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NIOSOMES: PRESENT SCENARIO AND FUTURE ASPECTS

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ABSTRACT

Drug targeting is a kind of phenomenon in which drug gets distributed in the body in such a manner that the drug interacts with the target tissue at a cellular or subcellular level to achieve a desired therapeutic response at a desire site without undesirable interactions at other sites. This can be achieved by modern methods of targeting the drug delivery system such as niosomes. Niosomes are the type of non-ionic surfactant vesicles, which are biodegradable, non-toxic, more stable and inexpensive, a new approach to liposomes. Their structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes. The niosomes have the tendency to load different type of drugs. This review article represents the structure of niosome, advantages, disadvantages, the methods for niosome preparation and characterization of pharmaceutical NSVs.

Keywords: Niosome, Cholesterol, Hydrophilic and Lipophilic drugs, Surfactant, Targeted delivery Bioavailability Improvement, Factors, Applications.

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INTRODUCTION

Drug targeting can be defined as the ability to direct a therapeutic agent at the desired site of action with little or no interaction with other tissue. Controlled drug delivery system is designed to obtain a desirable drug release profile for a longer period of time. There are various techniques to obtain controlled release system, one of them is niosomes. Niosomes are non-ionic surfactant vesicles with microscopic lamellar bilayer structure formed by self association of hydrated surfactant monomers. The multilamellar or unilamellar structure of niosomes is formed by mixing non-ionic surfactant, cholesterol and diethyl ether along with subsequent hydration in aqueous media [1].

Niosomes are microscopic lamellar structures of the size range between 10 to1000 nm. The niosome consists of non-immunogenic, biodegradable and biocompatible surfactants. Niosomes are better than liposomes and its higher chemical stability of surfactants than phospholipids which are easily hydrolyzed due to the ester bond and cost effective[2].

The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic response may offer several advantages are-

1) Higher patient compliance in comparison with oily dosage forms.

2) The vesicles may act as a depot, releasing the drug in a controlled manner.

3) Accommodate drug molecules with a wide range of solubilities [3].

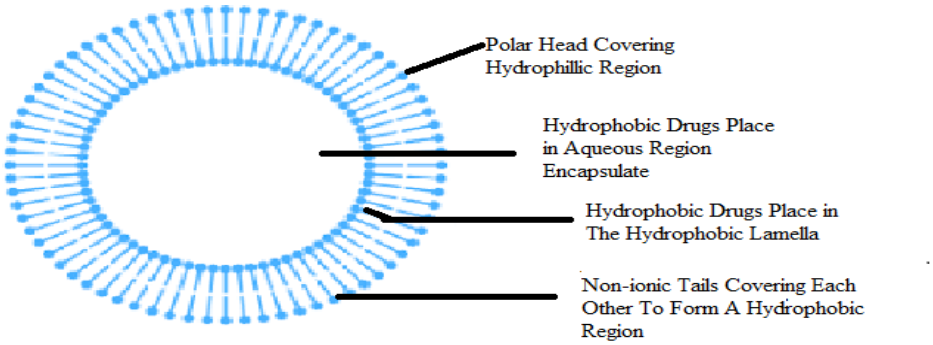

Figure 1: Structure of Niosome

COMPOSITION OF NIOSOMES- (Gayatri et al., 2000)

Two components use in niosome preparation are

- ✓ Cholesterol
- ✓ Non-ionic surfactants

A. Cholesterol is a steroid derivative, which is used to provide rigidity and proper shape, conformation to niosome form.

B. Non-ionic Surfactants are generally used for the preparation of niosomes.

Examples: **a.** Tweens (20, 40, 60, 80)

b. Spans (Span 60, 40, 20, 85, 80)

c. Brijs (Brij 30, 35, 52, 58, 72, 76).

DIFFERENT TYPES OF NON-IONIC SURFACTANTS

Table 1: Different Types of Non-Ionic Surfactants

Type of Non-Ionic Surfactant	Examples
Fatty alcohol	Cetyl alcohol, stearyl alcohol, cetostearylalcohol, oleyl alcohol
Ethers	Brij, Decyl glucoside, Lauryl glucoside, Octyl glucoside, Triton X-100, Nonoxynol-9
Esters	Glyceryl laurate, Polysorbates, Spans
Block copolymers	Poloxamers

TYPES OF NIOSOMES

The various types of niosomes are as:

i) Multi lamellar vesicles (MLV),

ii) Large unilamellar vesicles (LUV),

iii) Small unilamellar vesicles (SUV).

Table 2: Types of Niosomes

Parameters	Multi lamellar Vesicles	Small Unilamellar Vesicles	Large Unilamellar Vesicles
Vesicle Size	Greater than 0.05µm	0.025 – 0.05µm	Greater than 0.10µm
Method of Preparation	Hand Shaking Method	Sonication Extrusion Method Solvent Dilution Technique	Reverse Phase evaporation Method

ADVANTAGES

1. Niosome can accommodate a variety of drug moieties such as hydrophilic, lipophilic, as well as ampiphilic drugs.
2. Vesicle characteristics can be controlled by altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration.
3. The drug can release in the sustained/controlled manner.
4. No special conditions required for handling and storage of surfactants.
5. Due to the depot formulation, it allows controlled release of the drug.
6. Poorly soluble drugs have increased oral bioavailability.
7. Surfactants posses following response biodegradable, biocompatible, non-toxic and non-immunogenic.

8. They can protect the active moiety from biological circulation.
9. Drug protection from enzyme metabolism.
10. Improve the stability of entrapped drug.
11. They can enhance the permeation of drugs through the skin.
12. They improve the therapeutic profile of the drug molecules due to delayed clearance from the circulation [4,5].

DISADVANTAGES [6]

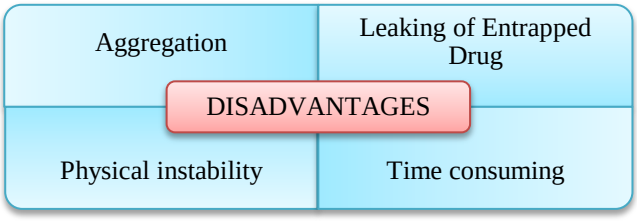

Figure 2: Disadvantages of niosomes

Table 3: Comparison between Niosomes and Liposomes[7]

LIPOSOMES	NIOSOMES
More Expensive	Less Expensive
Require special methods for storage and handling of the final formulation.	No special methods require for such formulations.
Phospholipids may be neutral and charged.	Non-ionic surfactant is uncharged.

FORMULATION AND EVALUATION OF NIOSOMES

Method of preparation

A. Passive Trapping Techniques - This category includes most of the techniques used in preparation of niosomes in which drug is incorporated during the preparation of niosomes i.e. during their formation.

1. Sonication - Mixture of drug solution in the buffer, surfactant and cholesterol

↓

Sonicated with a titanium probe sonicator at 60°C for 3 minutes to yield niosomes [8.]

2. Ether Injection Method –

Niosomes by slowly introduce in a solution of surfactant dissolve in diethyl ether into warm water maintain at 60°C

↓

Mixture in ether is injected through 14-gauge needle into an aqueous solution of material

↓

Vaporization of ether leads to the formation of the single layer vesicles

↓

Diameter of the vesicle range from 50 to 1000 nm depends upon the conditions use [9,10].

3. Reverse Phase Evaporation Technique - Cholesterol and surfactant (ratio of 1:1) dissolves in the mixture of organic solvent (ether and chloroform). Addition of the aqueous drug solution to this and water in oil emulsion is formed; two phases are sonicated at 4-5ºC. The emulsion is dried in a rotary evaporator at 40°C to form a semisolid gel of large vesicles. Small amounts of phosphate buffered saline (PBS) are added to the clear gel and sonicate again. The organic phase is removed at 40ºC and lower pressure. Viscous niosomal suspension is further diluted with phosphate buffered saline, then heat on a water bath at 60ºC for 10 min to form niosomes [11.]

4. The "Bubble" Method

Bubbling unit involves round-bottomed flask with three neck position in water bath to control the temperature

↓

Water-cool reflux is positioned in the first neck and thermometer is positioned in the second neck and nitrogen supply through the third neck

↓

Cholesterol and surfactant are dispersed in the buffer (pH 7.4) at 70°C

Dispersion mixing for 15 seconds with high shear homogenizer

↓

"Bubbled" at 70°C using nitrogen gas [12].

5. Hand Shaking Method (Thin Film Hydration Technique/Rotary Evaporator) –

The mixing ingredients - surfactant and cholesterol and charge inducer

↓

Dissolves in a volatile organic solvent (chloroform, diethyl ether or methanol) in a round bottom flask

↓

By using a rotary evaporator organic solvent is evaporated at room temperature 20°C

↓

Forming a thin layer of solid mixture

↓

The dry surfactant film can be re-hydrated with an aqueous phase at 0-60°C with gentle agitation

↓

Formation of niosomes [13].

6. Multiple Membrane Extrusion Method -Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform forms thin film by rotary evaporator. The film hydrates with aqueous drug polycarbonate membranes. Solution and resultant suspension extrude through polycarbonate membrane and placed in series for up to 8 passages. It is a good method for niosome size control [14.]

7. Ethanol Injection Method

An ethanol solution of surfactant is injected rapidly through a fine needle

↓

Into excess of saline or other aqueous medium

↓

Vaporization of ethanol

↓

Formation of vesicles [15.]

8. Micro Fluidization – In this technique the principle involves is submerged jet principle in which two fluidized streams interact with each other at ultra high velocities and in the micro channels within the interaction chamber. Thin liquid sheet impingements along with common front are arranged such as that the energy supplies remain same within the area of niosomes formation, formation of niosomal vesicles of greater uniformity, smaller size and better reproducibility [16.]

B. Active Trapping Techniques - This includes the loading of the drug after the formation of niosomes. The niosomes are prepared and then the drug is load of maintaining a pH gradient or ion gradients to facilitate uptake of drug into niosomes. Various advantages of noisome form are 100% entrapment, high drug lipid ratios, absence of leakage, cost effectiveness and suitability for labile drugs.

1. Trans Membrane pH Gradient Drug Uptake Process

In remote loading process surfactants and cholesterol are dissolved in organic solvent (chloroform)

↓

Solvent evaporates under reduced pressure to get a thin film on the wall of the round bottom flask

↓

Film hydrates with 300 mM citric acid (pH4.0) by vortex mixing

↓

Multilamellar vesicles are frozen and thawed 3 times and later sonication

↓

For niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortex

↓

Sample pH is raises to 7.0-7.2 with 1M disodium phosphate

↓

The mixture is later heated at 60°C for 10 minutes to yield niosomes [17].

C. Miscellanous Methods –

1. Emulsion Method: This is a simple method to form niosome in which oil in water (o/w) emulsion is prepared from an organic solution of surfactant, cholesterol, and an aqueous solution of the drug. Finally, the organic solvent is evaporated leaving niosomes dispersed in the aqueous phase [18].

2. Heating Method: This method is in one-step, scalable and non-toxic and also based on the patent procedure. A suitable aqueous medium such as buffer distilled water, etc. in which mixtures of non-ionic surfactants, cholesterol and/or charge inducing molecules are added in the presence of the polyol like as glycerol. The mixture is heated with (at low shear forces) until the vesicles were form [19].

3. Formation of Niosomes from Proniosomes: Proniosome is a dry formulation in which each water-soluble particle are covered with a thin film of dry surfactant. The niosomes are recognizing by the adding aqueous phase at T > Tm with brief agitation. T is the Temperature and Tm is the mean phase transition temperature [20].

Carrier + surfactant = proniosomes,

Proniosomes + water = niosomes.

4. Lipid Injection Method: This method does not require expensive organic phase. Mixture of lipids and surfactant is first melted and then injected into a highly agitate heated aqueous phase contains the dissolved drug. Drug dissolves in molten lipid and the mixture will be injected into agitate, heat aqueous phase containing surfactant.

FACTORS INFLUENCING NIOSOMAL FORMULATION:[21-25]

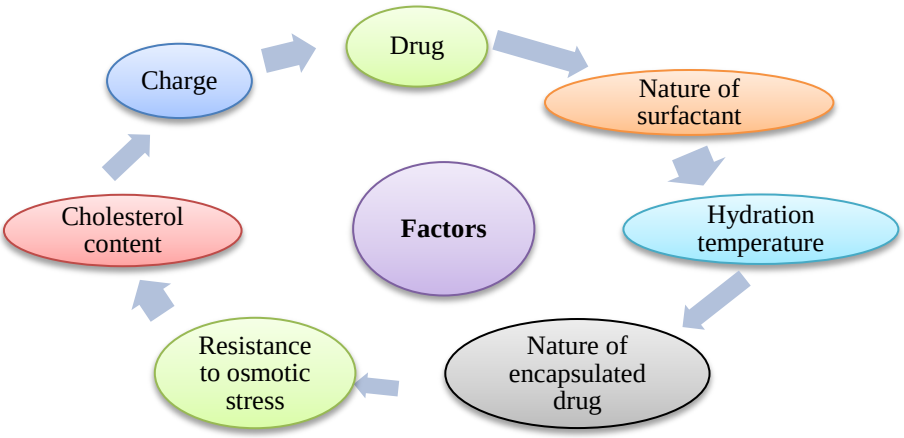

Figure 3: Factors Influencing Niosomal Formulation

1. Nature of Surfactant: Increase in the HLB value of surfactants leads to the increase in the mean size of niosomes due to the decrease in surface free energy with an increase in the surfactant hydrophobicity. The bilayers of the niosomes can exist either as a liquid state or in a gel state. It depends upon the temperature, type of surfactant and cholesterol. Alkyl chains are well ordered in the gel state, whereas disordered in the liquid state. Entrapment efficiency is affected by the gel, liquid phase transition temperature (TC) of the surfactant.

Eg: span 60 with higher TC exhibits better entrapment.

The HLB value of surfactants ranging between 14 and 17 are not suitable for niosomal preparations. Decrease in the HLB value of surfactants from 8.6 to 1.7 decreases the entrapment efficiency and highest entrapment efficiency is found with the HLB value of 8.6.

2. Nature of Encapsulated Drug: The charge and the rigidity of the niosomal bilayer are greatly influenced by physical chemical properties of the encapsulated drug. Entrapment of drug occurs by interacting with the surfactant head groups leading to the increasing charge and creates mutual repulsion of the surfactant bilayer and thus increases the vesicle size. The HLB of drug influences the degree of entrapment.

3. Hydration Temperature: The size and shape of the niosome are affected by the temperature of hydration. Hydration temperature should be above the gel, liquid phase transition temperature. Change in temperature affects the assembly of surfactants into vesicles and vesicle shape modification. Hydration time and volume of hydration medium also accounts for the modification. Improper selection of the hydration temperature, time and hydration medium volume produces fragile niosomes / drug leakage problems may arise.

4. Cholesterol Content: Incorporation of cholesterol increases the entrapment efficiency and hydro-dynamic diameter of niosomes. Cholesterol acts in two ways:

- Increases the chain order of liquid state bilayers.
- Decreases the chain order of gel state bilayers.

An increase in the cholesterol concentration causes an increase in the rigidity of the bilayers and decrease in the release rate of encapsulated material.

5. Charge: Presences of charge leads to an increase in inter lamellar distance between successive bilayers in multi lamellar vesicle structure and greater overall entrapped volume.

6. Resistance to Osmotic Stress: Addition of hypertonic solution causes reduction in vesicle diameter. In hypotonic solution, inhibition of eluting fluid from vesicles results in the slow release initially followed by the faster release due to the mechanical loosening of vesicle structure under osmotic stress.

SEPARATION OF UNENTRAPPED DRUG [26,27,28]

The removal of unentrapped solute from the vesicles can be accomplished by various techniques, which include: -

1) Dialysis: The aqueous niosomal dispersion is dialyzed in dialysis tubing against phosphate buffer or normal saline or glucose solution.

2) Gel Filtration: 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.

3) 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.

CHARACTERIZATION OF NIOSOMES [29-35]

1. Bilayer Rigidity and Homogeneity: The biodistribution and biodegradation of niosomes are influenced by rigidity of the bilayer. In homogeneity can occur both within niosome structures and between niosomes in dispersion and could be identified via. p-NMR, Differential scanning calorimetry (DSC) and Fourier transform-infra red spectroscopy (FT-IR) techniques.

2. Size and Shape: Various methods is used for the determination of mean diameter like as laser light scattering method besides it also determines by electron microscopy, molecular sieve chromatography, photon correlation microscopy, optical microscopy.

3. Stability Study: Niosomal formulations are subject to stability studies by storing at 4°C, 25°C and 37°C in thermostatic oven for the period of three months. After one month, drug content of all the formulations are checked by entrapping efficiency parameter.

4. *In-vitro* Release: In-vitro release rate study carried out by the use of

1. Dialysis Tubing,
2. Reverse dialysis and
3. Franz diffusion cell.

a. Dialysis Tubing: A dialysis sac is washed with distilled water. The prepared vesicle suspension is pipetted into a bag made up of the tubing dialysis and after that the bag is sealed. Then the bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C. At various time intervals, the buffer is an analysis of the drug content of an appropriate assay method.

b. Reverse Dialysis: A number of small dialysis as containing 1ml of dissolution medium is placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method and the rapid release cannot be quantified by using this method.

c. Franz Diffusion Cell: The in vitro diffusion studies can be performed by using Franz diffusion cell. Proniosomes is placed in the donor chamber of a Franz diffusion cell fitted with cellophane membrane. The proniosomes is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals and analyze for drug content using suitable method such as U.V spectroscopy, HPLC, etc. the maintenance of sink condition is essential.

5. Scanning Electron Microscopy: The niosomes were observed under a scanning electron microscope (SEM) (JSM 6100 JEOL, Tokyo, Japan). They were mounted directly onto the SEM sample stub using double sided sticking tape and coated with gold film of thickness of 200 nm under reduced pressure of 0.001 mmHg. Photographs were taken at suitable magnification.

6. Vesicle Charge: The vesicle surface charge can play an important role in the behavior of niosomes in vivo and in vitro. Charged niosomes are more stable against aggregation and fusion then unchanged vesicles. In order to obtain an estimate of the surface potential, the zeta potential of individual niosomes can be measured by microelectrophoresis. An alternative approach is the use of pH-sensitive fluorophores. More recently, dynamic light scattering have been used to measure the zeta potential of niosomes.

7. Niosomal Drug Loading and Encapsulation Efficiency : To determine drug loading and encapsulation efficiency, the niosomal aqueous suspension was ultracentrifuged, supernatant was removed and sediment was washed twice with distilled water in order to remove the adsorb drug.

- The niosomal recovery can be calculated as:

$$\% \text{ Recovery} = \frac{\text{amount of niosomes recovered}}{\text{amount of polymer} + \text{drug} + \text{excipients}} \times 100$$

- The entrapment efficiency (EE) was then calculated using formula:

$$\text{Entrapment Efficiency} = \frac{\text{amount of drug in niosomes}}{\text{amount of drug}} \times 100$$

- The drug loading was calculated as:

$$\text{Drug Loading } (\%) = 1 + \frac{\text{amount of drug in niosomes}}{\text{amount of niosome}} \times 100$$

NATURE OF DRUG AND ITS EFFECT ON STABILITY

Table 4: Nature of drug and its effect on stability

Nature of the Drug	Leakage from the Vesicles	Stability
Hydrophobic drug	Decreases	Increases
Hydrophobic drug	Increases	Decreases
Amphiphilic drug	Decreases	-
Macromolecules	Decreases	Increases

APPLICATIONS OF NIOSOMES [36-45]

The application of niosomal technology is widely varied and can be used to treat a number of diseases.

1. Niosomes as Drug Carriers - Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for X-ray imaging.

2. Targeting of Bioactive Agents

a. To Reticulo-Endothelial System (RES) - The cells of the RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in the treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of the liver.

b. To Organs, Other than RES - Carrier system can be directed to specific sites in the body by the 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 the direct carriers system to particular cells.

3. Anti-neoplastic Treatment - Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism prolong the circulation and half life of the drug, decreasing the side effects of the drugs. Niosomes decrease the rate of proliferation of tumor and higher plasma levels by slower elimination.

4. Leishmaniasis - Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Niosomes use in tests, conduct and shows that it was possible to administer higher levels of the drug without the triggering of the side effects, allows greater efficacy in the treatment.

5. Delivery of Peptide Drugs - Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in-vitro study conducts by oral delivery of a vasopressin entrap derivative in niosomes shows that entrapment of the drug increases the stability of the peptide.

6. Use in Studying Immune Response - Due to their immune system selection, low toxicity, greater stability niosomes are used to study the nature of the immune response provoke by antigens. Non-ionic surfactant vesicles have clearly demonstrated their ability to function as adjuvants as parenteral administration with a number of different antigens and peptides.

7. Cosmetics - The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L'Oreal. Niosomes develop and patent by L'Oréal in the 1970s and 80s. The first product 'Niosome' introduce in 1987 by Lancôme. Niosome advantage in cosmetic and skin care an application include their ability to increase the stability of entrapped drugs and also improves bioavailability of poorly absorb ingredients and enhances skin penetration.

8. Other Applications-

a) Sustained Release- Sustained release action of niosomes can be applied to drugs having a low therapeutic index and low water solubility then they maintains in the circulation via niosomal encapsulation.

b) Localized Drug Action- Approach of nisomal drug delivery is to achieve local drug action, since their size and low penetrability through the epithelium and connective tissue keeps the drug localized at the site of administration.

c) Niosome Formulation As A Brain Targeted Delivery System For The Vasoactive Intestinal Peptide (VIP)- Radio labelled (I125) VIP-load glucose bearing niosomes is injected intravenously to mice. Encapsulate VIP within glucose bearing niosomes exhibits higher VIP brain uptake as compared to control.

d) Niosomes As Carriers For Hemoglobin - Niosomes can be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum super-imposable to that of free hemoglobin. Vesicles are permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulate hemoglobin.

ROUTE OF APPLICATION OF NIOSOMAL DRUG

Table 5: Drugs used in Niosomal Delivery

Route of Administration	Examples of Drug
Nasal Route	Sumatriptan
Transdermal Route	Piroxicam, Nimesulide, Estradiol
Intravenous Route	Doxorubicin, Insulin, Rifampicin
Ocular Route	Cyclopentol

MARKETED FORMULATIONS OF NIOSOMES

Table 6: Marketed Formulations of Niosomes

S.No.	Brand	Name of the Product
1.	Lancome- Foundation and complexation	Flash Retouch Brush on Concealer
2.	Britney Spears – Curious	Curious Coffret: Edp Spray 100ml +Dualended Parfum & Pink Lipgloss + Body soufflé 100 ml
3.	Loris Azzaro – Chrome	Chrome Eau De Toilette Spray 200 ml
4.	Orlane – Lipcolor and Lipstick	Lip Gloss

PATENT CITATIONS

Table 7: Patent Citations

Publication number	Priority date	Publication date	Assignee	Title
US4873088A	1983-09-06	1989-10-10	Liposome Technology, Inc.	Liposome drug delivery method and composition
US4891208A *	1985-04-10	1990-01-02	The Liposome Company, Inc.	Steroidal liposomes
US5741515A *	1994-10-20	1998-04-21	Bayer Aktiengesellschaft	Ketoprofen liposomes
US6403056B1 *	1997-03-21	2002-06-11	Imarx Therapeutics, Inc	Method for delivering bioactive agents using cochleates
US6428811B1 *	1998-03-11	2002-08-06	Wm. Marsh Rice University	Temperature-sensitive polymer/nanoshell composites for photothermally modulated drug delivery
US20020143385A1 *	2000-03-13	2002-10-03	Jun Yang	Stent having cover with drug delivery capability

CONCLUSION

Niosomes have been studied as an alternative to liposomes. Some advantages over liposomes, such as their relatively higher chemical stability, improved purity and relatively lower cost in comparison with liposomes. Non-ionic surfactant vesicles alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug.

FUTURE PROSPECTS

Niosomes represent a promising drug delivery molecule. There is a lot of scope to encapsulate toxic anti-cancer drugs, anti-infective drugs, anti-AIDS drugs, anti-inflammatory drugs, anti-viral drugs, etc. in niosomes and to use them as promising drug carriers to achieve better bioavailability and targeting properties and for reducing the toxicity and side-effects of the drugs. The ionic drug carriers are relatively toxic and unsuitable whereas niosomal carriers are safer. Handling and storage of niosomes require no special conditions.

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