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Review Article

Niosomes: as novel vesicular drug delivery system

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ABSTRACT

Target-specific drug-delivery systems for the administration of pharmaceutical compounds enable the localization of drugs to target sites within the body. The basic component of drug delivery systems is an appropriate carrier that protects the drug from rapid degradation or clearance and thereby enhances drug concentration in target tissues. Niosome are microscopic non-ionic surfactant bilayer vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or their lipids. The amphiphilic nature of niosomes promotes their efficiency in encapsulating lipophilic or hydrophilic drugs. Niosomes are promising vehicle for drug delivery and being non-ionic, more stable, inexpensive, biodegradable, biocompatible, non immunogenic and exhibit flexibility in their structural characterization. Various additives in niosomes include nonionic surfactant as film forming agent, cholesterol as stabilizing and rigidizing agent for the bilayer and various charge inducers which develop a charge on the surface of niosomes and stabilize the prepared formulation by the resulting repulsive forces. Niosomes have been widely evaluated for controlled release and targeted delivery for the treatment of cancer, viral infections, microbial diseases, psoriasis, leishmaniasis, migraine, parkinson and other diseases. Niosomes can prolong the circulation of the entrapped drug in body. Encapsulation of drug in vesicular system can be predicted to prolong the existence of drug in the systemic circulation and enhance penetration into target tissue, perhaps reduce toxicity if selective uptake can be achieved. In addition to conventional, oral and parenteral routes, they are amenable to be delivered by ocular, transdermal, vaginal and inhalation routes. Delivery of biotechnological products including vaccine delivery with niosomes is also an interesting and promising research area. More concerted research efforts, however, are still required to realize the full potential of these novel systems. This review article focuses on the concept of niosomes, advantages and disadvantages, composition, method of preparation, separation of untrapped drug, factors influencing the niosomal formulation and characterization, marketed formulations of niosomes and also gives up to date information regarding recent applications of niosomes in drug delivery.

Keyword: Drug-delivery system, Niosomes, Bilayer vesicles, Amphiphilic, Methods of preparation, Applications

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INTRODUCTION

Transporting drug with a controlled rate and targeted delivery received much attention in recent years. The application of nanotechnology to medicine has provided the development of multifunctional nanoparticles that, acting as drug carriers, can be loaded with different drugs. Nanocarriers present a great approach in drug delivery with promising features such as protection of drug from degradation and cleavage, controlled release and in case of targeted delivery approach the delivery of drug molecules to the target sites ¹.

Niosomes (Fig.1) are one of the best among these carriers such as immunoglobulin, serum proteins, synthetic polymers, liposome, microspheres, erythrocytes and

niosomes. The self-assembly of microscopic non-ionic surfactants into vesicles was first reported in the 70s by researchers in the cosmetic industry. Niosomes obtained on hydration are microscopic lamellar structures formed upon combining non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class with cholesterol.² The non-ionic surfactants form a closed bilayer vesicle in aqueous media based on its amphiphilic nature using some energy for instance heat, physical agitation to form this structure. In the bilayer structure, hydrophobic parts are oriented away from the aqueous solvent, whereas the hydrophilic heads remain in contact with the aqueous solvent. The properties of the vesicles can be changed by varying the composition of the vesicles, surface charge size, lamellarity, tapped volume and concentration. Various forces act inside the

vesicle, eg, Van Der Waals forces among surfactant molecules, repulsive forces emerging from the electrostatic interactions among charged groups of surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces, etc. These forces are responsible for maintaining the vesicular structure of niosomes. But, the stability of niosomes are affected by type of surfactant, storage temperature, nature of encapsulated drug, detergents, use of membrane spanning lipids, the interfacial polymerisation of surfactant monomers in situ, inclusion of charged molecule.

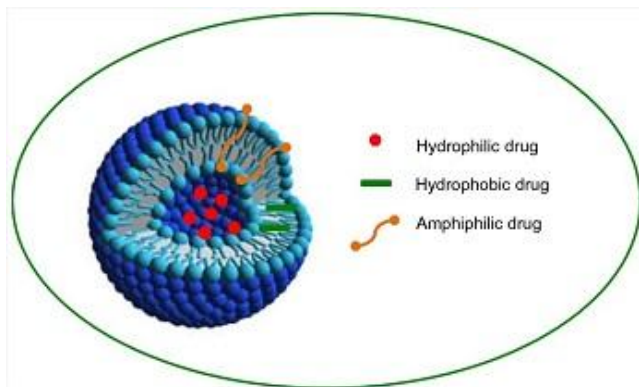


Figure 1: Schematic representation of a niosomal vesicle.

Due to presence of hydrophilic, amphiphilic and lipophilic moieties in the structure, these can contain drug molecules with a wide range of solubility.³ These may act as a depot, releasing the drug in a controlled manner. The therapeutic performance of the drug molecules can also be improved by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells⁴. A dry product known as proniosomes may be hydrated immediately before use to yield aqueous niosome dispersions. The problems of niosomes such as aggregation, fusion and leaking and provide additional convenience in transportation, distribution, storage and dosing⁵. Niosomes behave in vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability⁶. As with liposomes, the properties of niosomes depend on the composition of the bilayer as well as method of their production. It is reported that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation and thus entrapment efficiency⁷. However, differences in characteristics exist between liposomes and niosomes, especially since niosomes are prepared from uncharged single-chain surfactant and cholesterol, whereas liposomes are prepared from double-chain phospholipids (neutral or charged). The concentration of cholesterol in liposomes is much more than that in niosomes. As a result, drug entrapment efficiency of liposomes becomes lesser than niosomes. Besides, liposomes are expensive and its ingredients, such as phospholipids are chemically unstable because of their predisposition to oxidative degradation; moreover, these require special storage and handling and purity of natural phospholipids is variable. Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. It can also be used as vehicle for poorly absorbable drugs to design the novel drug delivery system. It enhances the bioavailability by crossing the anatomical barrier of gastrointestinal tract via transcytosis of M cells of Peyer's patches in the intestinal lymphatic tissues⁸. The niosomal vesicles are taken up by reticulo-endothelial system. Such localised drug accumulation is used in treatment of diseases, such as

leishmaniasis, in which parasites invade cells of liver and spleen.^{9,10} Some non-reticulo-endothelial systems like immunoglobulins also recognise lipid surface of this delivery system.^{2-8, 10-12} Encapsulation of various anti-neoplastic agents in this carrier vesicle has minimised drug-induced toxic side effects while maintaining, or in some instances, increasing the anti-tumour efficacy.¹³ Niosomes have been used for studying the nature of the immune response provoked by antigens.¹⁴ Niosomes can be used as a carrier for haemoglobin.^{15,16} Vesicles are permeable to oxygen and haemoglobin dissociation curve can be modified similarly to non-encapsulated haemoglobin. Slow penetration of drug through skin is the major drawback of transdermal route of delivery.¹⁷ Certain anti-inflammatory drugs like flurbiprofen and piroxicam and sex hormones like estradiol and levonorgestrel are frequently administered through niosome via transdermal route to improve the therapeutic efficacy of these drugs. This vesicular system also provides better drug concentration at the site of action administered by oral, parenteral and topical routes. Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility. Drug delivery through niosomes is one of the approaches to achieve localised drug action in regard to their size and low penetrability through epithelium and connective tissue, which keeps the drug localised at the site of administration. Localised drug action enhances efficacy of potency of the drug and, at the same time, reduces its systemic toxic effects, eg, antimonials encapsulated within niosomes are taken up by mononuclear cells, resulting in localisation of drug, increase in potency, and hence decrease in dose as well as toxicity.¹³ The evolution of niosomal drug delivery technology is still at the stage of infancy, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.

ADVANTAGES OF NIOSOMES. 18-20

1. Use of niosomes in cosmetics was first done by L'Oreal as they offered the following advantages
2. The vesicle suspension being water based offers greater patient compliance over oil based systems
3. 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.
4. The characteristics such as size, lamellarity etc. of the vesicle can be varied depending on the requirement.
5. The vesicles can act as a depot to release the drug slowly and offer a controlled release.
 1. They are osmotically active and stable.
 2. They increase the stability of the entrapped drug
 3. Handling and storage of surfactants do not require any special conditions
 4. Can increase the oral bioavailability of drugs
 5. Can enhance the skin penetration of drugs
 6. They can be used for oral, parenteral as well topical.
 7. The surfactants are biodegradable, biocompatible, and non-immunogenic.
 8. 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.

9. 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.

DISADVANTAGES OF NIOSOMES

1. Physical instability
2. Aggregation
3. Fusion
4. Leaking of entrapped drug
5. Hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.

COMPOSITIONS OF NIOSOMES

The two major components used for the preparation of niosomes are,

1. Cholesterol
2. Nonionic surfactants

1. Cholesterol

Cholesterol is used to provide rigidity and proper shape, conformation to the niosomes preparations.

2. Nonionic surfactants

The role surfactants play a major role in the formation of niosomes. The following non-ionic surfactants are generally used for the preparation of niosomes;

- Spans (span 60, 40, 20, 85, and 80)
- Tweens (tween 20, 40, 60, 80)
- Brij's (brij 30, 35, 52, 58, 72, 76).

The non ionic surfactants possess a hydrophilic head and a hydrophobic tail.

METHOD OF PREPARATION OF NIOSOMES²¹⁻²⁵

Various methods are reported for the preparation of niosomes such as:

- ✓ Ether injection method
- ✓ Hand shaking method (Thin film hydration technique)
- ✓ Sonication method
- ✓ Reverse phase evaporation technique (REV)
- ✓ Micro fluidization
- ✓ Multiple membrane extrusion method
- ✓ Trans membrane pH gradient (inside acidic) drug uptake process (remote loading)
- ✓ Bubble method
- ✓ Formation of niosomes from proniosomes

Ether injection method

This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether (volatile organic solvent) 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 (volatile organic solvent) leads to formation of single layered vesicles. Depending upon the conditions used the diameter of the vesicle range from 50 to 1000 nm

Hand shaking method (Thin film hydration technique)

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 0-

60°C with gentle agitation. This process forms typical multilamellar niosomes.

Sonication

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 probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.

Reverse phase evaporation technique

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 4-5°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.

Micro fluidization

It 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 smaller size, greater uniformity and better reproducibility of niosomes formed.

Multiple membrane extrusion method

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug polycarbonate membranes, solution and the resultant suspension extruded through which are placed in series for up to 8 passages. Multiple membrane extrusion method is better for the controlling of niosome size.

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

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 300 mM 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.

Bubble method

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.

Formation of niosomes from proniosomes

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 (Fig 2). The niosomes are recognized by the addition of aqueous

phase at $T > T_m$ and brief agitation T =Temperature. T_m = mean phase transition temperature. It is 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.

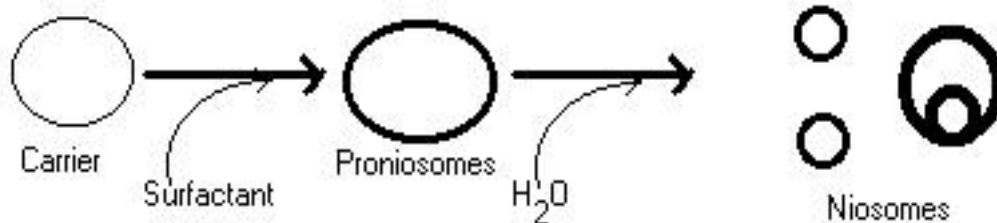


Figure 2: Proniosome Method

TYPES OF NIOSOMES

The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (E.g. LUV, SUV) or as a function of the method of preparation (eg. REV, DRV). The various types of niosomes are described below:

- i) Multi lamellar vesicles (MLV),
- ii) Large unilamellar vesicles (LUV),
- iii) Small unilamellar vesicles (SUV).

1. Multilamellar vesicles (MLV):

It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 μm diameter. Multilamellar vesicles are the most widely used niosomes. It is simple to make and are mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds.

2. Large unilamellar 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 economical use of membrane lipids.

3. Small unilamellar vesicles (SUV):

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press extrusion electrostatic stabilization is the inclusion of diacetyl phosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes ²⁶.

SEPARATION OF UNENTRAPPED DRUG

Dialysis

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

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.

Centrifugation

The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then re-suspended to obtain a niosomal suspension free from unentrapped drug ²⁷

APPLICATIONS

Therapeutic application

There are very less marketed niosomal formulations found in market. But some experimentally evaluated application of niosomal formulation identified in literature listed below ²⁸⁻³³.

Anti-cancer drug

Daunorubicin HCl

Niosomal daunorubicin hydrochloride exhibited an enhanced anti-tumor efficacy when compared to free drug. The niosomal formulation was able to destroy the Dalton's ascitic lymphoma cells in the peritoneum within the third day of treatment, while free drug took around six days and the process was incomplete. The hematological studies also prove that the niosomal formulation was superior to free drug treatment. An enhanced mean survival time was achieved by the niosomal formulation that finally substantiates the overall efficacy of the niosomal formulation.

Doxorubicin

Rogerson et al., studied distribution of niosomal doxorubicin prepared from C16 monoalkyl glycerol ether with or without cholesterol. Niosomal formulation exhibited an increased level of doxorubicin in tumor cells, serum and lungs, but not in liver and spleen. Doxorubicin loaded cholesterol-free niosomes decreased the rate of proliferation of tumor and increased life span of tumorbearing mice. The cardio toxicity effect of doxorubicin was reduced by niosomal formulation. Niosomal formulation changes the general metabolic pathway of doxorubicin.

Methotrexate

Azmin et al., quoted in their research article that niosomal formulation of methotrexate exhibits higher AUC as compared to methotrexate solution, administered either intravenously or orally. Tumoricidal activity of niosomally-

formulated methotrexate is higher as compared to plain drug solution.

Bleomycin

Niosomal formulation of bleomycin containing 47.5% cholesterol exhibits higher level drug in the liver, spleen and tumour as compared to plain drug solution in tumorbearing mice. There is no significant difference in drug concentration with niosomal formulation in lung as compared to plain drug solution. Also, there is less accumulation of drug in gut and kidney in case of niosomal formulation.

Vincristine

Niosomal formulation of vincristine exhibits higher tumoricidal efficacy as compared to plain drug formulation. Also, niosomal formulation of carboplatin exhibits higher tumoricidal efficacy in S-180 lung carcinoma-bearing mice as compared to plain drug solution and also less bone marrow toxic effect.

Anti-infective agents

Sodium stibogluconate is a choice drug for treatment of visceral leishmaniasis is a protozoan infection of reticuloendothelial system. Niosomal or liposomal formulation of sodium stibogluconate exhibits higher levels of antimony as compared to free drug solution in liver. Antimony level is same in both formation i.e. niosome and liposome. Niosomal formulation of rifampicin exhibits better antitubercular activity as compared to plain drug.

Anti-inflammatory agents

Niosomal formulation of diclofenac sodium with 70% cholesterol exhibits greater anti-inflammation activity as compared to free drug. Niosomal formulation of nimesulide and flurbiprofen also exhibits greater anti-inflammation activity as compared to free drug.

Diagnostic imaging with niosomes

Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglumine with [N-palmitoyl-glucosamine (NPG)], PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging.

Transdermal drug delivery

Administration of drugs by the transdermal route has advantages such as avoiding the first pass effect, but it has one important drawback, the slow penetration rate of drugs through the skin. Various approaches are made to overcome slow penetration rate, one approach for it is niosomal formulation. Studied transdermal delivery proniosomal formulation of ketorolac prepared from span 60 exhibits a higher ketorolac flux across the skin than those proniosome prepared from tween20. It is also identified in literature that the bioavailability and therapeutic efficacy of drug like diclofenac, flurbiprofen and nimesulide are increased with niosomal formulation.

Ophthalmic drug delivery

It is difficult to achieve excellent bioavailability of drug from ocular dosage form like ophthalmic solution, suspension and ointment due to the tear production, impermeability of corneal epithelium, non-productive absorption and transient residence time. But to achieve good bioavailability of drug various vesicular systems are proposed to be used, in experimental level, like niosomes, liposomes. Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendency for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide). The chitosan-coated niosomal formulation timolol maleate (0.25%) exhibits more effect for reduction intraocular pressure as compared to a marketed formulation with less chance of cardiovascular side effects.

CONCLUSION

The concept of incorporating the drug into liposomes or niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes represent a promising drug delivery module. They present a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multi environmental structure. Niosomes are thought to be better candidate's drug delivery as compared to liposomes due to various factors like cost, stability etc. Various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parental etc.

Table 1: List of drugs formulated as niosomes ³⁴

Routes of drug administration	Examples of Drugs
Intravenous route	Doxorubicin, Methotrexate, Sodium Stibogluconate, Iopromide, Vincristine, Diclofenac Sodium, Flurbiprofen, Centchroman, Indomethacin, Colchicine, Rifampicin, Tretinoin, Transferrin and Glucose ligands, Zidovudine, Insulin, Cisplatin, Amarogentin, Daunorubicin, Amphotericin B, 5-Fluorouracil, Camptothecin, Adriamycin, Cytarabine Hydrochloride
Peroral route	DNA vaccines, Proteins, Peptides, Ergot, Alkaloids, Ciprofloxacin, Norfloxacin, Insulin
Transdermal route	Flburiprofen, Piroxicam, Estradiol, Levonorgestrol, Nimesulide, Dithranol, Ketoconazole, Enoxacin, Ketorolac
Ocular route	Timolol Maleate, Cyclopentolate
Nasal route	Sumatriptan, Influenza Viral Vaccine
Inhalation	All - trans retinoic acids

Table 2 Marketed formulations ³⁵

Brand	Name of The Product
Givenchy - Amarige	Amarige Eau De Toilette Spray 100ml
Lancome - Foundation & Complexion	Flash Retouch Brush on Concealer
Britney Spears - Curious	Curious Coffret: Edp Spray 100ml+ Dualended Parfum & Pink Lipgloss+ Body Souffle 100 ml
Loris Azzaro - Chrome	Chrome Eau De Toilette Spray 200ml
Helena Rubinstein - HR - Golden Beauty - Body Care	Golden Beauty After Sun Soothing Moisturizer 150ml
Estee Lauder - Beyond Paradise	Beyond Paradise After Shave Lotion 100ml
Orlane - Lipcolor & Lipstick	Lip Gloss
Liz Claiborne - Realities	Realities Shower Gel 200ml
White Shoulders	White Shoulders Eau De Cologne Spray 130ml
Jean Paul Gaultier - Le Classique	Le Classique Eau De Toilette Spray 100ml
Hugo Boss - Boss Soul	Boss Soul After Shave 90ml
Lancaster - Suractif - Night Care	Suractif Non Stop Lifting Advanced Night Cream 50ml
Givenchy - Blanc Parfait - Day Care	Blanc Parfait W4-L Universal Brightening Spots Corrector SPF 45 1.6ml
Nina Ricci - Love In Paris	Love In Paris Deodorant Spray 100ml
Gatineau - Moderactive - Cleanser	Moderactive Almond Make-Up Remover 250ml
Guinot - Night Care	Deep Action Whitening Serum 30ml

Table 3 Method for evaluation of niosomes ³⁶

Evaluation parameter	Method
Morphology	SEM, TEM, freeze fracture technique
Size distribution, polydispersity index	Dynamic light scattering particle size analyzer
Viscosity	Ostwald viscometer
Membrane thickness	X-ray scattering analysis
Thermal analysis	DSC
Turbidity	UV-Visible diode array spectrophotometer
Entrapment efficacy	Centrifugation, dialysis, gel chromatography
In-vitro release study	Dialysis membrane
Permeation study	Franz diffusion cell

Table 4 Patent citations ³⁷

Cited Patent	Applicant	Title
US5741515	Bayer Aktiengesellschaft	Ketoprofen liposomes
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
FR2571963B1	Oreal	Composition for cosmetic or pharmaceutical use containing niosomes and at least one water soluble polyamide and method of preparing this composition.
FR2756177B1	Oreal	aqueous dispersion of vesicles resistant to dehydration
GB9706195D0	Univ London Pharmacy	Particulate drug carriers
US6537246B1	Imarx Therapeutics, Inc.	Oxygen delivery agents and uses for the same
US6309664B1	Igen, Incorporated	Methods, uses and compositions of fluid petrolatum

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