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NIOSOMES: A NOVEL APPROACH IN DRUG DELIVERY

VRUNAL V MORE[1], DR. RITU M. GILHOTRA[2], DR. MANOJ M. NITALIKAR[2]

1.SVERI's College of Pharmacy, Pandhrpur, Maharashtra.

2.Rajarambapu College of Pharmacy, Kasegaon, Sangli, Maharashtra

3.Head and Prof. of ECE Dept. (Jaipur National University, Jaipur, India).

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Abstract: Niosomes are Vesicular drug delivery systems that can improve bioavailability of encapsulated drug and offers therapeutic activity in a controlled manner for a prolonged time period. Niosomes have low cost and more of stability at various pHs as compare with Liposome. Niosomes are a nonionic surfactant vesicular system, which can be easily and reliably prepared in the laboratory. Many factors affect niosome formation such as the method of manufacture, nature of surfactant and encapsulated drug, temperature at which the lipids are hydrated and the critical packing parameter. This review explores all aspects of niosomes including their compositions, the various methods of preparation, the effect of changing manufacturing parameters, methods of characterization, factors that affect their stability, their use by various routes of administration, their therapeutic applications and the most important patents. The review also describes detailed information of a variety of types of niosomes that gives effective drug delivery.

Keywords: Niosomes, Drug Delivery

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Corresponding Author: VRUNAL V MORE

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INTRODUCTION

Vanlerbeghe et al. (1972) first reported the niosomes as a feature of cosmetic industry. In 1979, Handjanivila et al. reported that the hydration of a mixture of cholesterol and single alkyl chain resulted in formation of non-ionic surfactant vesicular system niosomes [1]. Vesicular carriers are used for drug targeting, release of drug in controlled manner. Now a day's niosomes are used as carriers preparations, which has the property of carrying both hydrophilic and lipophilic drugs. [2] Niosome is stable and less irritation during its action on dermal route compared to other colloidal vesicle carrier.

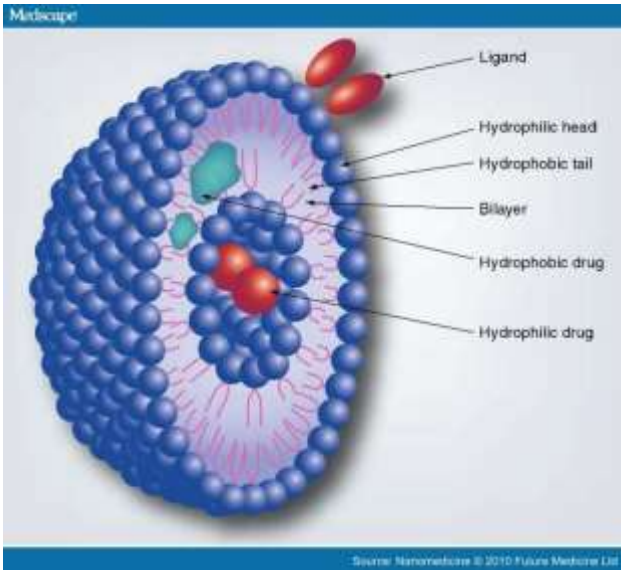
Advantages:

1. Niosomes increases the stability of entrapped drug as they are stable.
2. Handling and storage of niosomal formulation requires no special conditions.
3. Niosomes improves oral bioavailability of the drugs and enhances the permeation of the drugs through the skin because of the presence of surfactants.
4. They help in reaching the target site of action by various routes such as oral, parenteral, ocular, nasal as well as topical routes.
5. Niosomes are nontoxic, biodegradable, biocompatible and non-immunogenic.
6. Niosomes improve the therapeutic performance of the drug, since the drug is not distributed to non target sites and reduces the chances of drug toxicity.
7. Niosomes help to sustain the drug release by forming a depot and offer a controlled release. The vesicle suspension is water–based vehicle thus offers high patient compliance in comparison with oily dosage forms.
8. Due to the unique infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together they, as a result can accommodate drug molecules with a wide range of solubilities.
9. The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
10. The vesicles may act as a depot, releasing the drug in a controlled manner.
11. They are osmotically active and stable, and also they increase the stability of entrapped drug.
12. Handling and storage of surfactants requires no special conditions.
13. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
14. They can be made to reach the site of action by oral, parenteral as well as topical routes.
15. The surfactants are biodegradable, biocompatible and non-immunogenic.
16. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation [2, 3].

Structure of Niosome:

A niosomal vesicle system would consist of a vesicle forming amphiphile i.e. a non-ionic surfactant such which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant which also helps in stabilizing the vesicle [4]

Structure of Niosome:



Niosomes are classified based on size and method of preparation.

1) According to the nature of lamellarity [5]

* Multilamellar vesicles (MLV) 1-5 um in size.
* Large unilamellar vesicles (LUV) 0.1 – 1µm in size.
* Small unilamellar vesicles (SUV) 25 – 500 nm in size.

2) According to the size

* Small niosomes (100 nm – 200 nm).
* Large niosomes (800 nm – 900 nm).
* Big niosomes (2 µm – 4 µm).

Proniosomes:

These are the niosomal formulation made up of carrier and surfactants, which are to be hydrated before use Carrier + surfactant = Proniosomes .Proniosomes + Water = Niosomes.

Composition of Niosome:

Niosome Formation

Theoretically, niosomal formation requires the presence of a particular amphiphile and aqueous solvent. The association of amphiphile monomers into vesicles on hydration is the result of a high interfacial tension between water and hydrocarbon portion (or any other hydrophobic group) of the amphiphile, causing them to associate. Simultaneously, the steric hydrophilic and ionic repulsion between the head groups ensure that these groups are in contact with water. These two contrary forces lead to a supramolecular assembly. The essential components in the preparation of niosomes are membrane additives such as cholesterol and non-ionic surfactants [6, 7].

Non-ionic surfactants:

A variety of nonionic surfactants and their combinations have been reported to have great potential to encapsulate many of drugs in niosomes [8]. The most common types of niosome forming nonionic surfactants include alkyl ethers, alkyl esters, alkyl amides, sorbitan fatty acid esters, etc [9, 10]. These nonionic surfactants are used in various niosomes formulations and showed different effects on the properties of niosomes [11]. For instance, polysorbate 80 (Tween 80) as a nonionic surfactant has a specific role in brain targeting which can be due to the interaction between Tween 80 and brain micro-vessel endothelial cells [12]. There are some new types of nonionic surfactants such as sucrose esters, bola-form amphiphiles and tyloxapol which have been used to prepare niosomes. Sucrose esters consist of sucrose as the hydrophilic head group and fatty acids as lipophilic end [13]. These natural surfactants have vesicle formation capabilities and are used to formulate niosomal drug delivery systems. Honeywell-Nguyen and Bouwstra formulated pergolide-loaded vesicles from sucrose laurate and PEG-8-L. Also, rotigotine-loaded vesicles using sucrose ester surfactant was prepared for transdermal delivery [14]. New classes of surfactants have been synthesized for development of innovative niosomal systems, for example, the bola-form amphiphiles. Bola-form amphiphiles consist of two similar azacrown ether units (polar heads) linked to a long alkyl chain and represents a new group of nonionic surfactants, which are able to form vesicles if formulated by thin film layer hydration method in the presence of cholesterol [15]. Bola surfactant niosomes encapsulating 5-fluorouracil are prepared for skin cancer treatment [16]. Tyloxapol is nonionic biological surfactant of the alkyl aryl polyether alcohol type with a HLB value of 12.5. It is mostly used in marketed ophthalmic products and as a mucolytic agent for treating pulmonary diseases. Tyloxapol molecules accumulate in aqueous solution to form vesicles systems [17, 18].

Cholesterol: - Cholesterol is frequently used as an additive in preparation of niosomes. The basic idea behind the use of cholesterol is to influence the stability and membrane permeability, which is mainly due to the interaction between surfactant and cholesterol. Stable vesicles with reduced permeability of water into the vesicle core can be achieved by cholesterol inclusion into the niosomal formulation [19]. Cholesterol as an amphiphilic molecule interacts with surfactants through hydrogen bonding between its -OH group and surfactant's

hydrocarbon chain which increase the mechanical stiffness of the membranes and membrane cohesion [20]. This function of cholesterol restricts the movement of carbons of hydrocarbon which results in a decrease in permeability of cholesterol-containing membranes compared to cholesterol-free membranes [21]. It has been reported that the value of surface elasticity (which is a measure of membrane strength) increases by addition of cholesterol which makes the membrane more rigid and reached at a maximum value of around 47.5 mol% cholesterol. Further addition of cholesterol can cause the formation of cholesterol clusters thus disturbing the uniformity, strength and permeability of bilayers. In general, it has been reported that 1:1 molar ratio of surfactants and cholesterol is an optimal ratio for the preparation of physically stable niosomal formulations [22, 23].

Cholesterol also helps in controlling the vesicle formation by modifying the total HLB value and packing parameter of the system [24]. Addition of cholesterol completes the lipophilic moiety of nonionic surfactants with high HLB values to form vesicles [25]. HLB value of surfactants determines the minimum amount of cholesterol required to form vesicle. As the HLB value of the niosomal systems increases, the minimum amount of cholesterol required to regulate the larger hydrophilic head groups also increases. For instance, a nonionic surfactant belongs to Pluronic surfactant category (L64) can form niosomes only by addition of cholesterol. For insulin encapsulation into niosome, Brij 35 (HLB 16.9) and Brij 58 (HLB 15.7) were not able to form vesicles without the presence of cholesterol due to the dominance of large hydrophilic head groups over the low volume of the lipophilic hydrocarbon chain [26].

Methods of preparation:

A. Hand shaking method (Thin film hydration technique) [27]

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 60°C with gentle agitation. This process forms typical multilamellar niosomes.

B. Microfluidization [28]

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed.

C. Reverse Phase Evaporation Technique (REV) [29]

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 45°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.Raja Naresh et al [13] have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

D. Ether injection method [30, 31]

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14 gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000 nm.

E. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading) [32]

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes

F. The "Bubble" Method [33]

It is novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round bottomed flask with three necks positioned in water bath to control the temperature. Water cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70°C using nitrogen gas.

G. Sonication [32]

A typical method of production of the vesicles is by sonication of solution as described by Cable (32) In this method an aliquot of drug solution in buffer is added to the surfactant/choleste mixture in a 10ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.

H. Formation of niosomes from proniosomes [33]

Another method of producing niosomes is to coat a water soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed "Proniosomes". The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation. T=Temperature. Tm = mean phase transition temperature. Blazek-Walsh A.I. et al have reported the formulation of niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free flowing powder, which could be rehydrated by addition of warm water.

Recent studies on niosomes

Type of the drug	Name of the drug	Composition	Experimental model	Year	References
Angiotensin receptor blockers	Candesartan cilexetil	Span 60, cholesterol, dicetyl phosphate, maltodextrin	In vitro dissolution test for proniosomal tablets, in vivo evaluation of proniosomal tablets, pharmacokinetic analysis	2016	[39]
Anti-inflammatory	Naproxen Dexamethasone	Tween 80, Tween 20, cholestero pan 60, cholestero	In vitro drug release study, preformulation study Characterization of niosomes,in vitro release studies, stability test	2016 2015	[41] [41]
Antibacterial	Moxifloxacin Cefixime	Tween 60, cholesterol C-Glycoside derivative surfactant, cholesterol	In vitro release studies, antimicrobial activity In vitro release study, biocompatibility and bioavailability studies using experimental animals	2016 2016	[40] [36]

Anticancer	Doxorubicin Paclitaxel	Span 60, cholesterol, dicetyl phosphate, N-lauryl glucosamine Span 40, cholesterol, dicetyl phosphate	Optimization studies for formulation, skin irritancy, histopathological investigation of rat skin Formulation studies, Pharmacokinetic and tissue distribution studies	2016 2015	[35] [34]
Antiviral	Nevirapine	Tyloxapol, cholesterol	Diffusion kinetics of drug, microviscosity studies, in vitro release study	2015	[35]
H2 receptor antagonist	Famotidine	Span 60, cholesterol	Kinetic analysis of drug-release profiles, ex vivo permeability study	2016	[40]

Characterization of Niosomes

1. Vesicle Size and Morphology.

Dynamic light scattering (DLS)[42], scanning electron microscopy (SEM) [43], transmission electron microscopy (TEM) [44], freeze fracture replication-electron microscopy (FF-TEM) , and cryotransmission electron microscopy (cryo-TEM) are the most used methods for the determination of niosome sizes and morphology. DLS provides simultaneously cumulative information of particle size and valuable information on the homogeneity of the solution. A single sharp peak in the DLS profile implies existence of a single population of scatterers. The PI is helpful in this respect. It less than 0.3 corresponds to a homogenous population for colloidal systems. The microscopic approaches are generally used to characterize the morphology of the niosomes [45].

2. Zeta Potential.

Surface zeta potential of niosomes can be determined using zetasizer and DLS instruments. The surface charge of niosome plays an important role in the behavior of niosomes. In general, charged niosomes are more stable against aggregation than uncharged vesicles. Bayindir and Yuksel prepared paclitaxel loaded niosomes and investigated the physicochemical properties

such as zeta potential of niosomes. They found that negative zeta potential values ranging between−41.7 and−58.4 mV are sufficiently high for electrostatic stabilization of niosomes [46]

3. Bilayer Characterization.

Bilayer characteristics of niosomes have an importance on drug entrapment efficiency. The number of lamellae can be determined by AFM, NMR, and small angle X-ray scattering (SAXS) for multilamellar vesicles [47]. Membrane rigidity of niosomal formulations can be measured by means of the mobility of fluorescence probe as a function of temperature [48]. DPH (1,6 diphenyl-1,3,5-hexatriene) is most used fluorescent probe and added to niosomal dispersion. DPH normally exists in hydrophobic region in the bilayer membrane. The microviscosity of niosomal membrane is determined by fluorescence polarization.High fluorescence polarization means high microviscosity of the membrane. Moreover, the bilayer thickness can be characterized using the latter method, together with the insituenergy-dispersive X-ray diffraction (EDXD) [49].

4. Entrapment Efficiency.

Entrapment efficiency (EE %) is defined as the portion of the applied drug which is entrapped by the niosomes. Unencapsulated free drug can be removed from the niosomal solution using centrifugation [51], dialysis [50], or gel chromatography [52]. After this step the loaded drug can be released from niosomes by destruction of vesicles. Niosomes can be destroyed with the addition of 0.1% TritonX-100ormethanoltoniosomalsuspension.Th loaded and free drug concentration can be determined by a spectrophotometer [53] or high-performance liquid chromatography (HPLC) [54].

5. Stability.

The stability of niosomes can be evaluated by determining mean vesicle size, size distribution, and entrapment efficiency over several month storage periods at different temperatures. During storage the niosomes are sampled at regular intervals of time and the percentage of drug which is retained into the niosomes is analyzed by UV spectroscopy or HPLC methods [53, 55]

6. *In Vitro* Release.

One often applied method to study in vitro release is based on using of dialysis tubing. A dialysis bag is washed and soaked in distilled water. After 30 mins, the drug loaded niosomal suspension is transferred, into this bag. The bag containing the vesicles is immersed in buffer solution with constant shaking at 25°C or 37°C. At specific time intervals, samples were removed from the outer buffer (release medium) and replaced with the same volume of fresh buffer. The samples are analyzed for the drug content by an appropriate assay method [56].

Applications of niosomes:

Niosomes as Drug Carriers

Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for X-ray imaging. Topical niosomes may serve as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs [57].

Leishmaniasis therapy

Leishmaniasis is a disease caused by parasite genus Leishmania which invades the cells of the liver and spleen. Most Commonly prescribed drugs for the treatment are the derivatives of antimony – which, in higher concentrations – can cause liver, cardiac and kidney damage. Use of niosomes as a drug carrier showed that it is possible to administer the drug at high levels without the triggering the side effects, and thus showed greater efficacy in treatment [58].

Niosome as a carrier for Haemoglobin

Niosomal suspension shows a visible spectrum super imposable onto that of free haemoglobin so can be used as a carrier for haemoglobin. Vesicles are also permeable to oxygen and haemoglobin dissociation curve can be modified similarly to non-encapsulated Haemoglobin [59].

Neoplasia

Doxorubicin, the anthracyclic antibiotic with broad spectrum antitumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumour 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 tumour bearing mice resulted in total regression of tumour and also higher plasma level and slower elimination [60].

Use in Studying Immune Response

Due to their immunological selectivity, low toxicity and greater stability; niosomes are being used to study the nature of the immune response provoked by antigens. Non-ionic surfactant vesicles have clearly demonstrated their ability to function as adjuvants following parenteral administration with a number of different antigens and peptides[15.]

Antibiotics

The feasibility of using non-ionic surfactant vesicles (niosomes) as carriers for the ophthalmic controlled delivery of a water soluble local antibiotic, gentamicin sulphate was investigated and the results demonstrated niosomes to be promising ophthalmic Carriers for the topical application of gentamicin sulphate. Preparation and evaluation of Cefpodoxime proxetil niosomes showed controlled release of 65.25% for 24 hours with zero order kinetics, thus

reducing the chances of dose dumping during usage. The bioavailability of Cefuroxime axetil which is just 25% was improved by preparing niosomes. The prepared niosomes showed good entrapment efficiency and in vitro release and also were stable in bile salts [60].

Transdermal delivery of drugs by niosomes

Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Jayraman et al has studied the topical delivery of erythromycin from various formulations including niosomes or hairless mouse. From the studies, and confocal microscopy, it was seen that non-ionic vesicles could be formulated to target pilo sebaceous glands [60].

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

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. Bio adhesive-coated niosomal formulation of acetazolamide prepared from span60, cholesterol steary lamine or dicetyl phosphate exhibits more tendencies for reduction of intraocular pressure as Compared to marketed formulation (Dorzolamide) [61].

CONCLUSIONS:

The vesicular systems have been gaining a lot of interest of various researchers and scholars, because of their advantages of sustained and controlled release action. Niosomes offer a great opportunity for loading hydrophilic, lipophilic drugs, or both drugs together. These carrier systems have immense scope in future, especially in the area of transdermal drug delivery. It is noticeable that niosome appears to be a well preferred drug delivery system as niosome are stable and economic; also niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. They have ability to encapsulate different type of drugs within their multi-environmental structure. Niosomes are considered to be better candidates for drug delivery system due to various factors like cost, stability etc. The drug delivery potential of niosome can be enhanced by using novel concepts like proniosomes, discomes and aspasome.

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