A REVIEW ON NIOSOMES: A NOVEL DRUG DELIVERY SYSTEMS AND ITS VARIOUS APPLICATIONS IN PHARMACEUTICALS

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Abstract:
Niosomes are non-ionic surfactant vesicles in which aqueous solution of solute is completely encapsulated by bilayer membrane made up of surfactant molecules. Niosomes are formed by self-assembly of hydrating mixture of cholesterol and non-ionic surfactants. Hence, they are also referred as non-ionic surfactant vesicles (NSVs). Niosome technology is used to treat several diseases. Niosomes are structurally similar to liposomes and offer several advantages over liposomes. Niosomes are biodegradable, biocompatible, non-carcinogenic, non-immunogenic and non-toxic. The present review describes preparation methods, applications, recent studies and future prospects on niosomal drug delivery systems.

Key words: Niosome, Non-ionic surfactant vesicle, Drug, Cholesterol, Self-assembly, Biodegradable

Introduction:
Niosomes are non-ionic surfactant vesicles (either unilamellar or multilamellar) in which aqueous solution of solute is completely encapsulated by bilayer membrane made up of non-ionic surfactant molecules. They are also referred as non-ionic surfactant vesicles (NSVs). These NSVs are formed when non-ionic surfactant molecules are hydrated, which undergo self-assembly to result in closed bilayer structures consisting of central aqueous core. Such self-assembly generally requires application of energy in the form of heat or agitation.

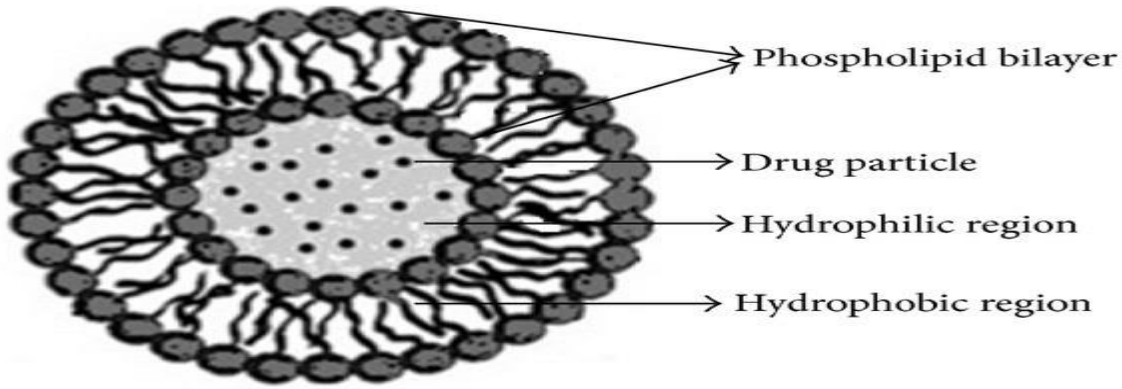

Figure 1: Structure of Niosome.

Niosomes are microscopic lamellar structures of size range between 10 to 1000nm.[1] Niosomes contain hydrophobic tails and hydrophilic heads. The hydrophobic tails of the molecules are aligned away from aqueous solvent while the hydrophilic heads are directed towards the aqueous solvent, thereby attaining maximum contact with solvent.

Niosomes are structurally and physically similar to liposomes. Since they can encapsulate the aqueous solutes, they may be (like liposomes) also used as vesicular drug carriers. Niosomes offer several advantages over liposomes. The non-ionic surfactants used for the production of niosomes are inexpensive, relatively more stable, provide ease storage, have precise chemical composition and can form a variety of aggregates ranging from micelles to large vesicles.

Composition of Niosomes:
The main components of Niosomes are:
1. Non-ionic surfactants
2. Cholesterol

1. Non-ionic surfactants: Non-ionic surfactants are a class of surfactants, which have no charged groups in their hydrophilic heads. They are more stable and biocompatible and less toxic compared to their anionic or cationic counterparts.[2] Non-ionic surfactants consists of 2 different regions: hydrophilic (water soluble) and hydrophobic (organic soluble).

Examples: Alkyl ethers, alkyl esters, alkyl amides, fatty acids are the main non-ionic surfactants used for Niosome preparation.

2. Cholesterol: cholesterol is a steroid derivative, which is used to provide rigidity and proper shape, conformation to niosome form. Cholesterol content influences the structure of niosomes and physical properties such as entrapment efficiency, long time stability, release of payload, and biostability.[3,4]

Examples: Spans (span 20, 60, 40, 80, 85)

TYPES OF NIOSOMES:

The various types of niosomes are as;

1) Multi Lamellar vesicles (MLV)
2) Large unilamellar vesicles (LUV)
3) Small unilamellar vesicles (SUV)

Table 1: 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 OF NIOSOMES:

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.
6. They increase the stability of the entrapped drug.
7. Can increase the oral bioavailability of drugs
8. Can enhance skin penetration
9. 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.
10. The surfactants are biodegradable, biocompatible, and non-immunogenic.

DISADVANTAGES:

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.

METHOD OF PREPARATION:

1. Ether Injection method:

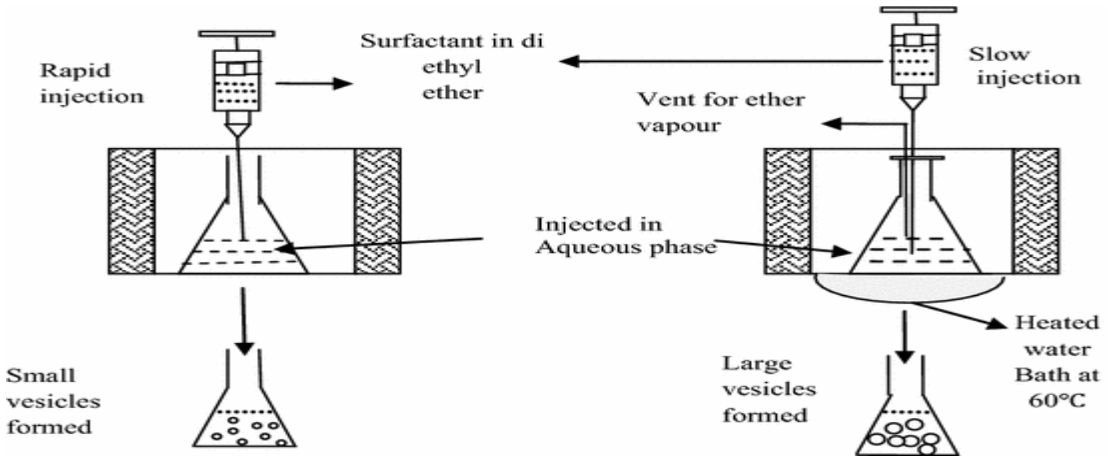

Figure 2: Ether injection method

In ether Injection method a solution of surfactant which is dissolved in diethyl ether is introduced into a warm water maintained at 60℃. The surfactant mixture in ether is injected into an aqueous solution of material through 14-guage needle. The organic solvent is evaporated using a rotary evaporator. Vaporization of ether leads to formation of single vesicles.

2. Hand shaking method:

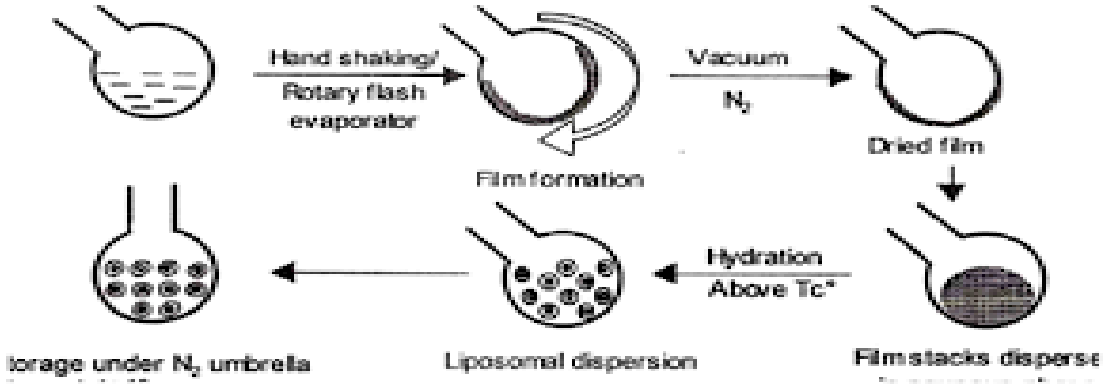

Figure 3: Hand shaking method

In this method mixing ingredients like surfactant and cholesterol and charge inducers are dissolved in a volatile organic solvent (such as diethyl ether, chloroform or methanol) in a round bottom flask. By using a rotary evaporator organic solvent is evaporated at room temperature 20℃. It forms a thin layer of solid mixture. The dry surfactant film can be rehydrated with an aqueous phase at 0-60℃ with gentle agitation to produce niosomes.[5]

3. Sonication method:

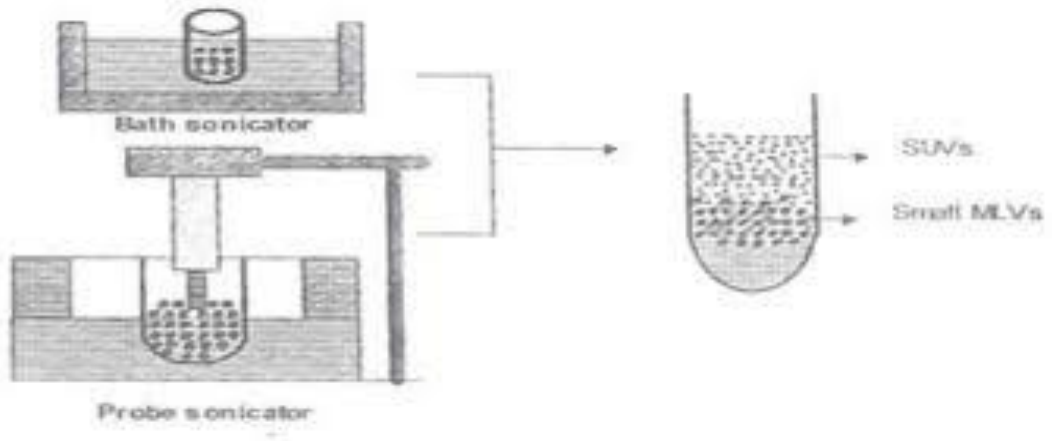

Figure 4: Sonication method

In this method a mixture of drug solution in the buffer, surfactant and cholesterol is sonicated with titanium probe sonicator at 60℃ for 30 minutes to yield niosomes.[6]

4. Bubble method:

Bubbling unit involves round bottom 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℃ and it is mixed for 15 seconds with high shear homogenizer and bubbled at 70℃ using nitrogen gas.[7]

5. Multiple membrane extrusion method:

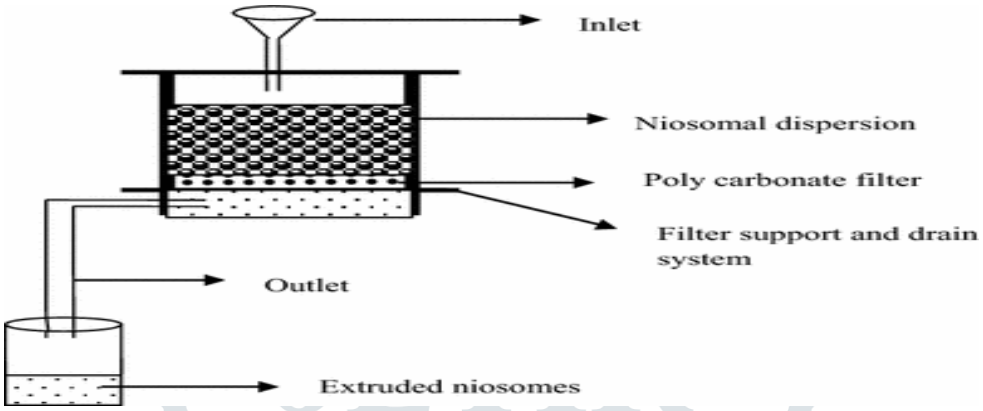

Figure 5: Multiple membrane extrusion method

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform forms a thin film by rotary evaporator. The thin film is hydrated with aqueous drug polycarbonate membranes. Solution and resultant suspension extrude through polycarbonate membrane and placed in series for up to 8 passages. It is the good method for controlling size of niosomes.[8]

6. 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 leads to formation of vesicles.[9]

7. Microfluidization:

In this method submerged jet principle is used in which two fluidized streams interact with each other at high velocities within the interaction chamber. Thin liquid sheet impingements along with common front are arranged such as that the energy supplies remain same within the niosomes formation. The niosomal vesicles formed is of greater uniformity, smaller size and better reproducibility.[10]

8. Reverse phase evaporation technique:

In this method cholesterol and surfactant (1:1) dissolves in the mixture of organic solvent (ether and chloroform). An aqueous phase containing drug is added to this and water in oil emulsion is formed. The resulting two phases are sonicated at 4-5℃. The emulsion is dried in a rotary evaporator at 40℃ to form a semisolid gel of large vesicles. Small amounts of phosphate buffered saline (PBS) are added to the clear gel and sonicated again. The organic phase is removed at 40℃ under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60℃ for 10 minutes to form niosomes.[11]

9. Formation of niosomes from proniosomes:

Here the niosomes are produced by coating the water-soluble carrier such as sorbitol with surfactant. In which each Water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed as "proniosomes". The niosomes are formed by the addition of aqueous phase at temperature greater than mean phase temperature.

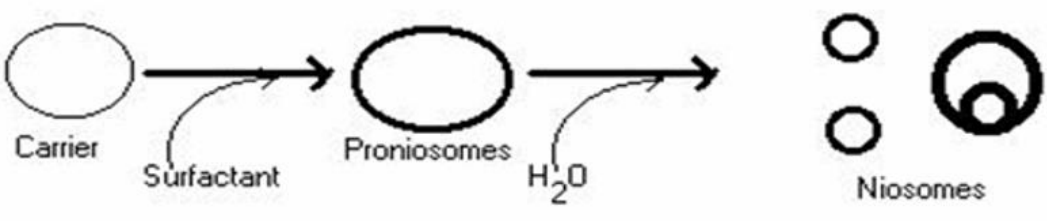

Figure 6: Formation of Niosomes from proniosomes

Routes of administration:

Depending on the type of drug, surfactant, disease and anatomical site involved, various routes of administration exists for niosomal drugs, i.e., intravenous, intramuscular, oral, ocular, subcutaneous, pulmonary, and transdermal.[12] Several others routes have been used to administer niosomal drugs, including the intraperitoneal and vaginal routes. Niosomes have been used for successful targeting of drugs to various organs like the liver and brain or to pathological districts such as tumour, enhancing drugs pharmacological actives while reducing side effects.[13] In particular, targeted niosomal systems have been designed with different mechanism of action, including active, passive and magnetic targeting, leading to more advance and specific macromolecular drug carriers.[14] +

Table 2: Routes of administration and drugs used.

S. No	Route of administration	Drugs used
1	Intravenous route	Ipromide, Vincristine, Indomethacin, Colchicines, Rifampicin, Transferring, Zidovudine, Cisplatin, Daunorubicin, Amphotericin B
2	Transdermal route	Flurbiprofen, Piroxicam, Levonorgestrol, Nimeluside, Estradiol, Ketoconazole, Enoxacin, DNA loaded niosome, Cyclosporin, Erythromycin
3	Oral route	Vaccine, Polysaccharide coated niosome, Ciprofloxacin, Insulin
4	Oncology route	Methotrexate, Doxorubicin, Adriamycin
5	Ocular route	Timolol, Cyclopentolate
6	Nasal route	Sumatriptan, Influenza
7	Immunological adjuvant	Bovine serum albumin, Haemoglobin
8	For treatment of leishmaniasis	Stibogluconate

APPLICATIONS:

1. Co-drug delivery:

Co delivery of multiple drugs for combination therapy via niosomes has been 3 focus of many recent studies.[15] Anticancer drugs often have serious side effects. Pasut et al. Developed simultaneous anticancer drug epirubicin and nitric oxide carrying system acts as protecting reagent against anthracycline induced cardiomyopathy but also acts as sensitizer of anticancer drug treatment. In order to increase anticancer efficacy and enhance cardiocyte protecting ability of Co delivery system, they use branched PEG instead of linear as polymer backbone.[16]

Sharma et al. developed dual encapsulation of hydrophobic curcumin and hydrophilic doxorubicin in niosomes for cancer multidrug delivery. Results showed that dual drug loaded niosomes had higher cytotoxicity on HeLa cells when compared to free drugs.[17]

2. Targeting of bioactive agents:

a) To Reticulo-Endothelial system: The cells of RES preferentially take-up the vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosome for clearance. Such localized drug accumulation has however, been exploited in the treatment of animal tumours known to metasize to liver and spleen and in parasitic infestation of the liver.

b) Organs other than RES: Niosomes can also be utilized for targeting drugs to organs other than RES. A carrier system such as antibodies can be attached to niosomes as immunoglobulin bind readily to the lipid surfaces of niosomes to target them to specific organs.

3. Anticancer treatment:

Most of the anticancer drugs have severe side effects. Niosomes can alter the metabolism prolong the circulation and half-life of the drug, thereby decreasing the side effects of drugs.

Melanoma: Artimisone is a 10-amino artemisinin derivative exhibiting anti-malarial activity and anti-tumour activity. Dwivedi et al. encapsulated artemisinin in niosomes using thin film hydration method. The results showed highly selective cytotoxicity towards the melanoma cells with negligible toxicity towards the normal skin cells.[18] Cisplatin was limited due to its toxic effects. Gude et al. synthesized niosomal cisplatin by using span 60and cholesterol. Their results showed that cisplatin encapsulated in niosomes has significant antimetastatic activity and reduced toxicity when compared to free cisplatin.[19]

Breast cancer: paclitaxel and curcumin coadminstration in novel PEGylated niosomal formulations exhibit enhanced synergistic antitumor efficacy. The combination therapy of PTX with CUR using the novel cationic PEGylated niosomal delivery is a promising strategy for more effective breast cancer treatment.[20]

Recently, tamoxifen citrate showed significantly enhanced cytotoxic activity on MCF-7 breast cancer cell line. In vivo experiments showed that reduction in turn or volume induced by niosomal tamoxifen when compared to free tamoxifen.[21] Cosco et al. prepared 5-FU- loaded polyethylene glycol-(PEG)-coated and uncoated bola niosomes were tested on breast cancer cell lines. Both formulations provided an increase in cytotoxic effect with respect to free drug.[22]

Ovarian cancer: Uchegbu et al. prepared doxorubicin in hexadecyl diglycerol ether and span60 niosomes was studied on a Homan ovarian cancer cell line and its doxorubicin resistant sublime. Their results showed that there was a slight reduction in IC50 against the resistant cell line when the drug was encapsulated in span60 niosomes in comparison to the free drug in solution.[23]

Lung cancer: Vinblastine (chemotherapeutic agent) widely used in treatment of different types of cancer. Its clinical application is limited due to its low water solubility, side effects and multi drug resistance. In order to increase the therapeutic efficacy of VB PEGylated niosomal formulation of Vinblastine was prepared by thin hydration method. Pn-VB indicated a significant increase in toxicity against TC-1 cells as compared to free VB. In animal model, Pn-VB exhibited stronger tumor inhibitory effect and longer life time in comparison to free VB. In conclusion, Pn-VB showed appropriate stability, high entrapment efficiency, lower releasing rate and stronger cytotoxic activity against lung cancer TC-1 cells as compared to free drug.[24]

In another study, pentoxifylline loaded niosomes were prepared by lipid film hydration method. iv administration of this niosomes resulted in significant reduction in lung nodules.[25]

4. Leishmaniasis:

leishmaniasis is a disease in which a parasite of the genus leishmania invades the cells of the liver and spleen. When tests were carried out by using niososmes shown that it was possible to administer higher levels of the drug without the triggering of side effects and allows greater efficacy in the treatment.

5. Magnetic drug targeting:

The potent drugs which have narrow therapeutic index have more side effects. Those drugs can be delivered by targeting them through vesicles. Targeting of niosomes by means of a strong magnetic field from outside of the body to attract the magnetic particles within the niososmes. This study revealed improved cytotoxicity when DOX was administered through magnetic niosomal drug targeting.[26]

6. Sonophoretic delivery:

losartan potassium was administered via sonophoretic delivery to the albino rat skin using proniosomal gel and was compared with aqua sonic gel. An invite skin permeation of LP with aqua sonic gel was found superior than proniosomal gel using sonophoretic delivery. The study revealed that aqua sonic gel could act better means of delivery for LP instead of proniosomal gel, when used in combination with ultrasound treatment.[27]

7. Niosomes in gene delivery:

This novel niosome formulation represents a promising approach to deliver genetic material into the retina to treat inherited retinal diseases.

8. Niosomes in cosmetics:

The first cosmetic product niosome was launched into the market by Lancome in 1987. Later the product 'Niosome plus' an anti-agening cream was developed. Niosomes increase the stability of entrapped drugs and have improved bioavailability of poorly absorbed ingredients thus enhancing skin penetration. Niosomes find extensive application in cosmetic and skin care products.

9. Niosomes in diagnostic and therapeutics:

Niosomes are considered as carriers of iobitridol, a diagnostic agent used for x-ray imaging.

10. Delivery of peptide drugs:

Use of niosomes to protect the peptides from gastrointestinal peptide breakdown in being investigated. In an invitro study conducts by oral delivery of niosomes entrap derivative shows that entrapment of drug increases the stability of peptide.

11. Use in studying Immune response:

Niosomes are used to study the nature of immune response provoke by antigens due to their immune system selection, low toxicity and greater stability.

12. Niosome formulation to brain targeting:

In recent studies, the oral alkylating agent temozolomide was Incorporated into niosomes and the surface was modified with chlorotoxin, a small 36 amino acid peptide discovered from venom of scorpion leiurus quinquestriatus. Active targeting using nanosized particles facilitates an increase in accumulation of drugs in cerebri by 3.04-folds. These are used in the target area specifically for glioblastoma, an aggressive brain tumor.[28]

13. Niosomes as transdermal drug delivery systems:

Niosomes containing celecoxib (CXB) as an anti-inflammatory drug were prepared using span 60 or span 40 and cholesterol in the ratio of 1:0, 1:1, 1:2. The invitro release studies shown that significant drug release over the other forms. The results also shown that the release of CXB from the niososmes and niosomal gel obeyed the Higuchi's diffusion model. The anti-inflammatory activity of the drug from different niosomal gel formulations was also studied using carrageenan induced rat paw oedema method. The results showed that there is a significant anti-inflammatory activity of poloxamer niosomal gel on rat paw.[29]

In another study, lornoxicam prepared niosomes using Carbopol 934(2%) to improve the permeation and anti-inflammatory of Lornoxicam (LX). Prepared LX niosomes exhibited an entrapment efficiency of more than 66% and when. It is applied onto the dorsal region of wistar rat; the skin irritation test proved that non-irritancy LX niosomal gel. Percentage oedema inhibition of LX niosomes was significantly higher than that of free LX group showing an enhanced anti-inflammatory activity of LX niosomes.[30]

14. Niosomes in ocular drug delivery:

Fluconazole loaded niosomal gels are used as topical ocular drug delivery system for corneal fungal infections. These niosomes were prepared using span 60 or span 80 and cholesterol. The selected niosomal formulation were Incorporated into poloxamer 407 and chitosangel. The results showed that the drug release and permeation from the poloxamer gel were higher than that from chitosan gel.[31]

Another study by kapadia et al., prepared Acyclovir niosomes for the treatment of herpes simplex type 1 keratitis. This study overcomes all the limitations of conventional and oral therapies like blurring vision, repeated administration of doses and patient non-compliances. In order to avoid nasolacrimal drainage of drug the possible way of using niosomes for ocular drug delivery system is by entrapping then in In-situ hydrogels which will provide controlled release and avoids the precorneal and nasolacrimal drainage. The results showed enhanced bioavailability and patient compliance.[32]

15. Niosomes as carriers for Haemoglobin:

Niosomes can be used as carriers for Haemoglobin. Niosomal suspension shows a visible spectrum super-imposable to that of free haemoglobin. Vesicles are permeable to oxygen and haemoglobin dissociation curve can be modified similarly to non-encapsulated haemoglobin.

16. Antibiotics:

Niosomal carriers are also suitable for the delivery of antibiotics. Begum et al., designed niosomal delivery system of rifampicin, a broad-spectrum antibiotic. Their studies showed that niosomal formulation of rifampicin is able to provide consistent and prolonged drug release.[33]

17. Anti-inflammatory drugs:

Topically applied NSAIDs loaded niosomes can substantially improve drug permeation. In order to investigate the potential applications of niosomes for anti-inflammatory agents. Marianecci et al. synthesized ammonium glycyrrhizinate (AM) loaded niosomes using surfactants and cholesterol at various concentrations. The results showed that AG-loaded niosomes demonstrated no toxicity and good skin tolerability and were able to improve anti-inflammatory activity in mice.[34]

Marketed products:

Lancome has come out with a variety of anti-agening products which are based on niosomes formulations. L 'Oreal is also conducting research on anti-agening cosmetic products.

Table 3: Marketed products

S. No	Brand	Name of the product
1	Lancome-Foundation and complexation	Flash Retouch brush on concealer
2	Loris Azzaro-Chrome	Chrome Eau De Toilette Spray 200 ml
3	Orlane - Lip color and Lipstick	Lip Gloss
4	Britney Spears- Curious	Curious coffee: Edp spray 100ml+Dualended perfume and pink Lipgloss+Body souffle 100ml

Future prospects:

Niosomes represent a promising drug delivery module. Over the past three decades, niosomes have been successfully used as a drug carrier to overcome biopharmaceutical problems such as side effects, insolubility and poor chemical stability of drugs. There is a lot of scope to encapsulate toxic anticancer drug, anti-inflammatory drug, anti-infective drugs, anti-AIDs and antiviral drugs etc in niosomes to achieve better bioavailability and targeting properties and decreasing toxicity and side effects of drugs. Handling and storage of niosomes require no special conditions. The ionic drug carriers are relatively toxic and unstable where as niosomal carriers are safer.

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