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PROGRESS IN THE FIELD OF NIOSOMES AS NOVEL DRUG DELIVERY SYSTEM

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Abstract:

Niosomes are novel drug delivery system that are having bilayer in structure and these vesicles are obtained during hydration of synthetic non-ionic surfactants, with the incorporation of cholesterol or their lipids. These vesicles present convenient, prolonged, targeted and effective drug delivery system with the ability of loading both hydrophilic and lipophilic drugs. The hydrophilic drugs are entrapped into aqueous core while the lipophilic drugs into the lipid membrane. Their potential can be enhanced by the use of novel preparations, loading and modification methods. This article reviews the current deepening and widening of interest of niosomes.

Keywords: *Introduction, Method of preparation, Marketed formulation, Patent citations, Opportunities and Challenges.*

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INTRODUCTION:

The self-assembled colloidal vesicles such as niosomes are bilayer in structure that are obtained during hydration of synthetic non-ionic surfactants, with the incorporation of cholesterol or their lipids that are utilized to capture both the hydrophilic and lipophilic drug molecules. The hydrophilic drugs are entrapped into aqueous core while the lipophilic drugs are entrapped into the lipid membrane.

Paul Ehrlich 1909, developed a unique delivery system i.e. targeted drug delivery system. This system may target the drugs directly to diseased cell.[1,2].

Vanlerbeghe *et al.* 1972 first reported that the niosomes are preferable in cosmetic industry due to its lots of advantages. Handjanivila *et al.*1979, reported that the mixture of cholesterol and single alkyl chain during hydration resulted to form niosomes. The first preparation of noisome vesicles came from the cosmetic formulation devised by L'Oreal. Niosomes are the vesicles that act like a drug depots/reservoir in the body and release the drug in a controlled manner through its bilayer that provides sustained release in body.

It can be used as a carrier for those drugs which have poor bioavailability or absorption. It improves bioavailability by crossing the barriers of gastrointestinal tract via transcytosis process and give safety to the drug from biological environment and restricting effects to target cell.

The stability of vesicles can be affected by the type of surfactant, nature of drug to be incapsulated, storage conditions such as temperature, addition of detergents, use of membrane lipids, interfacial polymerization of surfactant monomers *in-situ*, inclusion of charged molecules.[3-5].

Although noisome vesicles have shown advantages such as cheap and chemically stable, but these vesicles are associated with several problems related to physical stability such as fusion, aggregation, sedimentation and leakage on storage.[6]

Novel drug delivery system

A novel drug delivery system is a system that helps to maintain the concentration of drug in therapeutically effective range. Some drugs exhibit their maximum effect within an optimum concentration range. Either no therapeutic activity is produced by the drug below this optimum concentration or toxicity is produced above this concentration.[7]

Structure of niosomes

Structurally, niosomes are made up of a bilayer that is composed of non-ionic surface active agents, as in fig. 1. A typical niosomes consists of non-ionic surfactant, cholesterol and a small amount of diacetyl phosphate are used to stabilize the vesicle.[8,9].

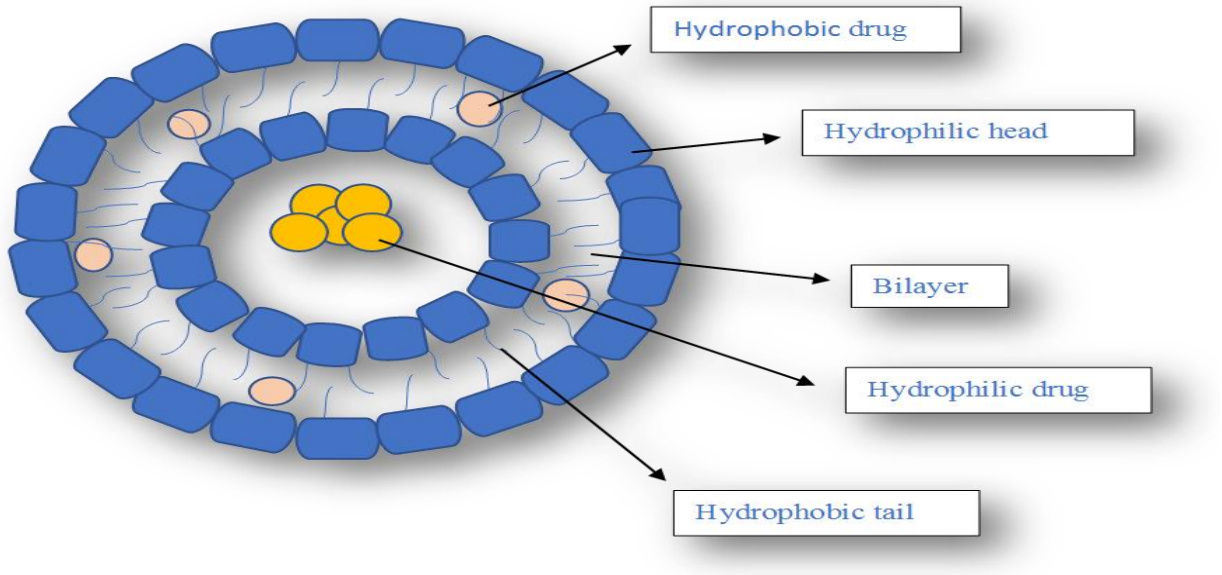

Fig. 1: Structure of a noisome[9]

COMPONENTS OF NIOSOMES

1. Non-ionic surfactant

Non-ionic surfactants are the major components of niosomal formulation. The vesicle size of niosomes is dependent on the HLB values of surfactant. Various types of non-ionic surfactants used in niosomal formulation are fatty alcohol, ethers, esters and block co-polymers etc.[10] Some researchers use Tweens as non-ionic surfactants in niosomes formation. Tweens used in niosomal preparations are Tween 20, Tween 40, and Tween 60.These are also known as polysorbates that derived from PEGylated sorbitan which are esterified with fatty acids.[11]

Other non-ionic surfactants are polyoxyethylene alkyl ethers (CnEOm, Brij TM). The different grades of Brij are Brij 30, 35, 52, 58, 72, 76, 92, and 97.[12].

2. Cholesterol

It is a waxy steroid metabolite that is found in cell membrane. It effects the physical properties as well as the structure of niosomes by interacting with non-ionic surfactants.[13] It provides membrane stabilization and prevents the leakage of the membrane. It also enhances entrapment efficiency.[14]

3. Other additives

Charged molecules are used to stabilize the niosomes. Negatively charged molecules such as Dicetyl phosphate (DCP) and phosphatidic acid and positively charged molecules such as stearyl amine and cetylpyridinium chloride are used to prevent aggregation of niosomes. Charged molecules are used in low concentration i.e. 2.5-5 mol%. Their high concentration could inhibit niosomes formation. Charged molecules can also be useful for an increase of drug encapsulation efficiency, for skin permeation enhancement and for hybrid niosomal complex formation.[15]

Advantages of niosomes

1. Niosomes are the vesicles that shows chemical stability and have longer storage time.
2. Niosomes are biocompatible and show low toxicity because of their non-ionic nature.
3. Niosomes improve therapeutic effect of the drug molecules by protecting them from biological environment that results in better availability and controlled drug delivery by restricting the effect of drug to target cells and delay the clearance of drug.
4. They increase oral bioavailability and skin penetration of drugs.
5. Niosomes are vesicle suspensions made up of water based vehicle that offers high patient compliance when compared with oily dosage forms.
6. Niosomes accommodate drug molecules having a wide range of solubility because of their unique infrastructure consists hydrophobic, amphiphilic and hydrophilic moieties.
7. Vesicles formulation have variable and controllable characteristics.
8. Niosomes as immunological adjuvent.
9. Niosomes act as contrasting agent in MRI imaging.
10. Their handling and storage requires no any special precautions and conditions because phospholipids are not used in formulation.
11. Niosomes exhibits flexibility in their structural characteristics.[16,17]

Table 1: Comparison between niosomes, transfersomes and ethosomes[18]

S.No.	Characters	Niosomes	Transferosomes	Ethosomes
1.	Vesicles	Bilayer	2nd generation elastic lipid vesicle carriers	3rd generation elastic lipid vesicle carrier
2.	Composition	Non-ionic surfactant of alkyl or dialkyl polyglcerol ether class and cholesterol	Phospholipids and edge activator	Phospholipids and Ethanol
3.	Characteristics	Vesicular formulations	Ultraflexible liposomes	Elastic Liposomes
4.	Flexibility	Rigid in nature	High deformability due to surfactant	High deformability and elasticity due to ethanol
5.	Permeation Mechanism	Diffusion/ Fusion/ Lipolysis	Deformation of vesicle	Lipid Perturbation
6.	Route of administration	Oral, Parenteral, Topical and Transdermal	Topical and Transdermal	Topical and Transdermal
7.	Marketed products	Lancome, L' Oreal	Transferosomes®	Nanominox

METHOD OF PREPARATION OF NIOSOMES

On the basis of desired size of the vesicles niosomes are prepared by different methods.

1. Preparation of Small Unilamellar Vesicles

a. Micro fluidization
b. Sonication

a. Micro fluidization

Microfluidization is a recent technique used to prepare small unilamellar vesicles of uniform size. This technique is based on the submerged jet principle. According to this, two fluidized streams get interact at ultrahigh velocities with help of microfluidizer, in precisely defined micro channels within interaction chamber. Energy is supplied to the system that remains within the area where niosomes is formed. Impingement of thin layer of Liquid in micro channels is arranged in such a way that the energy supplied to system causes the formation of uniform, smaller size and better reproducibility of niosomes.[19]

b. Sonication

In this method the mixture of drug solution in buffer is added into surfactant/cholesterol mixture in a 10 ml glass vials. Then the mixture is sonicated at 60º C for 3 min. using titanium probe sonicator to yield niosomes. Sonication method has been widely used for the preparation of diallyl disulfide (DADS) loaded niosomes.[20-22]

2. Preparation of Multilamellar Vesicles

a. Thin film hydration technique (Hand shaking method)
b. Trans-membrane pH gradient (inside acidic) drug uptake process (remote loading)

a. Thin film hydration technique (Hand shaking method)

Surfactants, cholesterol and other additives are dissolved in a volatile organic solvent such as chloroform and ethanol in a round bottom flask. Organic solvent is removed by using a rotary evaporator to form a thin film inside the wall of the flask. Then the completely dried film of solid mixture was directly hydrated with aqueous solution containing drug for about 1 h with gentle agitation to form niosomal dispersion with a milky appearance. This method used for preparation of niosomes entrapped morin hydrate (MH), diclofenac sodium (DCS), luteinizing hormone releasing Hormone (LHRH), adriamycin, flurbiprofen etc.[23,24]

b. Trans-membrane pH gradient (inside acidic) drug uptake process (remote loading)

In this method surfactants and cholesterol are dissolved in organic solvent. A thin film on the wall of the round bottom flask is formed after complete evaporation of solvent under the reduced pressure. The resulted film is hydrate with citric acid solution by vortex mixer. Thus, multilamellar vesicles are

formed. Then frozen it and thawed it several times and sonicate them. After that add aqueous solution containing 10 mg/ml of drug into the niosomal suspension and vortex it. pH of sample is increased 7.0-7.2 with 1M disodium phosphate. Later this mixture is heated at 60°C for 10 minutes to produce desired multilamellar vesicles.[25,26]

3. Preparation of Large Unilamellar Vesicles

a. Reverse phase evaporation technique (REV)
b. Solvent injection method

a. Reverse phase evaporation technique (REV)

Dissolve cholesterol and surfactant (1:1) in a mixture of ether and chloroform. Drug is dissolved in an aqueous phase and is added to this. Sonication of the resulting two phases is done at 4- 5°C. The clear gel formed which is further sonicated after addition of small quantity of phosphate buffered saline (PBS). Under low pressure the organic phase is removed at 40°C. The resulting viscous niosomes suspension is diluted with PBS. Heated it on a water bath at 60°C for 10 min to yield niosomes.[27]

b. Solvent injection method

Firstly the surfactant is dissolved in diethyl ether or other volatile solvents. The niosomes are prepared by slowly introducing surfactant solution into warm water maintained at constant temperature 60°C. Then the surfactant mixture is injected through 14-gauge needle into aqueous solution. Ether get vaporized that leads to formation of single layered vesicles. The diameter of vesicle may ranges from 50-1000 nm.[28,29]

4. Miscellaneous Methods

a. Multiple membrane extrusion method
b. Emulsion method
c. Lipid injection method
d. Bubble method
e. Formation of Niosomes from Proniosomes

a. Multiple membrane extrusion method

This method involves the production of multi lamellar vesicles as well as large unilamellar vesicles. In membrane extrusion method, the surfactant, cholesterol and dicetyl phosphate mixture in chloroform forms a thin film by evaporation. Hydration of thin film is performed with aqueous drug polycarbonate membrane solution and the resultant suspension is extruded through membrane filter. This method is used for controlling noisome size.[30]

b. Emulsion method

The oil in water (o/w) emulsion is prepared by this method. An organic solution of surfactant and

cholesterol, and an aqueous solution of drug is used for formation of o/w emulsion. Then organic solvent is evaporated that leaves niosomes dispersed in the aqueous phase.

c. Lipid injection method

In this method, surfactant and cholesterol is dissolved into organic solvent and is then injected into the agitated aqueous phase containing the drug in dissolved form. Heat the aqueous phase at 60-70°C that may leads to complete evaporation of organic solvent and the niosomes are formed.[31,32]

d. Bubble method

It is a novel one step preparation method that does not involves the use of any organic solvent. The bubbling unit consists of three neck round-bottomed flask positioned in water bath to control the temperature. Water-cooled reflux is positioned in first neck, the thermometer is position in second neck and supply of nitrogen is done through third neck. The cholesterol and surfactant are dispersed into buffer having pH 7.4 at 70°C. The resulted dispersion is then mixed for 15 seconds with the help of high shear homogenizer and immediately "bubbled" it at 70°C by using nitrogen gas.[33]

e. Formation of Niosomes from Proniosomes

This method involves the coating of a water-soluble carrier such as sorbitol with surfactant. It forms a dry formulation in which each water-soluble particle is covered with surfactant that forms a dry coat on the particle. This preparation is known as "Proniosomes". The niosomes can be detected by addition of aqueous phase at T > Tm and brief agitation.

T = Temperature

Tm = Mean phase transition temperature.[34]

CHARACTERIZATION OF NIOSOMES

1.Measurement of vesicle size

The vesicle dispersion of niosomes were diluted about 100 times with the phosphate buffer solution. Measured the vesicle size on a particle size analyzer (Laser diffraction particle size analyzer, Sympatec, Germany). All measurements were conducted at 25ºC.[35]

2.Transmission Electron Microscopy

Place a drop of the niosomal colloidal suspension onto a carbon coated grid and left it for 1 min thus allowing niosomes to adhere to the grid. The excess niosomal suspension is then drawn off by a piece of filter paper. A drop of negative stain solution, 1% (w/v) phosphotungstic acid solution, is then placed on the carbon copper grid and stain it. After 3 min, remove the excess staining agent with the tip of a filter. Allow it for air dry and examined using a transmission electron microscope.[36]

3.Optical Microscopy

The prepared niosomal vesicles are characterized for morphology, i.e., shape uniformity and lamellarity employing phase contrast microscope.[37]

4.Entrapment efficiency

Entrapment efficiency of niosomal dispersion is done by the separation of the unentrapped drug by dialysis, centrifugation or gel filtration. The drug that remain entrapped in niosomes is analyzed by spectrophotometrically. Where,

Percentage entrapment = total drug –diffused drug / total drug*100

5.Osmotic shock

Any change in vesicle size can be determined by osmotic studies. Niosomes dispersion was incubated with hypotonic, isotonic, hypertonic solutions for 3 hours. Then changes in the size of vesicles are viewed under optical microscopy.[38]

6.Zeta potential analysis

Zeta potential analysis is used for determining the colloidal properties of the prepared formulations. The niosomes that can be derived from the proniosomal dispersion is determined by using zeta potential analyzer that is based on the electrophoretic light scattering and laser Doppler velocimetry method. Adjust the temperature at 25°C. Any charge on vesicles and their mean zeta potential values can be obtained directly from the measurement.[39]

Table 2: Marketed Formulations[40]

S.No	Brand	Name Of The Product
1.	Lancome - Foundation & Complexion	Flash Retouch Brush on Concealer
2.	Britney Spears – Curious	Curious Coffret: Edp Spray 100ml+ Dualended Parfum & Pink Lipgloss+ Body Souffle 100 ml
3.	Loris Azzaro – Chrome	Chrome Eau De Toilette Spray 200ml
4.	Helena Rubinstein - HR - Golden Beauty - Body Care	Golden Beauty After Sun Soothing Moisturizer 150ml
5.	Givenchy – Amarige	Amarige Eau De Toilette Spray 100ml
6.	Estee Lauder - Beyond Paradise	Beyond Paradise After Shave Lotion 100ml
7.	Orlane - Lipcolor & Lipstick	Lip Gloss
8.	Liz Claiborne – Realities	Realities Shower Gel 200ml
9.	White Shoulders	White Shoulders Eau De Cologne Spray 130ml
10.	Jean Paul Gaultier - Le Classique	Le Classique Eau De Toilette Spray 100ml
11.	Hugo Boss - Boss Soul	Boss Soul After Shave 90ml
12.	Lancaster - Suractif - Night Care	Suractif Non Stop Lifting Advanced Night Cream 50ml
13.	Givenchy - Blanc Parfait - Day Care	Blanc Parfait W4-L Universal Brightening Spots Corrector SPF 45 1.6ml

Table 3: Patent Citations[41]

S. No.	Cited Patent	Applicant	Title
1.	US5741515	Bayer Aktiengesellschaft	Ketoprofen liposomes
2.	US20402482940	L'oreal, S.A.	Reconstructed epidermis/skin equivalent comprising a ceramide 7 and /or 5.5 and lipid lamellar vesicular compositions comprising ceramide 7 and/or 5.5 compounds
3.	FR2571963B1	Oreal	Composition for cosmetic or pharmaceutical use containing niosomes and at least one water soluble polyamide and method of preparing this composition.
4.	FR2756177B1	Oreal	aqueous dispersion of vesicles resistant to dehydration
5.	GB9706195D0	Univ London Pharmacy	Particulate drug carriers
6.	US6537246B1	Imarx Therapeutics, Inc.	Oxygen delivery agents and uses for the same
7.	US6309664B1	Igen, Incorporated	Methods, uses and compositions of fluid petrolatum

OPPORTUNITIES AND CHALLENGES

With an increase in drug resistance that is observed in most infectious diseases as well as some forms of cancer, and with the chances of development of new drug molecules to address this issue looking bleak, one of the most plausible ways to disease treatment is combination therapy. Combination therapy would ensure delay in drug resistance, if utilized rationally. However, the biggest difficulty in employing combination therapy are adverse effects due to potential drug-drug interactions and patient compliance due to multiple routes of administration or multiple dosing that may be required. To overcome these issues, researchers have utilized nanoparticle-based systems that can hold multiple drugs in a single carrier. There are several nanocarrier systems available for such purposes. The non-ionic surfactant-based vesicles (niosomes) are suitable for delivery of multiple therapeutic agents. Niosomes are artificially prepared drug delivery carriers. They are structurally similar to liposomes albeit more stable than them.[42]

CONCLUSION:

Niosomes are promising drug carrier for controlled drug delivery to the target area. These vesicles present convenient, prolonged, targeted and effective drug delivery system with the ability of loading both hydrophilic and lipophilic drugs. Their potential can be enhanced by the use of novel preparations, loading and modification methods. Niosomes are non-toxic, stable and offer successful drug localization into skin. These vesicular carriers protect the physical and chemical instability of active drug. The ionic nature of drug carriers are relatively toxic and unsuitable whereas on other hand niosomal carriers are safe and their handling and requires no special conditions during handling and storage. Among the all of these advantages there are still some challenges in this area. The type of surfactant used is main parameter because it affects the formation, toxicity and stability of the vesicles. So that's why the researchers should be more alert in selection of suitable surfactant for preparation of niosomes. 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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