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NIOSOMES A CONTROLLED AND NOVEL DRUG DELIVERY SYSTEM: A BRIEF REVIEW

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ABSTRACT

During the past many year's formulation of vesicles is used as a tool to improve the delivery of drugs, it has created a lot of interest among the scientists who are contributing in the particular area of drug delivery system.[1] The vascular system like liposomes, transferosomes, Niosomes, phytosomes and electrosomes provide an effective path to amend the drug delivery. Niosomes play vital role owing to their non-ionic properties, in this type of drug delivery system.[2] Conception and evolution of a novel drug delivery system (NDDS) have two requirements. Foremost, the drug should be pitched at a predetermined rate and second, it should release therapeutically effective amount of a drug at the site of activity. The conventional dosage form does not satisfy these demands. Niosomes are non-ionic surfactant based unilamellar or multilamellar vesicles these vesicles possess an aqueous solution in which solute is entirely enveloped by a membrane resulting from organization of surfactant macromolecules. Niosomes are widely considered as an alternative to liposomes.[3] Both the vesicles are used to better the therapeutic performance of the drug molecule by delaying clearance from the circulation, protecting the drug from the biological environment and restricting effects to target cell. The application of niosomal technology is widely practiced to treat a number of diseases.[4]

KEYWORDS: Niosomes, non-ionic surfactant, novel drug delivery system, vesicles.

INTRODUCTION

Paul Ehrlich, in 1909, initiated the development for the targeted delivery when he predicted a drug delivery mechanism that would target directly to diseased cells. Niosomes are a novel

drug delivery system, Niosomes or non-ionic surfactant vesicle are microscopic lamellar structures. Niosomes are formed mostly by non-ionic surfactant and cholesterol incorporation as an excipient. Other excipients can also be used. The method of preparation of Niosomes is based on liposome technology.[5] The main process of preparation is the hydration by aqueous phase of the lipid phase, which may be either a pure surfactant or mixture of surfactant with cholesterol. Niosomes have the efficient penetrating capability than the previous preparations. They are structurally emulsions similar to liposomes in having a bilayer, however, the ingredients used to prepare Niosomes make them more stable.[6] Niosomes are promising vehicles for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug.[6] Niosomes are active in drug delivery potential and increase drug efficacy as compared with that pf free drug. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells. The application of niosomal technology is widely used to treat number of diseases.[7]

Definition: Niosome can be defined as a non-ionic surfactant-based liposome. Niosomes are prepared mostly by cholesterol incorporation as an excipient. Other excipients can also be incorporated. Niosomes have more penetrating capability when compared the previous preparations of emulsions. They are structurally alternating to liposomes in having a bilayer.[8] The materials used to formulate niosomes make them more stable and thus niosomes offer many advantages over liposomes. The particle size ranges vary from 10nm-100nm.

General Characteristics of Niosomes

• The power of non-ionic surfactant to form bilayer vesicle is dependent on the HLB value of the • surfactant, the chemical structure of the ingredients and the critical packing parameter

• Niosomes have the ability to provide more serious resistance to hydrolytic degradation

• The composing of the participant and the method used to formulate Niosomes reflects the properties of Niosomes.[9]

• Niosomes are biodegradable non-immunogenic and non-carcinogenic.

Advantages of Niosomes

- The drug is rendered at the quarry site where the curative outcome is needed.
- Less quantity of dose is required for the desired effect.

‣ Niosomes when applied topically enhance the permeability of the drug.

‣Niosomes are osmotically active and suitable

‣ Improve oral solubility of poorly soluble drugs

‣ Active pharmaceutical ingredient is protected by bilayer from the various factors present both inside and outside body

‣ They are biodegradable, biocompatible, and non-carcinogenic

‣ Niosomes are amphiphilic in nature and can accommodate a large act of drugs with an extensive range of solubilities.

Disadvantages of Niosomes

‣ Inefficient drug loading

‣ Special equipment's are required

‣ Time consuming process

‣ Suspension of Niosomes may exhibit fusion, aggregation, leaching or hydrolysis

‣ Sometimes causes reduced shelf-life of Niosomes dispersion.

Structure of Niosomes

• Niosomes are microscopic lamellar structures.

• Basic structural components are

• Non-ionic surfactant

• cholesterol

• Charge inducing molecule

• A number of non-ionic surfactants are used: Polyglycerol alkyl ether, glucosyl di-alkyl ethers, ester, linked surfactants and a series of spans and tweens.[10]

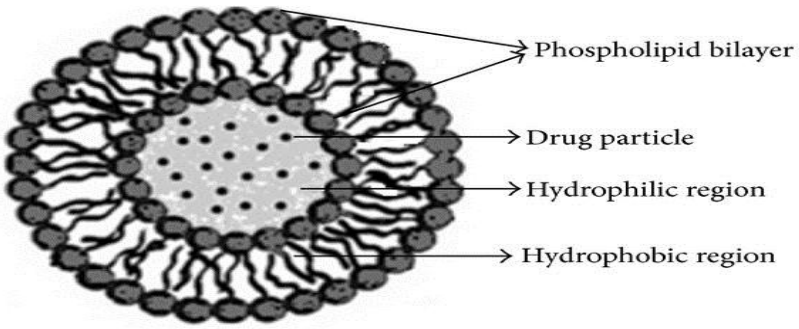


Fig. 1.

SEM image of niosome

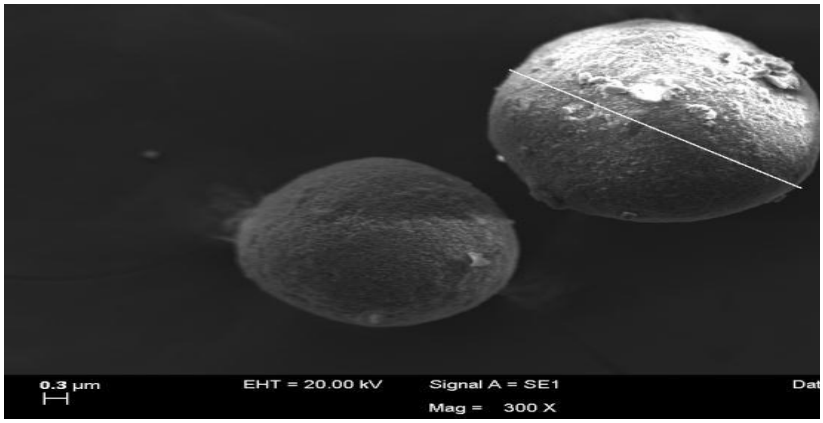


Fig. 2.

Optical Microscopy Image of Formulation

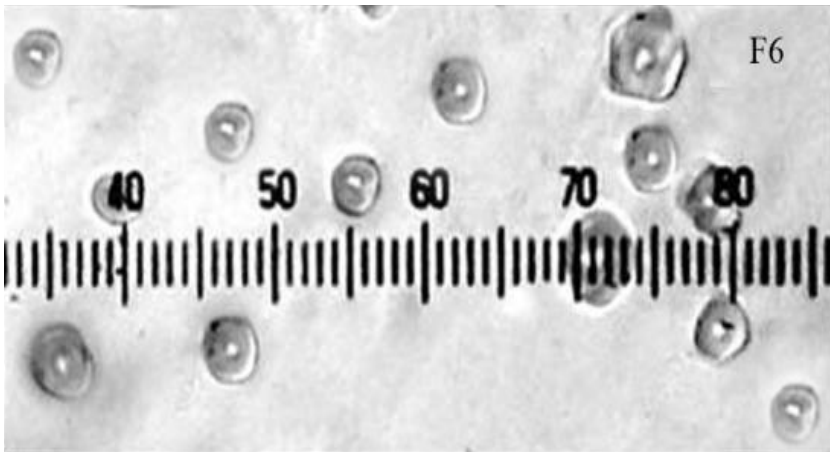


Fig. 3.

Preparation Methods of Niosomes

1. Ether Injection Method
2. Hand Shaking Method
3. Sonication
4. Multiple Membrane Extrusion Method
5. Reverse Phase Evaporation Method (Rev)
6. The Bubble Method
7. Thin film hydration method
8. Micro fluidization
9. Formation of Niosomes from Proniosomes

• **ether injection method:** The method provides ease in formulating Niosomes by gradually incorporating solution of surfactants dissolved in diethyl ether into warm water of temperature 55°C.-60c. 14-gauge needle is involved to inject surfactant mixture into an aqueous solution of material. The vaporization of ether leads to the production of single layered vesicles with the diameter between 50nm – 1000nm, and also depends upon the conditions applied.[11] single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000 nm.

Fig. 4.

Gauge needle

• **hand shaking method:** The mixture of ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent which can be diethyl ether, chloroform or methanol. In a round bottom flask. The organic solvent starts evaporating when exposed to room temperature using rotary evaporator, a thin film is left behind which is solid mixture deposited on the walls of flask. The formed film is then rehydrated using water at 0-60°C with gentle agitation.[12] This formulation process generally formulates multilamellar Niosomes having thermosensitive nature.

Fig. 5.

Rotating evaporator

• sonication

A very rich method which involves production of vesicles is sonication. In this process an aliquot of drug solution in buffer is incorporated to the surfactant/cholesterol mixture using 10 ml glass vial. The mixture is sonicated at 60°C for 3 minutes using good quality sonicator containing titanium probe to yield Niosomes.[13]

Fig. 6.

Sonicator

• multiple membrane extrusion method

A thin film is made from the mixture of surfactant, cholesterol and dicetyl phosphate in chloroform by evaporation process.[14] The prepared film is hydrated with aqueous drug solution and the formed suspension extruded through membranes of polycarbonate, these membranes are placed in series up to 8 passages, the method is very efficient in controlling the size of Niosomes.

• reverse phase evaporation technique (rev)

In a mixture of ether and chloroform, cholesterol and surfactant are dissolved in the ratio of 1:1. The aqueous phase which contains drug is added to this and sonication is performed for both the resulting phases at 4-5°C.[15] it leads to the clear gel formulation which is further sonicated after the incorporation of small amount phosphate buffered saline (PBS). The 40°C temperature is given which causes removal of the organic phase under low pressure the formed viscous suspension of Niosomes is diluted with PBS and heated for 10 minutes using water bath at 60°C to yield Niosomes.

• the bubble method

it is also called as novel technique because it involves single step process for the preparation of Niosomes and liposomes without using any organic solvent the unit which is also called as bubbling unit consists of round bottom flask which has three necks positioned towards water bath to control temperature. Water cooled reflux in first neck thermometer in second while as nitrogen supply through third neck. A mixture of cholesterol and surfactant is dispersed in this buffer having (pH 7.4) at 70°C, the mixture is homogenized with high shear homogenizer for 15 minutes and immediately bubbled at 70°C using nitrogen gas, which leads to the formation of Niosomes.[16]

• thin film hydration method

surfactants and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask.

The organic solvent is removed at room temperature using rotary evaporator leaving a thin film of solid mixture deposited on the wall of flask.

The dried film can be rehydrated with an aqueous phase at temperature slightly above the phase transition temperature of the surfactant used with gentle agitation.[17]

This process forms multilamellar Niosomes with good yield when compared with the formulated Niosomes by other methods.

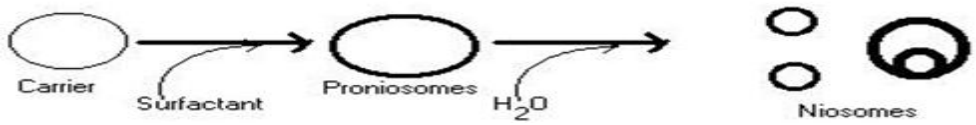
• micro fluidization

micro fluidization is a modern technique used to formulate unilamellar vesicles of required size distribution the method involved is based on submerged jet principle in this process two fluidized streams interact at ultrahigh velocities, the energy supplied mainly remains within the area of Niosomes formation.[18] It leads to the formation of Niosomes having smaller size, uniformity etc.

• formation of niosomes from proniosomes

The Niosomes can also be prepared by coating a water-soluble carrier like sorbitol with surfactants. The coating process is a dry formulation. In which each water-soluble particle is completely covered with a thin film of dry surfactant.[19] This prepared formulation is termed as “Proniosomes”. The Niosomes are differentiated by the addition of aqueous phase at T > Tm and slight agitation.

T=Temperature. And Tm = mean phase transition temperature

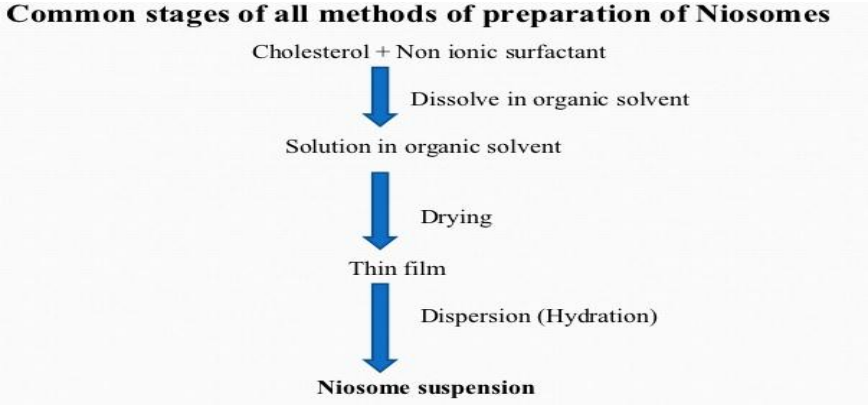


General Steps of Niosomes Preparation

Hydration of mixture of surfactant/lipid at elevated temperature

Sizing of Niosomes

Removal of un-entrapped material from vesicles



Applications of Niosomes

Niosomal novel drug delivery system shows various applications in

- drug targeting
- gene delivery
- drug targeting
- antineoplastic treatment
- leishmaniasis treatment
- delivery of peptide drugs
- studying immune response
- carriers for hemoglobin
- transdermal drug delivery systems
- cosmetics
- antineoplastic treatment
- Other Applications: Niosomes can also be incorporated for sustained drug release and localized drug action to greatly enhance the safety and efficacy of many drugs. Toxic drugs which require higher doses can possibly be delivered safely by using niosomal encapsulation.

Types of Niosomes

• proniosomes

Proniosomes are dry formulation of water-soluble carrier particles that are coated with surfactant. They are rehydrated to form niosomal dispersion immediately before use on agitation in hot aqueous media within minutes. Proniosomes are physically stable during the storage and conveyance.[20] Drug encapsulated in the vesicular structure of Proniosomes prolong the existence of drug in the systematic circulation and enhances the penetration into target tissue and reduce toxicity. From a technological level of view, Niosomes are promising drug carriers as they have greater chemical stability and lack of many disadvantages associated with liposomes, such as high- cost and variable purity problems of phospholipids. The present review emphasizes on overall methods of preparation, characterization and application of proniosomes in targeted drug action.[21]

•aspasomes

The vesicles prepared with amphiphiles are having antioxidant property and may have potential applications towards disorders implicated with reactive oxygen species. Vesicles with biological activity or with a targeting function with addition to carrier properties will suffer an added advantage.[22] A bilayer vesicle of Ascorbyl palmitate was formed (ASP). Aspasomes can be prepared by thin film hydration method and sonication in which the aqueous azidothymidine (AZT) solution was encapsulated in aqueous regions in the bilayer.

• niosomes in carbopol gel

The prepared niosomes were incorporated using Carbopol-934 gel 1%w/w). base containing propylene glycol (10% w/w) and glycerol (30% w/w). mean flux value and diffusion co-efficient were 5-7 times lower for niosomal gel when compared to plain drug gels.[23]

• niosomes of hydroxyl propyl methyl cellulose

This type of niosomes contain 10% glycerin of hydroxyl propyl methyl cellulose which is first prepared and then niosomes are added to it. The reduction and bioavailability of paw edema induced by carrageenan was found to be higher by this system when compared to plain formulation of flurbiprofen.

Drugs incorporated into niosomes by various methods

Method of preparation	Drug incorporated
Hand Shaking	Methotrexate Doxorubicin
Ether injection	Sodium stibogluconate Doxorubicin Doxorubicin
Sonication	9-desglycinamide 8-arginine Vasopressin Oestradiol

Comparision of Niosomes V/S Liposomes

a) Niosomes are widely considered as an alternative to liposomes. which have certain disadvantages such as –they are expensive, ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they need special storage and handling. purity of natural phospholipids varies.[24]

b) characteristics difference exists between liposomes and niosomes, because niosomes are prepared from uncharged single-chain cholesterol and surfactant on the other hand liposomes are prepared from double-chain phospholipids (neutral or charged).[25]

c) Niosomes likely behave *in-vivo* as liposomes, prolongs the circulation of entrapped drug and affecting its distribution and metabolic stability. Encapsulation of various anti neoplastic agents has shown to reduced drug induced toxicity, while increasing the anti-tumor efficacy. vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. They target the drug to its desired site of action and controls its release.[26]

Sl. No.	Liposomes	Niosomes
1.	Vesicles made up of concentric bilayer of phospholipids	Vesicles made up of surfactants with or without incorporation of cholesterol.
2.	Size ranges from 10-3000nm	Size ranges from 10-100nm
3.	Comparatively expensive	Inexpensive
4.	Special storage condition are required	No such special requirement
5.	Phospholipids used are unstable	Non-ionic surfactants are stable
6.	Comparatively more toxic	Less toxic

Various Drugs That Can Be Incorporated in Niosomes and Their Route of Administration

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

Evaluation of Niosomes

• entrapment efficiency

once niosomal dispersion is prepared, the unentrapped drug is separated by dialysis, centrifugation, or gel filtration and the remained drug entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzing the resultant solution is analyzed by appropriate assay for the drug.[27]

Where,

Entrapment efficiency (EF) = (Amount entrapped / total amount) x 100

• vesicle diameter

Niosomes and liposomes are spherical shape thus their diameter can be determined using light microscopy, freeze fracture electron microscopy and photon correlation microscopy. Freeze thawing (vesicles suspension is kept at –20°C for 24 hours and then heating at a particular temperature) of niosomes increases diameter of vesicles.[28]

• *in-vitro* release

in-vitro release rate study is carried out using dialysis tubing. The dialysis sac is washed and soaked in distilled water. The suspension of vesicles is pipetted into a bag which is made up of the tubing and is sealed. The bag possessing vesicles is kept in 200 ml of buffer solution in a 250 ml beaker with regular shaking at 25°C or 37°C. appropriate assay is carried out to analyze the drug content in buffer.[29]

• separation of unentrapped drug

The unentrapped solute from the vesicles can be removed by various techniques, which include.

• dialysis

The dispersion of aqueous niosomes is dialyzed in a dialysis tubing against phosphate buffer or normal saline.[30]

Fig. 7.

Dialysis machine

• gel filtration

The unentrapped solute material can be removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution is carried with phosphate buffer saline or normal saline.

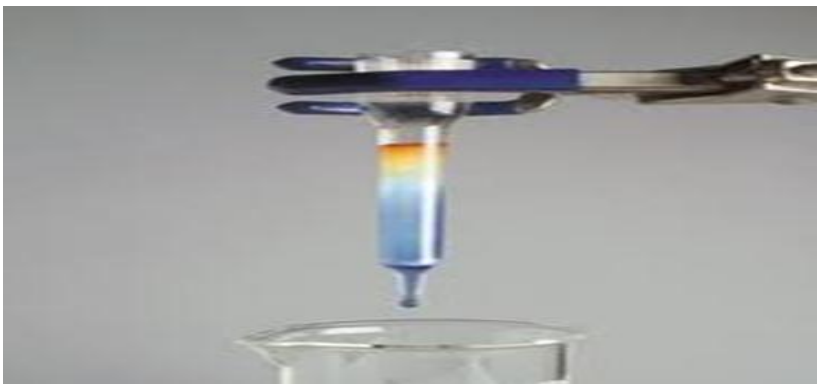


Fig. 8.

• membrane rigidity

the membrane rigidity is measured by means of mobility of fluorescence probe as a function of temperature.

• number of lamellae

Nuclear magnetic resonance (NMR) spectroscopy is incorporated to determine number of lamellae, this also can be done by small angle X-ray scattering and electron microscopy.

• ph measurement

The pH of Niosomes can be measured using pH meter at 25°C.

• zeta potential measurement

the diluted niosomal dispersion was determined using zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry method at 25°C temperature. The Charge on vesicles and their mean zeta potential values were obtained directly from the measurement.[31]

Factors affecting the physiochemical properties of niosomes

• Membrane additives

Stability of Niosomes can be increased by the number of additives into the niosomal formulation along with surfactant and drugs. The membrane stability, morphology and permeability of vesicles are affected by number of additives, e.g. addition of cholesterol in niosomal system increases the rigidity and decrease the permeability through membrane.

• Temperature of hydration

Shape and size of Niosomes are also influenced by the hydration temperature. Assembly of the Niosomes vesicles is affected by the temperature change of niosomal system. A temperature change can induce the vesicle shape transformation.

• Properties of drugs

The drug entrapment is affected by molecular weight, chemical structure, hydrophilicity, lipophilicity balance (HLB) value of the drug. Vesicle size may increase due to entrapment of the drug. Drug particle interact with the surfactant head groups, which may increase charge on polymer and thus cause repulsion of the surfactant bilayer which leads to increase in vesicle size.[32]

Effect of the Nature of Drug on the Formulation of Niosomes

Nature of the drug	Leakage from the vesicle	Stability	Other properties
Hydrophobic drug	Decreased	Increased	Improved trans-dermal delivery
Hydrophilic drug	Increased	Decreased	–
Amphiphilic drug	Decreased	–	Increased encapsulation, altered electrophoretic mobility
Macromolecule	Decreased	Increased	–

Marketed Formulation of Niosomes: Lancome has come out with variety of niosomal antiaging formulations and foundation creams which are better and advanced for their action.

Fig. 9: L'Oréal is also working for niosomal antiaging cosmetic products.

CONCLUSION

Niosomal drug delivery system is one of the best and greatest evolution in drug delivery technique. Before formulation of niosomal drug delivery, various preformulation were studied such as solubility studies and drug excipient compatibility.[33] studies were performed along with the optimization of process variables, which include hydration medium, hydration time, rotation speed of round bottom flask and charge inducing agents. This concept of drug incorporation in the niosomes and its target to the specific site is widely accepted by researchers and academicians.[34] They represent alternative to liposomes and are having various advantages over liposomes like cost, stability etc. Niosomes represent a promising and novel drug delivery technology and much more research has to be done in this to take out all the potential in this specific and novel drug delivery system.[35]

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