary beat frequency (CNF) of trachea, which is important for intranasal administration

1.2. the cell proliferation of keratinocytes which is important for the transdermal application of vesicles. A decrease in cerebral spinal fluid was considered to be a measure for the toxicity of the formulation. performed first in vivo experiment on drug delivery by means of synthetic non-ionic surfactant vesicles and reported that no adverse effects were observed in the experiment carried out performed in vivo experiment over 70 male BALB/C mice and reported that no fatalities were encountered that could be attributed to the preparation. The toxic or side effects directly related to drug are reduced.

Surfactants Used in Formation of Niosomes:

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:

Ether linked surfactant:

These are surfactants in which the hydrophilic hydrophobic moieties are ether linked, polyoxyethylene alkyl ethers; i.e., number of oxyethylene unit varies between 3 and 7. The surfactants used were $C_{12}EO_3$, $C_{12}EO_7$, $C_{18}EO_3$, and C_3 EO_7. Single alkyl chain surfactant C_{16} mono alkyl glycerol ether with an average of three glycerol units. It was used for the preparation of niosomes. The effect of this surfactant based niosomes on absorption, metabolism and excretion of methotrexate in the mice was studied. The drug entrapment, stability and release of drug from Adriamycin loaded niosomes based on this surfactant were studied. Effect on the absorption and distribution of methotrexate entrapped in niosomes was studied. Based on this surfactant stibogluconate bearing

niosomes were prepared and evaluated for various parameters for their effect on the in vivo absorption, distribution and elimination of the contained drug.

Di-alkyl ether chain:

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.

Ester linked:

These are the surfactants in which hydrophilic and hydrophobic moieties are ester linked. Ester linked surfactant, $C_{15}H_{31}CO$ [O-CH_2 -CH-CH_2] $_2$ -OH |

OH (mol. Wt. 393) 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. The commercial sorbitan esters are H-C-OH mixtures of the partial esters of sorbitol and its mono and di-an- hydrides with oleic acid.

Sorbitan Esters:
| H-C-OH | RCOO- C-H | H-C-OH | H-C-OOC-R | CH_2OOC-R CH_2. 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 bearingmice.

where, R is H or an alkyl chain

Poly-sorbates:
The typical structural formula of polysorbates is - CH_2 | H-C-O(CH_2 -CH_2 -O) H | (OCH-CH_2)- O-C-H | H-C-O-(CH_2 -CH_2 -O)y H | CH_2 -O(CH_2 -CH_2 -O)z OCR When n = x + y + z + 2 and R is an alkyl chain this series of surfactants has been used to study the pharmacokinetics of niosomal entrapped methotrexate.

Factors affecting formation of niosomes.

1.Drug:
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. In polyoxyethylene glycol (PEG) coated vesicles, some drug is entrapped in the long PEG chains, thus reducing the tendency to increase the size. The hydrophilic lipophilic balance of the drug affects degree of entrapment.

2. Amount and Type of Surfactant:
The mean size of niosomes increases proportionally with increase in the HLB of surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant. [18] 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 entrapment

3. Structure of Surfactant:
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) = v/lc ×a0 Where v = hydrophobic group volume, lc = the critical hydrophobic group length, a0 = 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 inverted micelles.

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

5. 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. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral niosome remains unaffected by adding low amount of solulan C24 (cholesteryl poly-24- oxyethylene ether), which prevents aggregation due to development of steric hindrance. In contrast spherical Niosomes are formed by C16G2: cholesterol: solulan (49:49:2). The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by C16G2 : solulan C24 in ratio (91:9) having bigger size (8.0 ± 0.03mm) than spherical/tubular niosomes formed by C16G2 : cholesterol: solulan

C24 in ratio (49:49:2) (6.6±0.2mm). Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces the leakage of drug from noisome.

6. Methods of Preparation:

Methods of preparation of niosomes such as hand shaking, ether injection and sonication, Hand shaking method forms vesicles with greater diameter (0.35-13nm) compared to the ether injection method (50-1000nm). Small sized niosomes can be produced by Reverse Phase Evaporation (REV) method (9,37). Micro fluidization method gives greater uniformity and small size vesicles. prepared niosomes by trans membrane pH gradient (inside acidic) drug uptake process. Niosomes obtained by this method showed greater entrapment efficiency and better retention of drug.

7. Temperature of Hydration:

Hydration temperature influences the shape and size of the noisome. 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. reported that a polyhedral vesicle formed by C16G2 : solulan C24 (91:9) at 25°C which on heating transformed into spherical vesicle at 48°C, but on cooling from 55°C, the vesicle produced a cluster of smaller spherical niosomes at 49°C before changing to the polyhedral structures at 35°C. In contrast vesicle formed by C16G2 : cholesterol: solulanC24 (49:49:2) shows no shape transformation on heating or cooling. Along with the above-mentioned factors, volume of hydration medium and time of hydration of niosomes are also critical factors. Improper selection of these factors may result in formation of fragile niosomes or creation of drug leakage problems.

8. 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 stress.

9. Niosomes As A Drug Carrier.

A number of workers have reported the preparation, characterization and use of niosomes as drug carriers. Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes. The niosomal encapsulation of Methotrexate and Doxorubicin increases drug delivery to the tumors and tumoricidal activity of the drug. Doxorubicin niosomes possessing muramic acid and triglycerol surfaces were not taken up significantly by liver. The triglycerol niosomes accumulated in the tumour and muramic acid vesicles accumulated in the spleen. Those vesicles with polyoxyethylene surface were rapidly taken up by the liver and accumulated to a lesser extent in tumour. some investigated the encapsulation and retention of entrapped solute 5,6-carboxy fluorescence (CF) in niosomes. They observed that stable vesicles could not be formed in the absence of cholesterol but were more permeable to entrapped solute. The physical characteristics of the vesicles were found to be dependent on the method of production. they reported that multiple dosing with sodium stibogluconate loaded niosomes was found to be effective against parasites in the liver, spleen and bone marrow as compared to simple solution of sodium stibogluconate. reported the preparation and oral as well as intravenous administration of Methotrexate loaded niosomes in mice. They observed significant prolongation of plasma levels and high uptake of Methotrexate in liver from niosomes as compared to free drug solution. The reported the formation and pharmacokinetic evaluation of Methotrexate niosomes in tumors bearing mice. modified the surface of niosomes by incorporating polyethylene alkyl ether in the bilayer structure. They compared the release pattern and plasma level of Doxorubicin in niosomes and Doxorubicin mixed with empty niosomes and observed a sustained and higher plasma level of doxorubicin from niosomes in mice studied absorption of Ciprofloxacin and Norfloxacin when administered as niosome encapsulated inclusion complexes. The reported the formulation and evaluation of Indomethacin loaded niosomes and showed that therapeutic effectiveness increased and simultaneously toxic side effect reduced as compared with free Indomethacin in paw oedema bearing rats the prepared niosomes of vincristine sulphate which had lesser toxicity and improved anticancer activity. prepared niosomes of Pentoxifylline and studied the in-vivo bronchodilator activity in guinea pigs. The entrapment efficiency was found to be 9.26 ± 1.93% giving a sustained release of drug over a period of 24 hrs.] reported the anti-inflammatory activity of niosome encapsulated Diclofenac sodium in arthritic rats. It was found that the niosomal formulation prepared by employing a 1:1 combination of Tween 85 elicited a better consistent anti-inflammatory activity for more that 72 hrs after administration of

single dose.

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. A. Targeting of bioactive agents:

1. Targeting of bioactive agents

1.1 To reticulo-endothelial system (RES)

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. To organs other than RES It has been suggested that carrier system can be directed to specific sites in the body by use of antibodies. 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.

1.2 Neoplasia:

Doxorubicin, the anthracyclic antibiotic with broad spectrum anti tumors activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumors increased their life span and decreased the rate of proliferation of sarcoma. 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 tumors bearing mice resulted in total regression of tumour and also higher plasma level and slower elimination.

Leishmaniasis:

Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting organism resides in the organ of reticuloendothelial system. Leishmaniasis is such a disease in which parasite invades cells of liver and spleen. The commonly prescribed drugs are antimonial, 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 showed high liver level after intravenous administration of the carrier forms of the drugDelivery of peptide drugs:

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.

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 stability.

Niosomes as carriers for Haemoglobin.

Niosomes can be used as a carrier for haemoglobin. Niosomal suspension shows a visible spectrum superimposable onto that of free haemoglobin. Vesicles are permeable to oxygen and haemoglobin dissociation curve can be modified similarly to non-encapsulated haemoglobin.

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 niosomes. 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 gland.

2.Other Applications:

2.1 Sustained Release: 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

2.2 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 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. 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.

CONCLUSIONS:

Drug incorporation in the niosomes to target the niosomes to the specific site is a promising drug delivery model. They present a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multi environmental structure. Niosomes are considered to be better candidates for drug delivery as compared to liposomes due to various factors like cost, stability etc. Niosomes are promising vehicles at least for lipophilic drugs. These advantages over the liposomes make it a better targeting agent. Ophthalmic, topical, parenteral and various other routes are used for targeting the drug to the site of action for better efficacy

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