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NIOSOMES AS VERSATILE NANOCARRIERS: FROM DESIGN TO THERAPEUTIC APPLICATIONS

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ABSTRACT

Niosomes are a novel drug delivery system that allows for sustained, controlled, and targeted drug delivery, addressing the disadvantages associated with liposomes. The chemical stability of niosomes is a key factor, with a focus on biodegradability, biocompatibility, low production cost, easy storage, handling, and low toxicity. Structurally, niosomes can be unilamellar, oligolamellar, or multilamellar, providing a bilayered structure that can encapsulate both hydrophilic and hydrophobic drugs. Niosomes can improve solubility, oral bioavailability of poorly soluble drugs, enhance drug skin permeability, increase stability, and improve drug performance at the site of action. Various studies have demonstrated the efficacy of niosomes as drug carriers in treating fungal diseases, wound healing, rheumatoid arthritis, psoriasis, and other inflammation-related disorders. Nowadays, disease-modifying anti-rheumatic drugs and biologic DMARDs (bDMARDs) are recommended for the treatments of rheumatoid arthritis. The poor aqueous solubility or permeability causes the limited oral bioavailability of synthetic DMARDs, while the high molecular weights along with the bulky structures of bDMARDs have posed few obstacles in their drug delivery. These challenges can be addressed through the development of nano formulations like cubosomes, nanospheres, nanoemulsions, solid lipid nanoparticles, nano micelles, liposome, niosomes, and nanostructured lipid carrier.

KEYWORDS: Niosomes, Nanocarriers, Design, Therapeutic Applications.

INTRODUCTION

Niosomes are vesicular, novel drug delivery system, which can be used for the sustained, controlled as well as targeted delivery of drugs. Liposomes were the first vesicular drug delivery systems but they have several disadvantages like toxicity, low cost and stability issues at different pH. Due to the disadvantages of liposomes, research interest shifted towards niosomes. Niosomes overcome the disadvantages associated with liposomes such as chemical instability. The chemical stability of liposomes is due to their predisposition to oxidative degradation and variable purity of phospholipids. The main purposeof developing a niosomal system is chemical stability, biodegradability, biocompatibility, chemical stability, low production cost, easy storage and handling, and low toxicity.[1,2]

The niosomes include their ability to encapsulate different types of drugs, enhance bioavailability, improve patient compliance, enable various routes of delivery, and offer targeted, controlled, and sustained drug delivery. However, niosomes may have limited shelf life due to physical instability issues, such as aggregation, leaking of entrapped drugs, and hydrolysis. The components of niosomes, including cholesterol and non-ionic surfactants, contribute to their structure and properties, while factors like drug properties, temperature, resistance to osmotic stress, preparation methods, cholesterol content, and charge influence niosomes characteristics. Various methods for niosomes formation, including the hand shaking method and microfluidization, influence their characteristics and performance.[3,4]

Niosomes have extensive applications in drug delivery, diagnostic imaging, ophthalmic drug delivery, neoplasia treatment, brain targeting, immunological applications, carriers for haemoglobin, and targeting bioactive agents to specific organs. Overall, niosomes offer a promising platform for effective and targeted drug delivery across various therapeutic areas.[5]

Structure of Niosomes

Niosomes can be unilamellar, oligolamellar or multilamellar. Niosomes are the bi- layered structure of non- ionic surface-active agents. These thermodynamically stable bilayered structures are formed only when surfactants and cholesterol are mixed

in a proper proportion, and the temperature is above the gel liquid transition temperature. This bi-layered structure contains a hollow space in the center. Because of their special geometry niosomes can encapsulate hydrophilic as well as a hydrophobic drug in their structure. Entrapment of hydrophilic drugs in niosomes can occur in the central aqueous domain or it can be adsorbed on the bilayer surface whereas hydrophobic drugs enter the bilayer structure by partitioning into it.[6]

Niosomes are non-toxic as they are made up of non-ionic surfactants. In addition to non-ionic surfactants, they may also contain cholesterol or its derivatives and charged molecules. Cholesterol provides rigidity to the structure and the charged molecule keeps the preparation stable. The formation of niosomes occurs when non-ionic surface-active agents assemble themselves. Because of their structure, they can be utilized for the loading and delivery of both hydrophilic and hydrophobic drugs.[7]

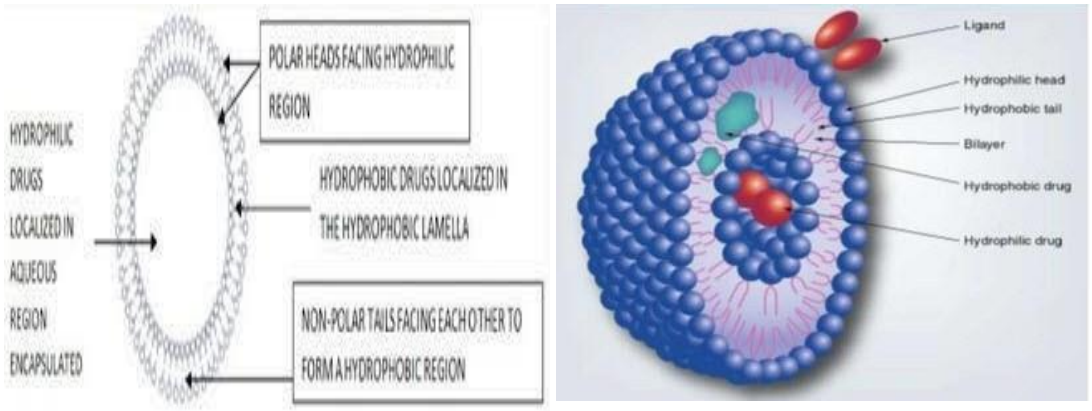


Figure 1: Structure of Niosomes.[8]

Salient Features of Niosomes

Niosomes can entrap solutes. Niosomes are osmotically active and stable. Niosomes have an infrastructure comprising of hydrophobic and hydrophilic for the most part together thus likewise oblige the medication atoms with an extensive variety of dissolvability. Niosomes discharge the medication in a controlled manner by means of its bilayer which gives supported the arrival of the encased medication, so niosomes fill in as medication warehouse in the body. Targeted medication conveyance can likewise be accomplished utilizing niosomes the medication is conveyed specifically to the body part where the remedial impact is required. Thereby lessening the measurement required to be managed to accomplish the coveted impact. They improve the solubility and oral bioavailability of poorly soluble drugs and enhance the skin permeability of drugs when applied topically. Niosomes exhibits flexibility in their structural character (composition, fluidity, and size) and can be designed according to the desired situation. Niosomes can improve the performance of the site of action of the drug. Better availability to the particular site of action, just by protecting the drug from a biological environment.[9]

Niosomes increase the stability of the entrapped drug in some manner. Many types of research have been conducted on the use of niosomes as drug carriers, and in various studies, it has been observed that niosomes as a carrier play an important role in the treatment of fungal diseases, wound healing, rheumatoid arthritis, psoriasis, and other inflammation-related disorders. Regard to inflammation-related diseases, autoimmune disorders such as Rheumatoid arthritis (RA), Psoriasis and Intestinal Bowel Syndrome (IBD) affect the large population of patients.[10]

Rheumatoid arthritis (RA) is an autoimmune condition that gradually destroys articular cartilage and can cause abnormalities in vascular, metabolic, bone, and psychological function. The proximal interphalangeal, wrists, cervical spine, metatarsophalangeal, and metacarpophalangeal joints are recurrently affected joints in RA. Various risk factors causing RA include smoking, menopause, hormonal disturbance, periodontal disease, and human leukocyte antigen (HLA), namely, HLA-DRB1 shared epitope alleles.[11]

Now-a-days, disease-modifying anti-rheumatic drugs (DMARDs) and biologic DMARDs (bDMARDs) are recommended for the treatments of RA. The poor aqueous solubility or permeability causes the limited oral bioavailability of synthetic DMARDs, while the high molecular weights along with the bulky structures of bDMARDs have posed few obstacles in their drug delivery. These challenges can be addressed through the development of nano formulations like cubosomes, nanospheres, nanoemulsions, solid lipid nanoparticles, nano micelles, liposome, niosomes, and nanostructured lipid carrier.[12]

Advantages of Niosomes[14,15]

- Niosomes are less toxic and more compatible since they do not carry any charge.
- Niosomes are degradable by the biological systems and do not initiate immunogenic reactions.
- Niosomes can be used to encapsulate both hydrophilic as well as hydrophobic drugs.

- Niosomes can enhance the bioavailability of the active pharmaceutical ingredient by increasing the physical as well as biological stability.
- Patient compliance is better since given as aqueous suspension.
- Niosomes can be given by almost all the routes of delivery, for example, oral, parenteral, transdermal, ocular and pulmonary.
- Their shape, size, and entrapment can be changed by modifying the various parameters like additives, their ratio or their use in combination.
- Niosomes can be used for targeted, controlled as well as sustained delivery of a drug.

Disadvantages of Niosomes[16]

- The aqueous suspensions of niosomes may have limited shelf life due to fusion, aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs.
- Physical instability Aggregation, fusion leaking of entrapped drug, hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion. The methods of preparation of multilamellar vesicles such as extrusion, sonication, are time consuming and may require specialized equipments for processing.

Components of Niosomes[17]

The two major components utilized for the readiness of niosomes are Cholesterol and Non-ionic surfactants. Cholesterol is utilized to give unbending nature and appropriate shape, adaptation to the niosomes. The part surfactants assume a noteworthy part in the development of niosomes. The accompanying non-ionic surfactants are for the most part utilized for the arrangement of niosomes the spans, tweens and Brij.

Cholesterol: Cholesterol is an amphiphilic nature; and it orients its OH group towards aqueous phase and aliphatic chain towards hydrocarbon chain of surfactant. Cholesterol a waxy steroid metabolite is usually added to the non-ionic surfactants to provide rigidity Cholesterol is also prevent leakage by abolishing gel to liquid phase transition.

Non-ionic surfactants: Niosomes are non-ionic surfactant unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. Non-ionic surfactant possesses hydrophilic head group and a hydrophobic tail. As HLB value increases, therefore, alkyl chain increases the size of niosomes increases. Formulation of niosomes is not suitable on the HLB value from 14 to 17. HLB value 8 has the highest entrapment efficiency. Non-ionic surfactants are as follows, Ether linked Surfactants are surfactants contain hydrophilic and hydrophobic moieties which are linked by ether, polyoxyethylene alkyl ethers with the general formula (CnEOm), where, n is the number of carbon atoms vary between 12 and 18 and the number of oxyethylene unit varies between 3 and 7.

Di-alkyl chain surfactant: 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 surfactants have ester linkage between hydrophilic and hydrophobic groups; hence it is also called as Ester linked surfactants. This surfactant also used in the preparation of stibogluconate bear the niosomes drug delivery and delivery the sodium stibogluconate to the experimental marine visceral leishmaniasis. These are polyoxyethylene alkyl ethers which have hydrophilic and hydrophobic moieties are linked with ether. The general formula of this group is (CnEOm), where n can be 12 to 18 and m can be 3 to 7. Surfactants with poly hydroxyl head and ethylene oxide units are also reported to be used in niosomes formation.

Sorbitan esters: These are the ester-linked surfactants. The commercial sorbitan esters are prepared by the mixtures of the partial esters of sorbital and its mono and di-anhydrides with oleic acid.

Fatty Acids and Amino Acid Compounds: These are amino acids which are made amphiphilic by addition of hydrophobic alkyl side chains and long chain fatty acids which form "Ufosomes" vesicles formed from fatty acid bilayers.

Alkyl Amides: These are alkyl galactosides and glucosides which have incorporated amino acid spacers. The alkyl groups are fully or partially saturated C12 to C22 hydrocarbons and some novel amide compounds have fluorocarbon chains.

Charge inducers: There are two types of charged inducers such as Positive and Negative charge inducers. It increases the stability of the vesicles by induction of charge on the surface of the prepared vesicles. It acts by preventing the fusion of vesicles due to repulsive forces of the same charge and provide higher values of zeta potential. The commonly used positive charge inducers are stearyl amine and cetyl pyridinium chloride and negative charge inducers are diacetyl phosphates, Di hexadecyl phosphate and lipoamide acid.

METHODS FOR PREPARATION OF NIOSOMES

Preparation of niosomes begins with the hydration of a surfactant and lipid mixture at elevated temperatures, followed by optional niosomes size reduction in order to obtain a colloidal suspension.[18]

i. **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. Vaporisation 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.[18, 19]

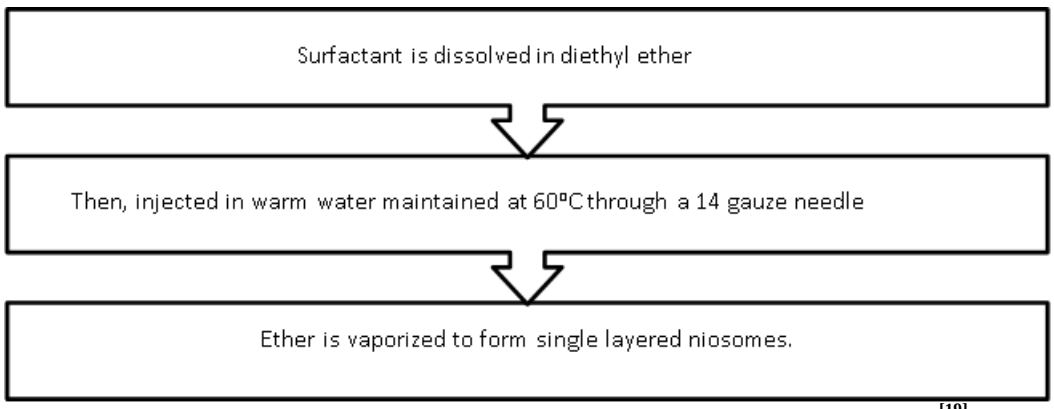


Figure 2: Steps for the Preparation of Niosomes by Ether injection method.[19]

ii. **Sonication:** Niosomes using the sonication method were prepared by Baillieet al 1986. In this method, surfactant: cholesterol (150 µmol). The Mixture was dispersed in a 2 ml aqueous phase in the vial. The dispersion is subjected to probe sonication for 3 minutes at 60°C. This method involved the formation of MLVs which are subjected to ultrasonic vibration. Sonicator are of two types Probe and Bath Sonicator. Probe Sonicator is use when sample volume is small and Bath Sonicator is used when sampling volume is large.[20]

iii. **Hand shaking method/Thin film hydration technique:** In this method, a surfactant: cholesterol (150 µmol) mixture was dissolved in 10 ml diethyl ether in RBF. The ether is evaporated under vacuum at room temperature in rotary evaporation. Upon hydration, the surfactant swells and is peeled off the support into a film. Swollen amphiphiles eventually fold to form vesicles. The liquid volume is entrapped in vesicles appears to be small which 5–10%.[21]

iv. **Extrusion method:** In this method, niosomes were prepared using C16G2, a chemically defined non-ionic surfactant by extrusion through a polycarbonate membrane. These studies not only demonstrate the effect of the number of extrusion on vesicle size but also the effect of size on encapsulation of drug.[22]

v. **Reverse phase evaporation technique:** In this method, the surfactant is dissolved in chloroform and added into the 0.25 volume phosphate saline buffer solution is emulsified to get w/o emulsion. The mixture is then solicited and subsequently, chloroform is evaporated under reduced pressure. The lipid or surfactant forms a gel first and subsequently hydrates to form vesicles. The ingredients are dissolved in a mixture of volatile organic solvents (ether and chloroform) and drug is dissolved in aqueous phase. Water in oil emulsion is formed of the two phases in a bath Sonicator. The basic principle involves evaporation of organic solvent to form niosomes. This emulsion is dried in a rotary evaporator at 40°C to form a semi solid gel of large vesicles. Small quantity of buffer is added and the semi solid form is sonicated at 4- 5°C to form small unilamellar vesicles.[23,24]

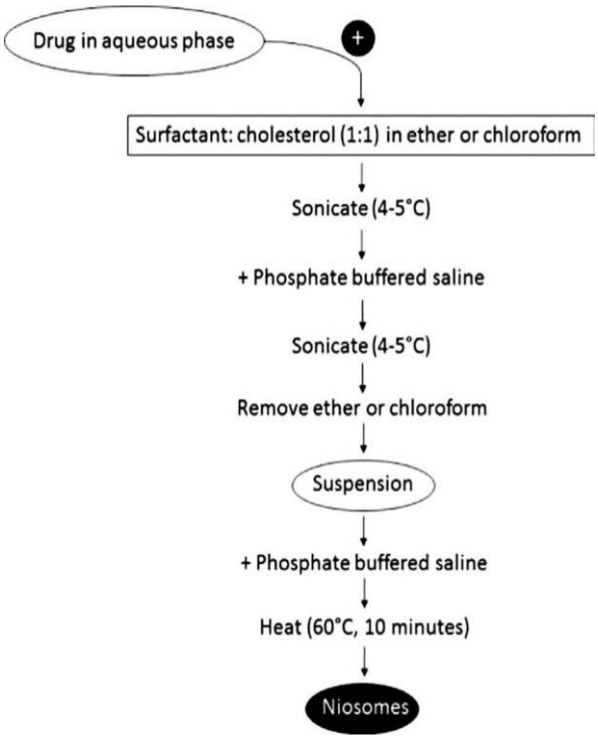


Figure 3: Steps for the Preparation of Niosomes by Reverse Phase Evaporation Technique.[25]

vi. **Micro fluidization method:** Micro fluidization is a current strategy to plan unilamellar vesicles of characterised estimated circulation. Based on the submerged jet principle, in this strategy, two fluidized streams connected at ultrahigh speeds incorrectly characterized smaller-scale channels inside the interaction chamber. The impingement of a thin liquid sheet along a common front is arranged in such a way that the energy supplied to the system remains within the area of niosomes formation. The outcome is a more prominent consistency, smaller size and better reproducibility of niosomes.[26]

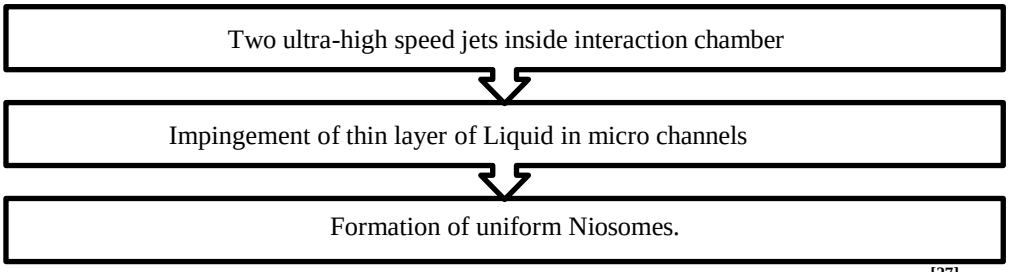


Figure 4: Steps for the Preparation of Niosomes by Microfluidization method.[27]

vii. **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."[28]

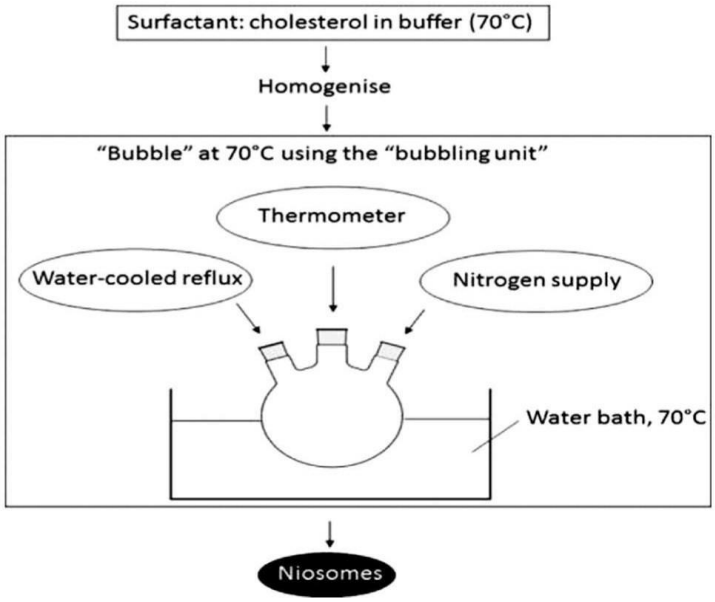
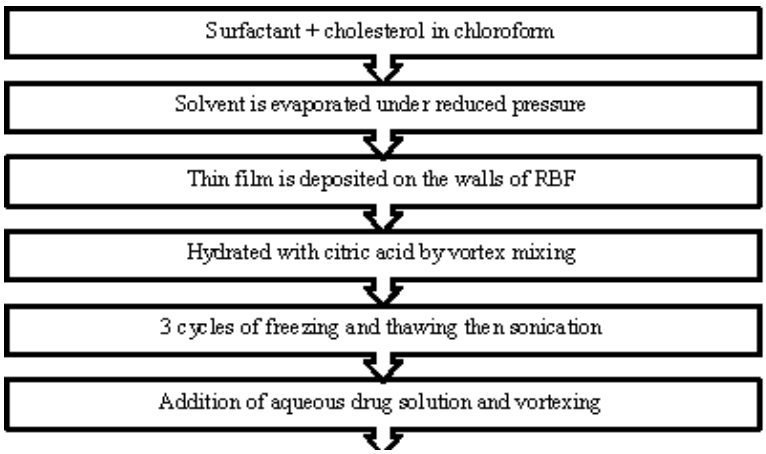


Figure 5: Schematic Diagram of Method for Preparation of Niosomes by Bubble Method.[28]

viii. **Trans membranes pH gradient (inside acidic) Drug Uptake Process or Remote Loading Technique:** 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 firm is hydrated with 300mM citric acid (pH 4.0 by vortex mixing. The multilamellar vesicles are frozen and shared 3 times and later sonicated. To this niosomal suspension. Aqueous solution containing 10 mg ml of drug is added and vortexes. The PH of the sample is then raised to 7.087.2 with 1M disodium phosphate. This mixture is later heated at 60°c for 10 minutes so give niosomes.[29]



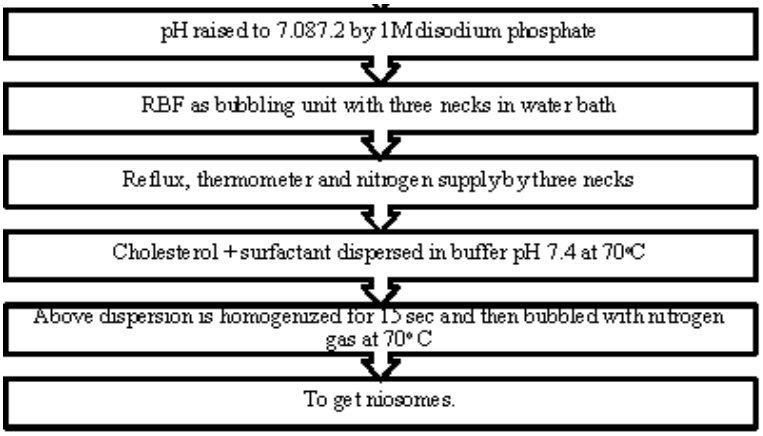


Figure 6: Steps for the Preparation of Niosomes by Trans membranes pH gradient (inside acidic) Drug Uptake Process or Remote Loading Technique.[29]

ix. **Single Pass Technique:** In some literature also mentioned as multiple membrane extrusion. In this method, a suspension of a lipid-containing drug is passed from a porous device and then through a nozzle. It produces uniform size niosomes, usually in the range of 50–500 nm.[30]

x. **The Handjani-Vila Method:** This method involves the mixing of cholesterol and surfactant to the aqueous solution of the drug. The resultant mixture is homogenized using ultracentrifugation or agitation and the temperature of the pro- cess is kept controlled.[31]

xi. **Heating method:** Heating method is patented by Mozafari et al. In this method hydration of surfactant and cholesterol is done separately in a buffer solution. After hydration, to dissolve cholesterol solution is heated for 1 h at around 120 °C. The temperature of the solution is lowered and to this buffer solution, surfactant and other additives are added, with continuous stirring. During this stage, niosomes formation occurs. These niosomes are kept at room temperature for 30 min. Finally, niosomes are stored at 4–5°C in nitrogen atmosphere.[32]

xii. **Freeze and thaw method:** By this method frozen and thawed multilamellar vesicles can be produced. The niosomes prepared using a thin-film hydration technique to freeze and thaw. They took 8 ml of niosomal suspension and subjected it to five cycles of freezing in liquid nitrogen for 1 min and for another 1 min thawed it in a water bath at 60°C. The niosomes of varying composition and did a comparative study of niosomes with liposomes. In their study, they found that freeze and thaw cycle shrinks the niosomes prepared using unsaturated surfactants. They also found that the freeze and thaw cycle reduced the entrapment efficiency of niosomes.[33]

xiii. **Microfluidic hydrodynamic focusing:** Prepared niosomes of two miscible liquids using microfluidic hydrodynamic focusing by diffusive mixing. The miscible liquids are mixed in microchannels in a rapid and controlled manner. This method produces niosomes which are better in size and size distribution than the niosomes prepared by a conventional method. Different parameters like conditions for the microfluidic mixing, chemical structure of the surfactant, and device material for the microchannel fabrication can affect the assembly of niosomes. They found that an increase in the flow rate ratio decreases diffusive mixing time and produces small size niosomes. If a wider microchannel is used, it will increase diffusive mixing time and hence large size niosomes.[34]

xiv. **Dehydration-rehydration method:** Kirby and Gregoriadis were the first ones to describe this method in 1984. These vesicles were first prepared by a thin-film hydration technique, and then these vesicles were frozen in liquid nitrogen and then freeze-dried overnight. Powder niosomes were hydrated with phosphate buffer saline (pH 7.4) at 60°C. Abdelkader et al. prepared niosomes of naltrexone by this method for ocular delivery. They compared the entrapment efficiency of niosomes formed using different methods. They found that the entrapment efficiency of niosomes formed using reverse-phase evaporation technique has shown the best entrapment efficiency in comparison to the niosomes formed using thin-film hydration technique, freeze and thaw method and dehydration and rehydration method, whereas the entrapment efficiency of niosomes prepared by dehydration rehydration method was better than the efficiency of niosomes.[35]

EVALUATION PARAMETERS OF NIOSOMES

Table 1: Evaluation Parameters of Niosomes.[36]

Sr.No.	Evaluation Parameter	Method/Instrument
1	Size distribution, Polydispersity index	Scanning electron microscopy(SEM), Malvern Mastersizer, Anderson cascade impactor, Dynamic light
2	Morphology	Optical microscopy, SEM, TEM, freeze fracture tech Phase Contrast microscopy, Quasi elastic light scattering technique, Small angle X-ray diffraction (SA- XRD).
3	Thermal analysis	DSC, DTA, Hot stage microscopy
4	Zeta Potential	Malvern Zetasizer (zeta meter), Microelectrophoresis meter.
5	Lamellarity	Optical microscopy, TEM
6	Membrane microstructure	Negative staining TEM
7	Viscosity	Low shear rheo analyzer, Oswalt-U-tube
8	Entrapment efficacy	Dialysis, gel chromatography, Centrifugation
9	Conductivity	Conductometer
10	In-vitro release study	Dialysis membrane
11	Permeation study	Franz diffusion cell

i. **Purification:** The prepared niosomes were purified to remove unentrapped drug by passing through Sephadex G-50 column. The elution was carried out using phosphate buffer saline solution (pH 7.4).[37]

ii. **Vesicle characterization:** The diameter of Niosomes can be determined using light microscope, photon correlation microscopy. Various other technique which are used to determine the vesicles the diameter are Scanning electron microscopy(SEM), Salad-1100 laser diffraction particle size analyzer, Coulter submicron particle size analyzer, Klotz® particle sizer and Anderson cascade impactor.[38]

iii. **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.[39]

iv. **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.[40]

v. **Particle size determination:** The niosomes were observed and measured along an arbitrarily chosen fixed line. Optical microscopy technique was used. A total of about 100 niosomes were observed and their size coinciding with the eye piece micrometre was recorded. Most of the niosomes were found to be spherical in shape, few being with triangular and slightly elongated.[41]

vi. **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 analyzed for the drug content by an appropriate assay method.[42]

FACTORS AFFECTING OF NIOSOMES FORMATION

Many factors which are affecting on physical and chemical property of niosomes and also affect the formation of vesicle.

i. **Drug Property:** Molecular weight, chemical structure, lipophilicity, hydrophilicity as well as HLB value of drug influence the size of niosomes. The HLB value also affect the entrapment efficiency of drug. Drug entrapment in niosomes increase with increasing size of vesicle. When drug entrapment in niosomes then interaction of solute charge and head group of surfactants take place due to that repulsion, size of vesicle increase. Some drug added in polyethylene glycol coated vesicle thus reduce the tendency of increasing size of vesicle.[43]

ii. **Temperature of hydration:** Temperature present during hydration of pro- niosomes are influence the size and shape of niosomes. Polyhedral vesicle of C16G2: Solulan C24 (91:9) is based at 25°C but this polyhedral vesicle converted into spherical vesicle at 45°C and on cooling it forms 55-49°C gives cluster of smaller spherical niosomes.[44]

iii. **Resistance to osmatic stress:** When hypertonic salt solution adds in suspension of niosomes then diameter of vesicle decreases. If hypotonic salt solution added in niosomal suspension, then initially slow release take place with swelling of vesicle structure due to inhibition of eluting fluid from vesicle and finally release occur very fast due to mechanical loosing of vesicle structure under osmatic stress.[45]

iv. **Structure of Surfactant:** The shape and size of niosomes vesicle are depends on Critical Packing Parameter (CPP), according to CPP we can predict the geometry of niosomes vesicle.[45]

Critical Packing Parameter (CPP) = $v / lc A_0$ Where,

v = hydrophobic group volume,

lc = the critical hydrophobic group length, A_0 = the area of hydrophilic head group.

CPP is helpful in predicting the structure of niosomes vesicles in following way; Spherical micelles formed if CPP less than 1/2 Bilayer micelles are formed if CPP between 0.5 to 1 Inverted micelles are formed if CPP more than 1.[45]

v. **Method of Preparation:** It also influences the property of niosomes. It observed that acyclovir niosomes prepared by hand shaking method having size about 2.7µm and same acyclovir niosomes prepared by ether injection method the vesicle size observed 1.5 µm. The small size vesicle can be obtained by reverse phase evaporation method. The niosomes having smaller size and more stability can be prepared by micro-fluidization method. The transmembrane pH gradient uptake process show more entrapment efficiency and good retention of drug.[45]

vi. **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.[45]

vii. **CMC (Critical Micelle Concentration):** The surfactant has ability to reduce the surface tension between two phases. If the concentration of surfactant is not going above to critic micelle concentration, then formation of niosomes are not takes place. Some surfactant is showing the micelle formation when concentration of surfactant goes above CMC, but some surfactant is showing the formation of circular bilayer structure and that are niosomes.[44,45]

APPLICATION OF NIOSOMES

i. **Niosomes as Drug Carriers:** 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 tumours in a similar manner to liposomes. The niosomal encapsulation of Methotrexate and Doxorubicin increases drug delivery to the tumor and tumoricidal activity of the drug. Doxorubicin niosomes possessing muramic acid and tri-glycerol surfaces were not taken up significantly by liver. The tri-glycerol niosomes accumulated in the tumor 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 tumor. On investigated the encapsulation and retention of entrapped solute 5, 6-carboxy fluorescence (CF) in niosomes. It was 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. It is reported that the formation and pharmacokinetic evaluation of Methotrexate niosomes in tumor bearing mice. The surface of niosomes is modified by incorporating polyethylene alkyl ether in the bilayered structure. If they are 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. It is reported the anti-inflammatory activity of niosomes 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 than 72 hours after administration of single dose. It is 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. 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. By prepared niosomes of vincristine sulphate which had lesser toxicity and improved anticancer activity. Jagtap and Inamdar prepared niosomes of Pentoxifylline and studied the in-vivo broncho dilatory 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 hours. It is reported the preparation and oral as well as intravenous administration of Methotrexate loaded niosomes in mice. It was observed significant prolongation of plasma levels and high uptake of Methotrexate in liver from niosomes as compared to free drug solution.[46,49,50]

ii. **Diagnostic imaging with niosomes:** Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenatedimeglcemine with [N- palmitoyl glucosamine (NPG)], PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging.[46]

iii. **Ophthalmic drug delivery:** Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearyl amine or dicetyl phosphate exhibits more tendency for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide) The chitosan coated 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.[46]

iv. **Neoplasia:** 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 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 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination. 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.[46]

v. **Niosomes formulation as a brain targeted:** Niosomal 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.[46]

vi. **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.[46]

Table 2: Drugs Incorporated into Niosomes by Various Methods.[47]

Method of Preparation	Drug Incorporated
Ether Injection	Sodium stibogluconate, Doxorubicin
Hand Shaking	Methotrexate, Doxorubicin
Sonication	9-desglycinamide, arginine, Vasopressin, Estradiol

vii. **Targeting of bioactive agents**

a) **To reticuloendothelial 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 tumours known to metastasize to the liver and spleen and in parasitic infestation of liver.[46]

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 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.[46]

Table 3: Route of Application of Niosomes Drugs.[47]

Route of Administration	Examples of Drugs
Intravenous route	Doxorubicin, camptothecin, insulin, zidovudine, cisplatin, rifampicin
Inhalation	All transretonic acids
Transdermal route	Piroxicam, estradiol, Nimesulide
Ocular route	Timolol maleate, cyclopentol
Nasal route	Sumatriptan, influenza viral vaccines

MARKETED PRODUCT[48]

The Lancome has used for variety of anti-aging product which are based on niosomal formulation present in market.

CONCLUSION

Niosomal drug delivery system is one of the best examples of great evolution in drug delivery technologies and nanotechnology. It is obvious that niosomes appears to be a well preferred drug delivery system over other dosage form as niosomes mostly stable in nature and economic The niosomes having similar structure like liposome but they have more advantage than liposome. Niosomes can entrapped many types of drug due to their multi-environmental structure. The concept of incorporation of the niosomes into the dosage form to target specific tissues and body. There is lots of drug can be encapsulated into niosomes such as toxic anti-cancer drug, anti-AIDS drug any many more. Niosomal increase the bioavailability of drug and also helpful to reduce its toxicity. Due to its smaller size it by pass or less metabolised by reticular-endothelial system (RES). The concept of incorporating the drug into or niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. The ionic drug carriers are relatively toxic and unsuitable whereas niosomal carriers are safer. And also handling and storage of niosomes require no special conditions. Niosomes represent a promising drug delivery module. Niosomes are thoughts to be better candidate drug delivery as compared to liposomes due to various factors like cost, stability etc. Niosomes have very important and key role in various types of drug deliveries; like targeting, topical, ophthalmic and parenteral. Niosomes are very useful in bright future for pharma industries. So far only animal experimentation

of this targeted drug delivery system is reported but further clinical investigations in human volunteers, pharmacological and toxicological investigations in animals and human volunteers may help to exploit niosomes as prosperous drug carriers for targeting drugs more efficiently, for treating cancer, infection and AIDS etc.

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