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DIFFERENT METHODS FOR PREPARATION OF NIOSOME WITH REFERENCE TO ITS EVALUATION PARAMETERS -A REVIEW

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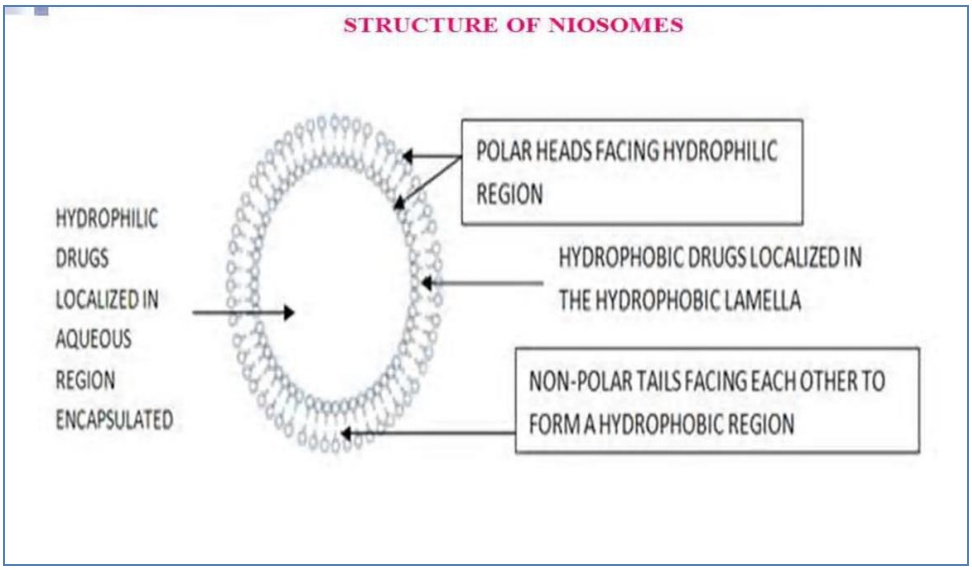
INTRODUCTION

Structure of Niosome

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



Structure

Compositions of niosomes

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

1. Cholesterol
2. Nonionic surfactants

1. Cholesterol

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

2. Nonionic surfactants

The following non-ionic surfactants are generally used for the preparation of niosomes.

e.g. Spans (span 60, 40, 20, 85, 80)
Tweens (tween 20, 40, 60, 80)
Brijs (brij 30, 35, 52, 58, 72, 76)

The non ionic surfactants possess a hydrophilic head and a hydrophobic tail.

METHOD OF PREPARATION

Preparation of small unilamellar vesicles

Sonication Method

This is a convenient method for preparation of niosomes where cholesterol and the surfactant are dispersed in an aqueous solution. This is then mixed with the drug solution in buffer. The resulting mixture is transferred to a vial and probe sonicated at 60°C for 3mins. The titanium probe is used for sonication. Multilamellar vesicles are formed by this method.[3]

Micro fluidization

It is a recent technique based on submerged jet principle. In this two fluidized streams interact at ultra high velocitiesand move forward through precisely defined micro channelwithin the interaction chamber. The impingement of thinliquid she*et al*ong a common front is arranged such that the energy supplied to the system remains within the area ofniosomes formation which results in a greater uniformity, smaller size and better reproducibility of niosomes formed.[4]

Preparation of multilamellar vesicles

Hand shaking method (Thin film hydration technique)

Surfactant and the other vesicles forming ingredients like cholesterol are blended and mixture is dissolved in a volatile organic solvent like diethyl ether, chloroform or methanol in a round bottom flask. Using rotary evaporator the organic solvent is removed at room temperature (20°C), by this a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 60°C with gentle agitation results in formation of multilamellar niosomes.[5]

Trans-membrane pH gradient (inside acidic) drug Uptake process

(Remote Loading): In trans membrane pH gradient drug uptake process the solution of surfactant and cholesterol is formed in chloroform, then the solvent is evaporated under reduced pressure to obtained a thin film on the walls of the round bottom flask. Then this film is hydrated with citric acid. The multilamellar vesicles are formed by freeze thaw method and finally sonicated. Lastly, to this niosomes suspension, aqueous solution of 10 mg/ml of drug is added and vortexed, then pH is increased to 7.0-7.2 with 1M disodium phosphate. This mixture is finally heated for 10 minutes at 60°C to give niosomes.[6]

Preparation of large Unilamellar Vesicles

Reverse phase evaporation method (REV)

The reverse-phase evaporation technique uses a mixture containing surfactant and cholesterol in a 1:1 ratio, in addition to ether and chloroform. An aqueous phase containing the target drug is added to the mixture followed by sonication at 4–5°C. Sonication is continued after adding a small amount of phosphate-buffered saline to the mixture. The organic solvent is removed at 40°C under a low pressure, and the remaining suspension is diluted with phosphate-buffered saline. After heating the mixture at 60°C for 10 min, the final product of niosomes is obtained.[20,27,32] The preparation of niosomes using the reverse-phase evaporation technique is illustrated in **Figure.**[7,8,9]

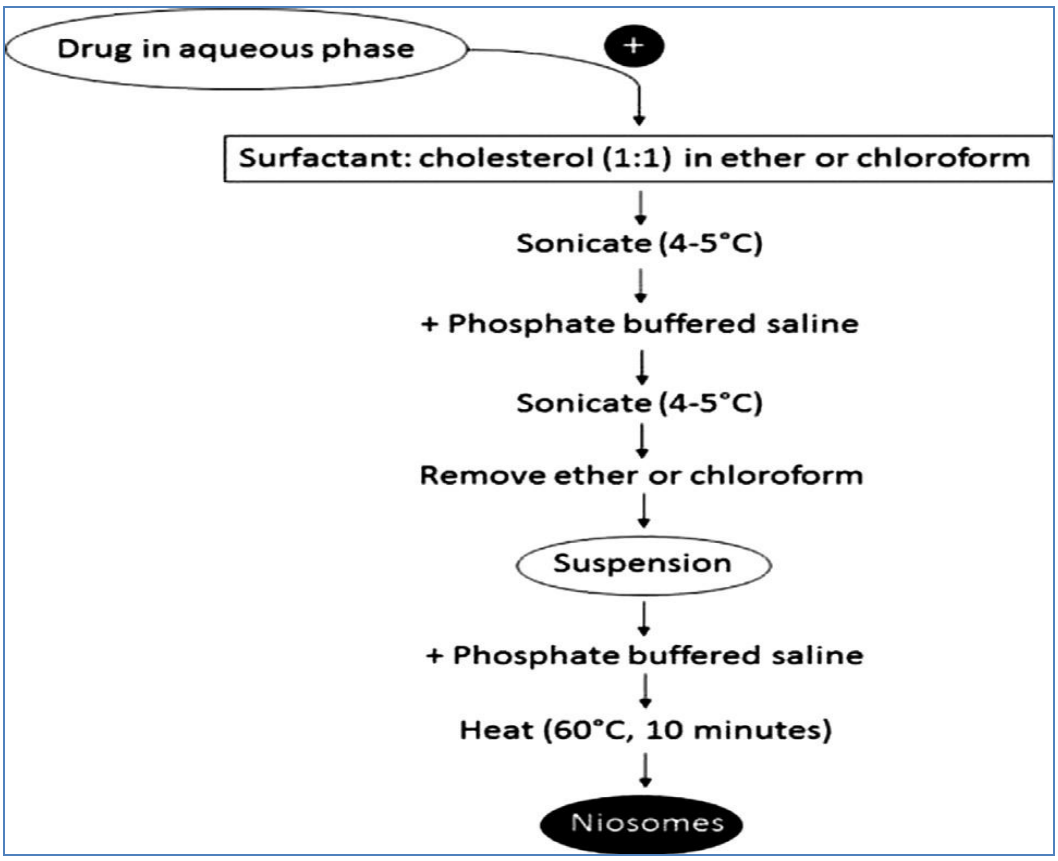


Figure 2: Schematic diagram of preparation of niosomes using the reverse-phase evaporation technique.

Ether injection method

The ether injection method is essentially based on 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. The particle size of the niosomes formed depend on the conditions used the diameter of the vesicle range from 50 to 1000 nm.[5]

Miscellaneous

Multiple membrane extrusion method: A blend of surfactant, cholesterol, and di acetyl phosphate is dissolved in chloroform and the solvent is evaporated leading to formation of thin film. Using aqueous drug solution the film is hydrated and the resultant suspension extruded through polycarbonate membranes, which are placed in a series for up to eight passages. This is a best method for controlling niosome size.[10]

The "Bubble" Method

Niosomes can be produced without the use of organic solvents using the "bubble" method. A "bubbling unit" consists of a round-bottomed flask with 3 necks positioned in a water bath; a water-cooled reflux condenser and thermometer are positioned in the first and second necks, respectively, while nitrogen is supplied through the third neck. Surfactant and cholesterol that are mixed at 70°C in a buffer are homogenized and "bubbled" at 70°C using the "bubbling unit".[11,12] The preparation of niosomes using this technique is illustrated in.

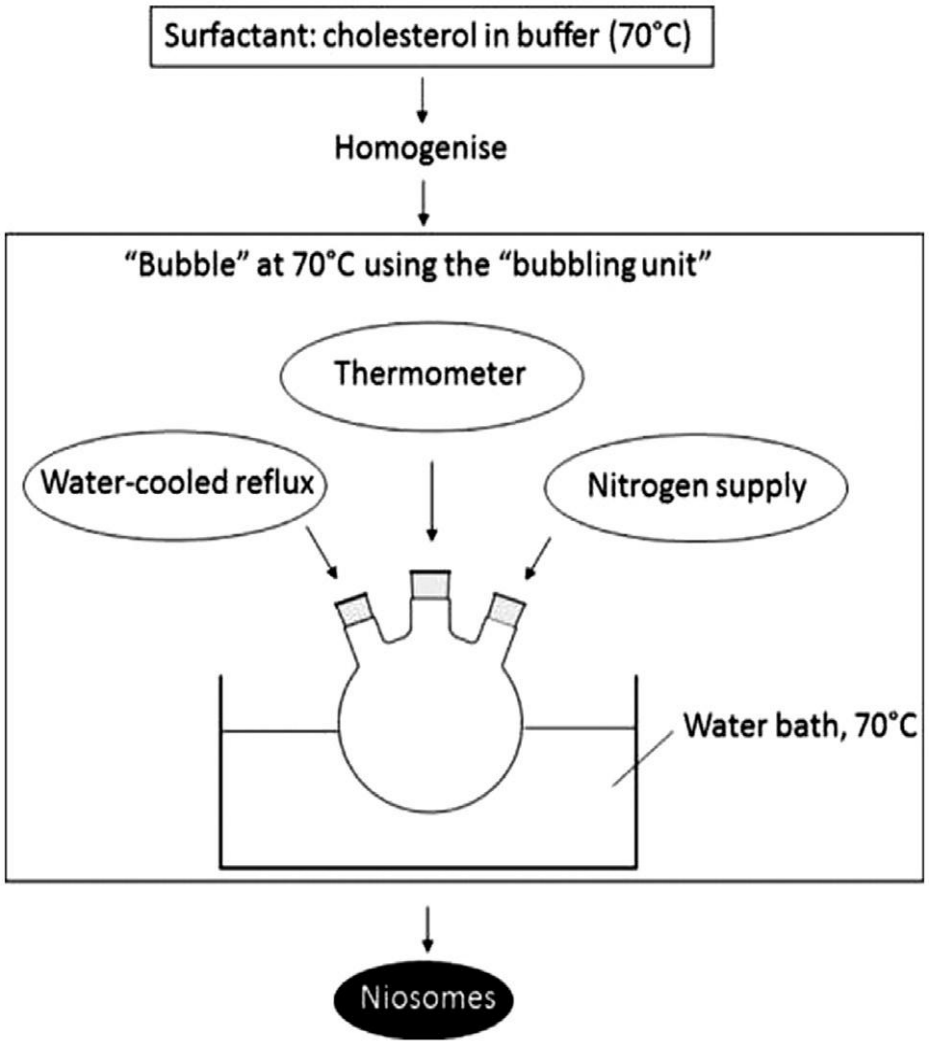


Figure 3: Schematic diagram of preparation of niosomes using the "bubble" method.

Multiple Membrane Extrusion

In this method of niosomes formation the basic technique includes extrusion of mixture of components which is then passed through polycarbonate membranes repeatedly to obtain niosomes of required size. The volatile phase is dried in a rotary evaporator and is hydrated by aqueous phase, the resultant is extruded through the membrane to give niosomes.

Formation of niosomes from proniosomes: In this method of producing niosomes a water-soluble carrier such as sorbitol is coated with surfactant resulting in the

formulation of dry formulation in which each watersoluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". Then proniosome powder is filled in a screw capped vial, and mixed with water or saline at 80 °C by vortexing, followed by agitation for 2 min results in the formation of niosomal suspension.[13]

Emulsion method

From an organic solution of surfactant, cholesterol, and aqueous solution of drug, oil in water (o/w) emulsion is prepared. The organic solvent is then evaporated, leaving niosomes dispersed in the aqueous phase.[14,15]

Lipid injection method

In this process, either mixture of lipids and surfactant is first melted and then injected into a highly agitated heated aqueous phase containing dissolved drug, or the drug can be dissolved in molten lipid and the mixture will be injected into agitated, heated aqueous phase containing surfactant. This method does not require expensive organic phase.[16]

Niosome preparation using Micelle

Niosomes may also be formed by the use of enzymes in a mixed micellar solution. A mixed micellar solution of C16 G2, dicalcium hydrogen phosphate (DCP), polyoxyethylene cholesteryl sebacetate di ester (PCSD) when incubated with esterases converts to a noisome dispersion. PCSD is cleared by the esterases action to yield polyoxyethylene, sebacic acid and cholesterol and then cholesterol in combination with C16 G2 and DCP then yields C16 G2 niosomes.[16]

Niosome preparation using polyoxyethylene alkyl ether

Charactersitics like the size and number of bilayers of polyoxyethylene alkyl ethers and cholestrol consisting vesicles can be changed in alternative way. Small unilamellar vesciles transforms to large multilamellar vesicles by temperature rise above 600° C, while multilamellar vesicles can be transformed into unilamellar ones by vigorous shaking at room temperature. It is the characteristics for the polyoxythelene alkyl ether surfactants to transfromation from unilamellar to multilamellar vesicles at higher temperature since it is known that polyethyleneglycol (PEG) and water at higher temperature demixes due to a breakdown of hydrogen bonding between water and PEG moieties.[17]

EVALUATION OF NIOSOMES

Shape, size and Morphology The structure of niosomes can be visualized by Electron Microscopy namely Scanning Electron Microsopy (SEM) and Transmission Electron Microscopy (TEM) or by Freeze Fracture Microscopy. Optical Microsopy and Photon Correlation Microscopy are also used to study the morphology. Molecular Sieve Microscopy gives us the mean diameter of the niosomes. Another popular method of measuring the size of vesicles is by Dynamic Light Scattering Technique. The mean diameter of the vesicles as well as their size distribution can be known by this method.

Vesicle charge

The surface charge on the vesicles aids us to determine the stability of the formulationCharged particles resist aggregation and fusion, hence result in better formulations. Dynamic Light Scattering Technique can be used to determine the zeta potential of the particles from which the surface charge can be estimated. Other methods are Micro-electrophoresis and pH Sensitive Flurophores.

Membrane Rigidity

Distribution of niosomes in the body and it biodegradation depends upon rigidity of its membranes. It is measured by the mobility of the fluroscence probe as a function of temperature.

Measurement of Angle of repose

The angle of repose of dry niosomes powder was measured by a funnel method. The niosomes powder was poured into a funnel which was fixed at a position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows down from the funnel to form a cone on the surface and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

Scanning electron microscopy

Particle size of niosomes is very important characteristic. The surface morphology (roundness, smoothness, and formation aggregates) and the size distribution of niosomes were studied by Scanning Electron Microscopy (SEM). Niosomes were sprinkled on to the double- sided tape that was affixed on aluminum stubs. The aluminum stub was placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).[19]

Optical Microscopy

The niosomes were mounted on glass slides and viewed under a microscope (Medilux-207RII, Kyowa-Getner, Ambala, India) with a magnification of 1200X for morphological observation after suitable dilution The photomicrograph of the preparation also obtained from the microscope by using a digital SLR camera.[19]

Entrapment efficiency

Entrapment efficiency of the niosomal dispersion in can be done by separating the unentrapped drug by dialysis centrifugation or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or

0.1% Triton X-100 and analyzing the resultant solution by appropriate assay method for the drug. Where.[19]

Osmotic shock

The change in the vesicle size can be determined by osmotic studies. Niosomes formulations are incubated with hypotonic, isotonic, hypertonic solutions for 3 hours. Then thechanges in the size of vesicles in the formulations are viewed under optical microscopy.[19]

Stability studies

To determine the stability of niosomes, the optimized batch was stored in airtight sealed vials at different temperatures. Surface characteristics and percentage drug retained in niosomes and niosomes derived from proniosomes were selected as parameters for evaluation of the stability, since instability of the formulation would reflect in drug leakage and a decrease. In the percentage drug retained. The niosomes were sample at regular intervals of time (0,1,2, and 3months), observed fo color change, surface characteristics and tested for the percentage drug retained after being hydrated to form niosomes and analyzed by suitable analytical methods(UV spectroscopy, HPLC methods etc).[20]

Zeta potential analysis

Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted niosomes derived from pronoisome dispersion was determined using zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry method (Zeta plus™, Brookhaven Instrument Corporation, New York, USA). The temperature was set at 25°C. Charge on vesicles and their mean zeta potential values with standard deviation of measurements were obtained directly from the measurement.[21]

IN-VITRO METHODS FOR NIOSOMES

In vitro drug release can be done by
Dialysis tubing
Reverse dialysis
Franz diffusion cell

Dialysis tubing

Studied in vitro drug release could be achieved by using dialysis tubing. The niosomes is placed in prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and analyzed for drug content using suitable method (U.V. spectroscopy, HPLC etc). The maintenance of sink condition is essential.

Reverse dialysis

In this technique a number of small dialysis as containing 1ml of dissolution medium are placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method; however the rapid release cannot be quantified using this method. (Azmin et al., 2005).[23]

Franz diffusion cell

The in vitro diffusion studies can be performed by using Franz diffusion cell. Proniosomes is placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The proniosomes is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable method (U.V spectroscopy, HPLC, etc). The maintenance of sink condition is essential.[24]

Evaluation parameter	Generally used method in evaluation parameter
Morphology	SEM, TEM, freeze fracture technique
Size distribution, polydispersity index	Dynamic light scattering particle size analyzer
Viscosity	Ostwald viscometer
Membrane thickness	X-ray scattering analysis
Thermal analysis	DSC
Turbidity	UV-Visible diode array spectrophotometer
Entrapment efficacy	Centrifugation, dialysis, gel chromatography
In-vitro release study	Dialysis membrane
Permeation study	Franz diffusion cell

APPLICATIONS OF NIOSOMES

Niosomes have been used for studying the nature of the immune response provoked by antigens.

1. It is used as Drug Targeting.
2. It is used as Anti-neoplastic Treatment i.e. Cancer Disease.
3. It is used as Leishmaniasis i.e. Dermal and Mucocutaneous infections e.g. Sodium stibogluconate.
4. Niosomes as Carriers for Hemoglobin.
5. It is used act as Delivery of Peptide Drugs.
6. Niosomes can be used as a carrier for hemoglobin.
7. It is used in Studying Immune Response.
8. Transdermal Drug Delivery Systems Utilizing Niosomes.
9. It is used in ophthalmic drug delivery.
10. Niosomal system can be used as diagnostic agents.

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Few of their therapeutic applications are as follows:

Targeting of bioactive agents

1. **To reticulo-endothelial system (RES)** -The vesicles occupy preferentially to the cells of RES. It is due to 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.[25]
2. **To organs other than reticulo-endothelial system (RES)** - By use of antibodies, carrier system can be directed to specific sites in the body. Immunoglobulins seem to have affection to the lipid surface, thus providing a convenient means for targeting of drug carrier. Many cells have the intrinsic ability to recognize and bind particular carbohydrate determinants and this property can be used to direct carriers system to particular cells.[26,27]

Neoplasia

The anthracyclic antibiotic Doxorubicin, with broad spectrum anti tumour activity, shows a dose dependant irreversible cardio toxic effect. The half-life of the drug increased by its niosomal entrapment of the drug and also prolonged its circulation and its metabolism altered. If the mice bearing S-180 tumour is treated with niosomal delivery of this drug it was observed that their life span increased and the rate of proliferation of sarcoma decreased38. Methotrexate entrapped in niosomes if administered intravenously to S-180 tumour bearing mice results in total regression of tumour and also higher plasma level and slower elimination.[28,29]

Delivery of peptide drugs

Niosomal entrapped oral delivery of 9-desglycinamide, 8arginine vasopressin was examined in an in-vitro intestinal loop model and reported that stability of peptide increased significantly.[30]

Immunological applications of niosomes- For studying the nature of the immune response provoked by antigens niosomes have been used. Niosomes have been reported as potent adjuvant in terms of immunological selectivity, low toxicity and stability.[31]

Niosome as a carrier for Hemoglobin

Niosomal suspension shows a visible spectrum superimposable onto that of free hemoglobin so can be used as a carrier for hemoglobin. Vesicles are also permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin.[32]

Transdermal delivery of drugs by niosomes

An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes as slow penetration of drug through skin is the major drawback of transdermal route of delivery for other dosage forms. The topical delivery of erythromycin from various formulations including niosomes has studied on hairless mouse and from the studies, and confocal microscopy, it was found that non-ionic vesicles could be formulated to target pilosebaceous glands.[33]

Diagnostic imaging with niosomes

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.[34]

Leishmaniasis therapy

Derivatives of antimony are most commonly prescribed drugs for the treatment of leishmaniasis. These drugs in higher concentrations – can cause liver, cardiac and kidney damage. Use of niosomes as a drug carrier showed that it is possible to overcome the side effects at higher concentration also and thus showed greater efficacy in treatment.[35]

Niosome formulation as a brain targeted delivery system for the vasoactive intestinal peptide (VIP)

Radiolabelled (I125) VIP-loaded glucose-bearing niosomes were injected intravenously to mice. Encapsulated VIP within glucose-bearing niosomes exhibits higher VIP brain uptake as compared to control.[36]

Ophthalmic drug delivery

From ocular dosage form like ophthalmic solution, suspension and ointment it is difficult to achieve excellent bioavailability of drug due to the tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. But niosomal and liposomal delivery systems can be used to achieve good bioavailability of drug. Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendencies for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide).[37]

Other Applications

a) **Sustained Release**-Drugs with low therapeutic index and low water solubility could be maintained in the circulation via niosomal encapsulation, through niosomes sustained release action can be obtained. suggested the role of liver as a depot for methotrexate after niosomes are taken up by the liver cells.[38]

b) **Localized Drug Action**-To achieve localized drug action, niosomal dosage form is one of the approaches because of the size of niosomes and their low penetrability through epithelium and connective tissue the drug localized at the site of administration. This results in enhancement of efficacy and potency of the drug and also 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.[39,40]

Table 1: List of Drugs formulated as Niosomes.

Routes of drug administration	Examples of drugs
Intravenous route	Doxorubicin, Methotrexate, Sodium Stibogluconate, Iopromide, Vincristine, Diclofenac Sodium, Flurbiprofen, Centchroman, Indomethacin, Colchicine, Rifampicin, Tretinoin, Transferrin and Glucose ligands, Zidovudine, Insulin, Cisplatin, Amarogentin, Daunorubicin, Amphotericin B, 5-Fluorouracil, Camptothecin, Adriamycin, Cytarabine Hydrochloride
Peroral route	DNA vaccines, Proteins, Peptides, Ergot, Alkaloids, Ciprofloxacin, Norfloxacin, Insulin
Transdermal route	Flurbiprofen, Piroxicam, Estradiol Levonorgestrol, Nimesulide, Dithranol, Ketoconazole, Enoxacin, Ketorolac
Ocular route	Timolol Maleate, Cyclopentolate
Nasal route	Sumatriptan, Influenza Viral Vaccine
Inhalation	All-trans retinoic acids

MERITS AND DEMERITS OF NIOSOMES

Merits of niosomes are following.[41,42,43]

1. Niosomes can be novel drug dosage form for drug molecules having a wide range of solubility as their infrastructure consists of hydrophilic and hydrophobic part
2. Vesicles had flexible characteristic properties; by altering vesicle's characteristics like vesicle composition, size, lamellarity, tapped volume, surface charge and concentration the niosomes of desired property can be obtained
3. As vesicle suspension is water based vehicle hence provide better patient compliancy than oil based dosage forms
4. By improving oral bioavailability of poorly absorbed drugs, by delaying clearance from the circulation and by protecting the drug from biological environment they improve the therapeutic performance of the drug molecules
5. They are osmotically active, stable and also increase the stability of entrapped drug. Oral, parenteral as well as topical routes can be adopted for their administration.
6. The biodegradable, biocompatible and nonimmunogenic surfactants are used in preparation of niosomes and also handling and storage of surfactants requires no special conditions The niosomes suffer certain demerits, which include the following9:
7. The aqueous suspensions of niosomes may have limited shelf life due to fusion, aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs
8. The methods of preparation of multilamellar vesicles such as extrusion, sonication, are time consuming and may require specialized equipments for processing.

Factores Affecting Niosomes Formulation

Drug

Entrapment of drug in niosomes influence charge and rigidity of the noisome bilayer. The hydrophilic lipophilic balance of the drug affects degree of entrapment.[43]

Nature and type of surfactant

The mean size of niosomes increases proportionally with increase in the HLB 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. A surfactant must have a hydrophilic head and hydrophobic tail. The hydrophobic tail may consist of one or two alkyl or perfluoroalkyl groups or in some cases a single steroidal group.[44]

Cholesterol content and charge

Hydrodynamic diameter and entrapment efficiency of niosomes is increased by cholesterol. It induces membrane stabilizing activity and decreases the leakiness of membrane. 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.[45]

Resistance to osmotic stress

The diameter is reduced by addition of hypertonic salt solution to suspension of niosomes.

Temperature of Hydration

Hydration temperature influences the shape and size of niosome.

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