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COMPREHENSIVE REVIEW ON FORMULATION AND EVALUATION OF NIOSOMES

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ABSTRACT

Vesicular medication delivery system, for example, Niosomes is a novel medication delivery system, in which the vesicles composed primarily of synthetic surfactants and cholesterol.. Niosomes are self-assembled vesicles, which are biodegradable, relatively nontoxic, more stable and inexpensive. The niosomes provides several important advantages over conventional drug therapy. Various drugs are enlisted and tried in niosomes surfactant vesicles. Niosomes proved to be a promising drug carrier and has potential to reduce the side effects of drugs and increased therapeutic effectiveness in various diseases. This article presents an overview of the techniques of preparation of niosomes, types of niosomes, characterisation and their applications.

KEYWORD: Noisome, Preparation, Characterizations, and Applications.

INTRODUCTION

The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localised on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localisation of drug, leading to get maximum efficacy of the medication. Different carriers have been used for targeting of drug, such as immunoglobulin, serum proteins, synthetic polymers, liposome, microspheres, erythrocytes and niosomes.[1]

Niosomes are one of the best among these carriers. The self-assembly of non-ionic surfactants into vesicles was first reported in the 70s by researchers in the cosmetic industry. Niosomes are one of the best among these carriers. The niosomes are ampiphillic in nature, in which the medication is encapsulated in a vesicle which is made by non- ionic surfactant and hence the name niosomes. The niosomes size is a very small and microscopic. In the presence of proper mixtures of surfactants and charge inducing agents from the thermodynamically stable vesicles. Niosomes are mostly studied as an alternative to liposomes because they alleviate the disadvantages associated with liposomes.[2-3]

Niosomes behave *in vivo* like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. As with liposomes, the properties of niosomes depend on the composition of the bilayer as well as method of their production. It is reported that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation, and thus entrapment efficiency.[4]

However, differences in characteristics exist between liposomes and niosomes, especially since niosomes are prepared from uncharged single-chain surfactant and cholesterol, whereas liposomes are prepared from double-chain phospholipids (neutral or charged). The concentration of cholesterol in liposomes is much more than that in niosomes. As a result, drug entrapment efficiency of liposomes becomes lesser than niosomes. Besides, liposomes are expensive, and its ingredients, such as phospholipids, are chemically unstable because of their predisposition to oxidative degradation; moreover, these require special storage and handling and purity of natural phospholipids is variable.[5]

Niosomes overcome the disadvantages associated with liposomes such as chemical instability. Chemical instability of liposomes is due to their predisposition to oxidative degradation and variable purity of phospholipids. The main purpose of developing niosomal system is chemical stability, biodegradability, biocompatibility, chemical stability, low production cost, easy storage and handling and low toxicity. Niosomes can be administrated through various routes such as oral, parenteral, topical. Niosomes are used as a carrier to deliver different types of drugs such as synthetic and herbal, antigens, hormones and other bioactive compounds.[6,7,8] Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. It can also be used as vehicle for poorly absorbable drugs to design the novel drug delivery system. It enhances the bioavailability by crossing the anatomical barrier of gastrointestinal tract via transcytosis of M cells of Peyer's

patches in the intestinal lymphatic tissues.[9]

Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility. Drug delivery through niosomes is one of the approaches to achieve localised drug action in regard to their size and low penetrability through epithelium and connective tissue, which keeps the drug localised at the site of administration. Localised drug action enhances efficacy of potency of the drug and, at the same time, reduces its systemic toxic effects, eg, antimonials encapsulated within niosomes are taken up by mononuclear cells, resulting in localisation of drug, increase in potency, and hence decrease in dose as well as toxicity.[10]

This article presents some Salient features of niosomes along with an overview of the preparation techniques, evaluations and the current applications of niosomes.

SALIENT FEATURES OF NIOSOMES[11]

- Niosomes can entrap solutes.
- Niosomes are osmotically active and stable.
- Niosomes have an infra-structure 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 way by means of its bilayer which give supported 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. There by lessening the measurement required to be managed to accomplish the coveted impact.
- They improve the solubility and oral bioavailability of poorly soluble drugs and also enhance the skin permeability of drugs when applied topically.
- Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
- Niosomes can improve the performance of the drug molecules.
- Better availability to the particular site, just by protecting the drug from biological environment.
- Niosomes increase the stability of the entrapped drug.

ADVANTAGES OF NIOSOMES[12-14]

- 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
- 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
- As vesicle suspension is water based vehicle hence provide better patient compliancy than oil based dosage forms
- 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
- 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
- The biodegradable, biocompatible and non- immunogenic surfactants are used in preparation of niosomes and also handling and storage of surfactants requires no special conditions.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.

TYPES OF NIOSOMES[15-16]

Proniosomes

Proniosomes is made from the carrier and surfactant mixture.After the hydration of proniosomes, Niosomes are produced.

Deformable niosomes

The mixture of non-ionic surfactants, ethanol and water forms the deformable niosomes. These are smaller vesicles and easily pass through the pores of stratum corneum, which leads to increase penetration efficiency. It can be used in topical preparation.[17]

The niosomes are also classified according to the number and size of bilayer which is as follows,

i) **Multi Lamellar Vesicles (MLV):** Multilamellar vesicles are the most widely used niosomes. It consists of a number of bilayer. The approximate size of vesicles is 0.5-10 μm diameter. It is simple to make and are mechanically stable upon storage for long periods.

ii) **Large Unilamellar Vesicles (LUV):** These are the large unilamellar vesicles which having a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped.

iii) **Small Unilamellar Vesicles (SUV):** These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press and extrusion method.

FACTORS AFFECTING NIOSOMES

Composition of niosome: Theoretically for the niosome formation the presence of a particular class of amphiphile and aqueous solvent is needed but in certain cases cholesterol is required in the formulation to provide rigidity, proper shape and conformation to the niosomes. Cholesterol also stabilizes the system by prohibiting the formation of aggregates by repulsive steric or electrostatic effects. An example of steric stabilisation is the inclusion of Solulan C24 (a cholesteryl poly-24-oxyethylene ether) in doxorubicin (DOX) sorbitan monostearate (Span 60) niosome formulations**.** An example of electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.[18]

Surfactant and lipid level: To make niosomal dispersions the surfactant/lipid level is generally kept 10-30 mM (1- 2.5% w/w). If the surfactant, water ratio is altered during the hydration step may affect the microstructure of the system and it's properties. If we increasing the surfactant/lipid level the total amount of drug encapsulated also increases, but the viscosity level of system also increase.[19]

Nature of the encapsulated drug: The nature of encapsulated drug influences the niosomal formation, generally the physico chemical properties of encapsulated drug influence charge and rigidity of the niosome bilayer. The encapsulated drug interacts with surfactant head groups and develops the charge that creates mutual repulsion between surfactant bilayers and hence vesicle size increases and also cause the aggregation of vesicles, which is prevented by using electrostatic stabilizers like dicetyl phosphate in 5(6)-carboxyfluorescein (CF).[20]

Structure of surfactants: The geometry of vesicle to be formed from surfactants is affected by surfactant's structure, which can be defined by critical packing parameters. Geometry of vesicle to be formed can be predicated on the basis of critical packing

parameters of surfactants. Critical packing parameters can be defined using following equation,

CPP (Critical Packing Parameters) = V/ lc× a_0 Where v = hydrophobic group volume,

lc = the critical hydrophobic group length, a_0= the area of hydrophilic head group.

From the critical packing parameter value type of miceller structure formed can be ascertained as given below,

If CPP < ½ formation of spherical micelles, If ½ < CPP < 1 formation of bilayer micelles, If CPP > 1 formation inverted micelles.[21]

Temperature of hydration

Hydration temperature influences the shape and size of the niosome, temperature change of niosomal system affects assembly of surfactants into vesicles by which induces vesicle shape transformation. Ideally the hydration temperature for niosome formation should be above the gel to liquid phase transition temperature of system.[22,23]

COMPOSITION OF NIOSOMES

Cholesterol and Non ionic surfactants are the two major components used for the preparation of niosomes. Cholesterol provides rigidity and proper shape. The surfactants play a major role in the formation of niosomes. non-ionic surfactants like spans(span 20,40,60,85,80), tweens (tween 20,40,60,80) are generally used for the preparation of niosomes.[24] Few other surfactants that are reported to form niosomes are as follows.[25,26]

Ether linked surfactant

Di-alkyl chain surfactant

Ester linked

Sorbitan Esters

Methods of Preparation

Niosomes are prepared by different methods based on the sizes of the vesicles and their distribution, number of double layers, entrapment efficiency of the aqueous phase and permeability of vesicle membrane.

Preparation of small unilamellar vesicles

Sonication: The aqueous phase containing drug is added to the mixture of surfactant and cholesterol in a scintillation vial.[27] The mixture is homogenised using a sonic probe at 60°C for 3 minutes. The vesicles are small and uniform in size.

Micro fluidisation: Two fluidised streams move forward through precisely defined micro channel and interact at ultra-high velocities within the interaction chamber.[28] Here, a common gateway 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.

Preparation of multilamellar vesicles

Hand shaking method (Thin film hydration technique): In the hand shaking method, surfactant and cholesterol are dissolved in a volatile organic solvent such as diethyl ether, chloroform or methanol in a rotary evaporator, leaving a thin layer of solid mixture deposited on the wall of the flask. The dried layer is hydrated with aqueous phase containing drug at normal temperature with gentle agitation.

Trans-membrane pH gradient (inside acidic) drug uptake process (remote Loading): Surfactant and cholesterol are dissolved in chloroform.[29] The solvent is then evaporated under reduced pressure to obtain 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 three 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 produce the desired multilamellar vesicles.

Preparation of large unilamellar vesicles

Reverse phase evaporation technique (REV): In this method, cholesterol and surfactant are dissolved in a mixture of ether and chloroform.[30] 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. The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with phosphate-buffered saline and heated in a water bath at 60°C for 10 min to yield niosomes.

Ether injection method: The ether injection method is essentially based on slow injection of niosomal ingredients in ether through a 14-gauge needle at the rate of approximately 0.25 ml/min into a preheated aqueous phase maintained at 60°C.[31] The probable reason behind the formation of larger unilamellar vesicles is that the slow vapourisation of solvent results in an ether gradient extending towards the interface of aqueous- nonaqueous interface. The former may be responsible for the formation of the bilayer structure. The disadvantages of this method are that a small amount of ether is frequently present in the vesicles suspension and is difficult to remove.

Miscellaneous

Multiple membrane extrusion method*:* A mixture of surfactant, cholesterol, and diacetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in a series for up to eight passages. This is a good method for controlling niosome size.

Niosomes preparation using polyoxyethylene alkyl ether

The size and number of bilayer of vesicles consisting of polyoxyethylene alkyl ether and cholesterol can be changed using an alternative method.[32] Temperature rise above 60°C transforms small unilamellar vesicles to large multilamellar vesicles (>1 μm), while vigorous shaking at room temperature shows the opposite effect, ie, transformation of multilamellar vesicles into unilamellar ones. The transformation from unilamellar to multilamellar vesicles at higher temperature might be the characteristic for polyoxyethylene alkyl ether (ester) surfactant, since it is known that polyethylene glycol (PEG) and water remix at higher temperature due to breakdown of hydrogen bonds between water and PEG moieties. Generally, free drug is removed from the encapsulated drug by gel permeation chromatography dialysis method or centrifugation method. Often, density differences between niosomes and the external phase are smaller than that of liposomes, which make separation by centrifugation very difficult. Addition of protamine to the vesicle suspension facilitates separation during centrifugation.

Emulsion method: The oil in water (o/w) emulsion is prepared from an organic solution of surfactant, cholesterol, and an aqueous solution of the drug.[33,34] The organic solvent is then evaporated, leaving niosomes dispersed in the aqueous phase.

Lipid injection method: This method does not require expensive organic phase. Here, the mixture of lipids and surfactant is first melted and then injected into a highly agitated heated aqueous phase containing dissolved drug. Here, the drug can be dissolved in molten lipid and the mixture will be injected into agitated, heated aqueous phase containing surfactant.

Niosomes preparation using Micelle

Niosomes may also be formed from a mixed micellar solution by the use of enzymes. A mixed micellar solution of C16 G2, dicalcium hydrogen phosphate, polyoxyethylene cholesteryl sebacetate diester (PCSD) converts to a niosome dispersion when incubated with esterases. PCSD is cleaved by the esterases to yield polyoxyethylene, sebacic acid and cholesterol. Cholesterol in combination with C16 G2 and DCP then yields C16 G2 niosomes.

Separation of unentrapped drug[35-39]

The removal of unentrapped solute from the vesicles can be done by various techniques, such as dialysis, gel filtration and centrifugation.

Dialysis: Dialysis is one of most important technique used for removal of unentrapped drug from vesicles. In this technique, the aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution.

Gel Filtration: In this technique, the unentrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.

Centrifugation: The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug.[40-41]

CHARACTERISATION OF NIOSOMES

Size

Shape of niosomal vesicles is assumed to be spherical, and various techniques can be used for determination of their mean diameter like laser light scattering method, electron microscopy, molecular sieve chromatography, ultracentrifugation, photon correlation microscopy and optical microscopy and freeze fracture electron microscopy.[42,43]

Bilayer formation, Membrane rigidity and Number of lamellae

Bilayer vesicle formation by assembly of non-ionic surfactants is characterized by X-cross formation under light polarization microscopy and membrane rigidity can be measured by means of mobility of fluorescence probe as function of temperature. NMR spectroscopy, small angle X-ray scattering and electron microscopy are used to determine the no of lamellae.[44,45]

Entrapment efficiency: As described above after preparing niosomal dispersion, unentrapped drug is separated by dialysis, centrifugation or gel filtration and/ or complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 is done for the estimation of the drug remained entrapped in niosomes and then analyzing the resultant solution by appropriate assay method for the drug. Where, Entrapment efficiency (EF) can be defined by:

Entrapment efficiency (EF) = (Amount entrapped/ total amount) x100.

Microscopic evaluation

Transmission electron microscopy was used for microscopic evaluation of niosomal dispersions. TEM used for determination of size and used for identified whether it is spherical or not.

***In vitro* Release Study Dialysis**

With the help of dialysis tubing *in vitro* release rate study can be done. A dialysis sac was washed and soaked in distilled water. The suspension of vesicle was pipetted into a bag made up of the tubing and then sealed and placed in 200 ml buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. The buffer was analysed at various time intervals, for the drug content by an appropriate assay method.[46]

Reverse dialysis

In this technique, niosomes are placed in a number of small dialysis tubes containing 1 mL of dissolution medium and the niosomes are then displaced from the dissolution medium.[47]

Franz diffusion cell

In a Franz diffusion cell, the cellophane membrane is used as the dialysis membrane. The niosomes are dialyzed through a cellophane membrane against suitable dissolution

medium at room temperature. The samples are withdrawn at suitable time intervals and analyzed for drug content.[48]

In vivo Release Study

For *in vivo* study niosomal suspension was injected intravenously (through tail vein) to the albino rats using appropriate disposal syringe. These rats were subdivided into groups.[49]

APPLICATIONS OF NIOSOMES

Niosomes as a carrier for hemoglobin

Niosomal suspension shows a visible spectrum super imposable 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.

Niosomes as drug carriers

Niosomes have likewise been utilized as transporters for iobitridol, a symptomatic operator utilized for X-ray imaging. Topical niosomes may fill in as solubilization grid, as a neighborhood station for maintained arrival of dermally dynamic mixes, as entrance enhancers, or as rate-restricting layer obstruction for the tweak of foundational ingestion of medications.

Ophthalmic drug delivery

It is difficult to achieve excellent bioavailability of drug from ocular dosage form like ophthalmic solution, suspension and ointment due to tear production, impermeability of corneal epithelium, non- productive absorption and transient residence time. But to achieve good bioavailability of drug niosomal vesicular systems have been proposed.[29] Carter et al. 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.[50]

Delivery of peptide drugs

Yoshida et al investigated the stability of peptide increased by niosomes. In Yoshida et al for oral delivery of 9-desglycinamide, 8-arginine vasopressin entrapped in niosomes in an *in-vitro* intestinal loop model and reported that the stability of peptide increased by niosomes.[51]

Transdermal delivery of drugs by niosomes

In transdermal route of delivery, when drug is incorporated in niosomes penetration of drug through skin is enhanced.

Neoplasia

The anthracyclic antibiotic such as Doxorubicin which shows broad spectrum anti tumour activity, produces a dose depend antirreversible cardio toxic effect. This drug increased the lifespan and decreased the rate of proliferation of sarcoma when administered by niosomal delivery into mice bearing S-180 tumor.[52]

Use in studying immune response[53]

Because of their immunological selectivity, low danger and more noteworthy solidness; niosomes are being utilized to ponder the idea of the insusceptible reaction incited by antigens. Nonionic surfactant vesicles have plainly exhibited their capacity to work as adjuvant after parenteral organization with various distinctive antigens and peptides.

Anti-inflammatory agents

Niosomal formulation of Diclofenac sodium with70% cholesterol exhibits greater anti-inflammator activity as compare to free drug. Niosomal formulation of Nimesulide and Flurbiprofen shows greater anti-inflammatory activity as compared to free drug. Sharma et al (2009) was developed span-60 niosomal oral suspension of fluconazole in the treatment of fungal infection. It is effective as compare to capsule and tablets.[54]

Leishmaniasis[55]

Niosomes can be utilized for focusing of medication in the treatment of maladies in which the contaminating life form lives in the organ of reticulo-endothelial framework. Leishmaniasis is such an infection in which parasite attacks cells of liver and spleen.

Immunological application

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 in gene delivery

Novel niosome detailing in light of the 2,3-di (tetradecyloxy) propan-1-amine cationic lipid, joining with squalene and polysorbate 80 to assess the transfection productivity in rodent

retinas. Lipoplexes at 15/1 proportion were 200 nm in measure, 25mV in zeta potential and displayed circular morphology. At this proportion, it was seen that niosomes consolidated and secured the DNA from enzymatic processing.

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.

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.[56-58]

Table 1: Explains about the 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

Table 2: List of patents cited on Niosomes.

Key words	List of Granted Patents
Niosomes	124
Niosomes AND Sustained	21
Niosomes AND Controlled	17
Niosomes AND Oral	14
Niosomes AND Occular	7
Niosomes AND Hydrogel	3

CONCLUSION

Niosomal drug delivery system is one of the examples of great evolution in drug delivery technologies. The concept of drug incorporation in the niosomes is widely accepted by researchers and academicians. It provides a promising carrier system in comparison with ionic drug carriers, which are relatively toxic and unsuitable. Niosomes capacity to exemplify distinctive sort of medications inside their multi environmental structure and furthermore because of different elements like cost, stability and so on. Niosomes have several advantages which 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. However, the technology utilised in niosomes is still in its infancy. Hence, researches are going on to develop a suitable technology for large production because it is a promising targeted drug delivery system.

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