EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 4
370-375
Year: 2018

NIOSOMES: A NOVEL FORMULATION FOR ANTI-AGEING COSMECEUTICALS

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Article Received on 11/02/2018 **Article Revised on 04/03/2018** **Article Accepted on 25/03/2018**

ABSTRACT
Niosome is non-ionic surfactant-based liposome having particle size ranges from 10nm-100nm. They are formed generally by cholesterol incorporation as an excipient. Supplementary excipients can also used. Niosomes have more penetrating ability than the others preparations of emulsions. Aged skin has uniqueness like loss of skin tone with loss of elasticity, raise in dryness & roughness, rough pigmentation, wrinkles, sunburn and different malignant skin cancers. A large amount used delivery systems are liposomes and they are being used in a variety of skin care rejuvenating products. Niosomes adsorb on to cell surface with minute or no internalization of either aqueous or lipid mechanism, it may take place by two reasons, that is attracting physical forces or as a result of binding by specific receptors to ligands on the vesicle membrane and then transfer of drug directly from vesicles to the skin. Niosomes may fuse with the cell membrane, which leads to complete mixing of the niosomal contents with the cytoplasm. Lastly, by the process of endocytosis, niosomes may be engulfed by the cell thus releasing the entrapped drug into the medium

KEYWORDS: Niosome, Anti-ageing, Pigmentation, Wrinkles.

INTRODUCTION
With rising average life span of people, the need for anti-ageing therapies is increasing since physical appearance is most essential in today's world. There are various technologies available for treatment of skin ageing such as facelifts, laser therapy, botox, microderma abrasion etc. These methods although quite famous are not used on a larger scale due to their invasive nature. Therefore, various novel non-invasive topical delivery systems are being developed. However, skin acts a major barrier for topical formulations, stratum corneum being the largest barrier. Hence, there is an urge to have a proper carrier to deliver the drugs through the skin which can be fulfilled using novel delivery systems.[1-5] The most widely used delivery systems are liposomes and they are being used in a variety of skin care rejuvenating products. Liposomes are capable of encapsulating various anti-ageing active ingredients and deliver them deep into the cells. The first liposomal anti-ageing cream to enter the market was "Capture" launched by Dior in 1986. But liposomes are associated with certain disadvantages so to overcome their drawbacks, surfactant based vesicles called niosomes were proposed.[6] Niosomes are preferred over liposomes because of several factors enlisted below.

i. Liposomes require phospholipids which are highly susceptible to oxidative degradation making them unstable whereas niosomes do not require phospholipids.

ii. In order to maintain the stability, liposomes and phospholipids have to be stored and handled in an inert nitrogen atmosphere.

iii. Since phospholipids are natural in origin their purity is variable and require extensive purification.

All the above problems contribute to the high cost of liposomal formulations. Since niosomes do not have any of these problems they are cheaper and more stable as compared to liposomes. Moreover, niosomes behave in-vivo like liposomes, prolonging the circulation of entrapped drug. They can be used as a tool for targeted drug delivery to the desired site of action and provide controlled release.

Niosomes were first discovered by Handjanivila et al. in 1979. Niosomes, also called as non-ionic surfactant vesicles are microscopic lamellar structures which are formed by the admixture of non-ionic surfactant and cholesterol.[7] They are formed by the self-assembly of amphiphilic molecules into closed bilayers.[8] Since they

have an amphiphilic bilayer structure they can entrap both hydrophilic as well as hydrophobic drugs.[9] Appropriate mixtures of surfactants and charge inducing agents give thermodynamically stable vesicles. Other factors contributing to the formation of niosomes include HLB value of the amphiphilic molecule, aqueous interlayer, lipid chain-length, chain-packing and membrane asymmetry. The structure of noisome is represented below:

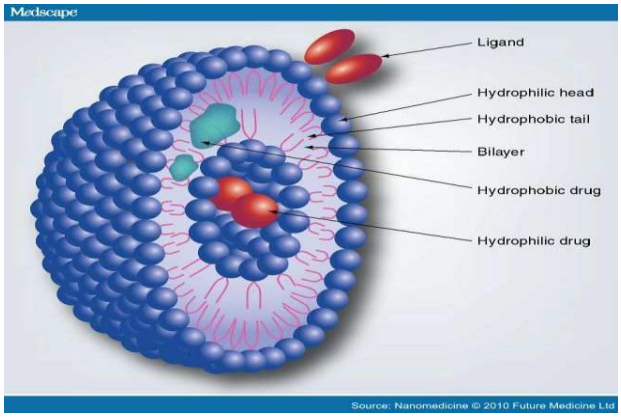

Figure. 1: Structure of Niosomes.

They can be formulated as small unilamellar vesicles (SUV, size=0.025-0.05 μm), large unilamellar vesicles (LUV, size=>0.10 μm) and multilamellar vesicles (MLV, size=>0.05 μm).[10]

These surfactant based vesicles provide targeted and controlled drug delivery and also enhance the permeation of drug through the skin thus providing efficient drug delivery. Niosomes are biodegradable, biocompatible, non-toxic, have low production cost, easy storage and handling.[11]

Mechanism of Skin Ageing: Aged skin has characteristics like loss of skin tone with resilience (loss of elasticity), increase in dryness & roughness, irregular pigmentation, accelerated skin ageing, wrinkles, sunburn, & various malignant skin cancers.

Ageing takes place because of two interactive and overlapping processes called primary and secondary ageing.

Primary aging, also known as "intrinsic senescence," is caused due to the progressive deterioration of the physical structure and biological functions of body which takes place with increasing age.[12,13]

Secondary ageing is caused due to the degradation which takes place in body caused by diseases like diabetes, hypertension etc. Environmental factors as well as lifestyle effects like smoking tobacco also have an impact on body which in turn leads to ageing. Excessive exposure to sun leads to harmful impacts on skin.[13-15]

Exact mechanisms for both these processes are not known, but the probable factors include the following

1. Damage to protein and DNA which takes place due to oxidative stress along with improper repairment of DNA damage and genetic instability that takes place in mitochondria as well as in nuclear genomes.[15]
2. Increased production of adipokine and cytokine that causes non-infectious chronic inflammation.[16]
3. During fatty acid metabolism, excessive free fatty acids are released which undergoes alteration with subsequent tissue insulin resistance.[17]
4. Interference in normal cellular functioning which takes place due to the accumulation of components like advanced glycation end products, proteins and amyloids.[18-21]
5. Alterations in neuroendocrine systems along with activation of sympathetic nervous systems.[22-24]
6. Deterioration of structure and function of cells of all tissues and organs with loss of post mitotic cells which leads to decrease in the number of neurons and mast cells.[25]

Ageing is primarily found to be caused due to the free radicals present in the body which are known as reactive oxygen species (ROS).

Through different studies, various mechanisms have been found for skin ageing and age related skin changes which include oxidative stress theory of free radicals, mitochondrial dysfunction, telomere shortening and UV radiation. Also, there are various other mechanisms that are taken together or alone which may or may not accelerate the changes in skin.[26-28]

Oxidative stress is considered to be a very important mechanism in the management of skin ageing. As per the free radical theory of ageing, molecular activity takes place due to the free radicles which are formed during the lifetime of a person.These free radicals are mainly the free oxygen radicals present in the body formed during aerobic metabolism. Thus in this situation ROS level rises and antioxidant activity declines. Mitochondria also play an important role and if there is any accumulation of mutations in mitochondrial DNA, then there is an imbalance in the expression of antioxidant enzymes leading to over production of ROS. Shortening of DNA telomerase is another cause for skin ageing. Additionally, there can be some premature ageing syndromes as well as nutritional factors responsible for ageing.[29]

Senescence is yet another mechanism causing skin ageing and it is called as 'biological ageing'. It involves gradual deterioration of functional characteristics of many life forms and can cause both cellular as well as whole organism senescence. The study of biological aging is known as Biogerontology. However, it's not the primary cause of skin ageing and it depends on conditions like oxidative deterioration, genetic makeup and lifestyle.[30]

Types of Niosomes

1. Multi lamellar vesicles (MLV)

It consists of a number of bilayer surrounding the aqueous lipid compartment individually. The approximate size of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes. These vesicles are highly suited as drug carrier for lipophilic compounds.[31-32]

2. Large uni lamellar vesicles (LUV)

Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very inexpensive use of membrane lipids.[32]

3. Small unilamellar vesicles (SUV)

These small unilamellar vesicles are generally prepared from multilamellar vesicles by sonication technique, French press extrusion electrostatic stabilization is the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.[32]

Advantages

Niosomes used first by L'Oreal in cosmetics, they have following advantages

- The vesicle suspension being water based so it offers a greater patient compliance over oil based systems.
- Since the structure of the niosome offers place to accommodate hydrophilic, lipophilic as well as amphiphilic drug moieties, they can be used for a variety of drugs.
- The characteristics such as size, lamellarity etc. of the vesicle can be varied depending on the requirement.
- The vesicle act as depot to release the drug slowly and offers a controlled release.[33,34]

Other advantages of Niosomes are

- Osmotically active and stable.
- Increase the stability of the entrapped drug.
- Do not require any special conditions for the handling and storage of surfactants.
- It can increase the oral bioavailability of drugs.
- It can enhance the skin penetration of drugs.
- They have used for oral, parenteral as well as topical.
- The surfactants are biodegradable, biocompatible, and non-immunogenic.
- It can be improve the therapeutic performance of the drug by protecting it from the biological environment and restricting effects to target cells, thereby reducing the clearance of the drug.
- The niosomal dispersions in an aqueous phase can be emulsified in a non-aqueous phase to control the release rate of the drug and administer normal vesicles in external non-aqueous phase.[33,34]

Method of Preparation of Niosomes: The methods of development should be selected according to the make use of the niosomes, because the development methods influence the number of bilayers, size, size distribution, and entrapment efficiency of the aqueous phase and membrane permeability of the vesicles.

A. Ether injection method: The ether injection method provides a means of building niosomes by gradually introducing a solution of surfactant dissolved in diethyl ether into hot water at 60°C. The surfactants mixture is injected in ether through 16-gauge needle into an aqueous solution of material. Vaporization of ether takes place which leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm.[31]

B. Hand shaking method (Thin film hydration technique)

In the hand shaking methodthe mixture of surfactant and cholesterol are dissolved in volatile organic solvent (diethyl ether, chloroform or methanol) in a RBF (round bottom flask). The organic solvent is removed at room temperature (20°C) by using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the RBF. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This procedure forms typical multilamellar niosomes.

C. Sonication: The sonication method is a typical method for the preparation of vesicles by sonication of solution as described by Cable. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is sonicated at 60°C for 3 minutes using a probe sonicator with a titanium probe to produce small and uniform size of niosomes.[31]

D. Micro fluidization

This is recent technique used for the development of uni-lamellar vesicles of defined size. 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.[31]

E. Multiple membrane extrusion method

In this method the mixture of surfactants, cholesterol and dicetyl phosphate in chloroform is prepared into thin film by evaporation. The film is hydrated with aqueous drug polycarbonate membranes, solution and the resulting suspension is extruded through which are placed in series for upto 8 passages. It is a good method for controlling niosomes size.[32]

F. Reverse Phase Evaporation Technique (REV)

Cholesterol and surfactant (1:1) both are dissolved in a combined mixture of ether and chloroform. An aqueous phase phosphate buffer solution containing drug is added and the resulting two phases are sonicated at 50°C for 5

minutes. The clear gel formed which is further sonicated after the addition of a small amount of phosphate buffer saline (PBS). The organic phase is removed at 40°C under low pressure using a rotary vaccume evaporator until the thin film was formed inside the flask. The resulting film was hydrated with PBS and heated on a water bath at 60°C for 10 min to yield niosomes.[31,32]
Raja Naresh et al. prepare the niosomes of Diclofenac Sodium by using Tween 85 with this method.

G. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading technique)
Surfactant and cholesterol both are dissolved in chloroform in 1:1 ratio. The solvent is evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated by using 30 ml citric acid (pH 4.0) with the help of vortex mixing. The multi lamellar 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 raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes.[32]

H. The "Bubble" Method: It is fresh technique for the one step preparation of liposomes and niosomes without use of organic solvents. The bubbling unit made up of RBF with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is placed in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant both are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and instantly afterwards "bubbled" at 70°C using nitrogen gas.[31]

Charactrization of Niosomes: The characterization of niosome is necessary for the clinical applications. Characterization parameters have a direct impression on the stability of niosomes and a significant outcome on their *in vivo* performance. Therefore these parameters such as morphology, size, polydispersity index (PI), number of lamellae, zeta potential, encapsulation efficiency, and stability must be evaluated.

- **Size and Morphology**

Dynamic light scattering (DLS)[35], scanning electron microscopy (SEM)[36], transmission electron microscopy (TEM)[37], freeze fracture replicationelectron microscopy (FF-TEM)], and cryotransmission electron microscopy (cryo-TEM) are the most used methods for the determination of niosomes size andmorphology. 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.[36] The microscopic approaches are generally used to characterize the morphology of the niosomes.

- **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 −58.4mV are sufficiently high for electrostatic stabilization of niosomes.[38]

- **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.[39] Membrane rigidity of niosomal formulations can be measured by means of the mobility of fluorescence probe as a function of temperature. 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 niosomalmembrane is determined by fluorescence polarization. High fluorescence polarization means high microviscosity of the membrane.[40] Moreover, the bilayer thickness can be characterized using the latter method, together with the *insitu*energy-dispersive X-ray diffraction (EDXD).[41]

- **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, dialysis, or gel chromatography.[42] 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% Triton X-100 or methanol to niosomal suspension. The loaded and free drug concentration can be determined by a spectrophotometer[43] or high-performance liquid chromatography (HPLC).[44]

- **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.[42,45,46]

- **In Vitro Release**

One often applied method to study *in vitro* release is based on using of dialysis tubing. A dialysisbag is washed and soaked in distilled water. After 30mins, the drug loaded niosomal suspension is transferred, into thisbag. The bag containing the vesicles is immersed in

buffersolution with constant shaking at 25ºC or 37ºC. At specifictime intervals, samples were removed from the outer buffer (release medium) and replaced with the same volume of freshbuffer. The samples are analyzed for the drug content by anappropriate assay method.[36]

Applications of Niosomes[47,48]

The application of niosomes technology is widely varied and can be used to treat a number of diseases. The following are a few uses of niosomes which are either proven or under research.

- It is used as Drug Targeting.
- It is used as Anti-neoplastic Treatment i.e. Cancer Disease.
- It is used as Leishmaniasis i.e. Dermal and Mucocutaneous infections e.g. Sodium stibogluconate.
- It is used act as Delivery of Peptide Drugs.
- It is used in Studying Immune Response.
- Niosomes as Carriers for Hemoglobin.
- Transdermal Drug Delivery Systems Utilizing Niosomes
- It is used in Ophthalmic drug delivery

Other Applications: Niosomes can also be utilized for sustained drug release and localized drug action to greatly increase the safety and efficacy of many drugs. Toxic drugs which need higher doses can possibly be delivered safely using niosomal encapsulation.

Marketed Formulation

Lancôme has come out in the market with a variety of anti-ageing property which is based on niosomes formulations. L'Oreal is also conducting research on many cosmetic products.Niosomes Preparation present in the Market is –**Lancôme.**

CONCLUSION

Niosomes are the capable dermal drug delivery system with extraordinary advantages like good permeation, cost effective, extra stable, and comparatively non-toxic. Therefore, niosomes have demonstrated to be new creation drug delivery systems behind liposomes. Niosomal preparation techniques along with variety of excellent non-ionic surfactant, cholesterol content and character of incorporated drug can show to be a prospective consideration in the field of cosmeceuticals which help in the treatment of skin ageing and wrinkles.

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