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Niosomes: A Novel Approach in Modern Drug Delivery Systems

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ABSTRACT

Niosomes are a novel drug delivery system that encapsulates drug in vesicles. Niosomes are non-ionic surfactant vesicles which have potential applications in hydrophilic and hydrophobic drug delivery. Niosomes success as drug carriers has been reflected in a number of formulations based on surfactants that are available commercially or are currently undergoing clinical trials. Vesicular drug delivery system has many benefits over other drug delivery system types. Niosomes are involved in the capacity of drug delivery and improve drug efficacy compared to free drug delivery. The main object of this review the application of niosome technology is used to treat a number of diseases, niosome have good opportunity in research and beneficial for researcher and pharma industries. Niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Thus these areas need further exploration and research so as to bring out or to make for commercially available niosomal preparation.

INTRODUCTION

Niosomes are produced by self-assembly of non-ionic surfactants, but Niosomes vesicles are structurally similar to liposomes and have been developed as an alternative liposome delivery system, as Niosomes can overcome the problems associated with large-scale processing, sterilization and physical stability (5). The L'Oréal were developed and patented first noisome formulation in 1975. We were first used in drug delivery for anticancer drugs (1). The growing interest in designing new drug delivery vehicles stems from the need to resolve drug action obstacles such as restricted half-life distribution, decreased solubility, and undesirable side effects associated with a given therapeutic agent. In parenteral formulations or systemic concentrations, the pharmaceutical API is not bioavailable, making the drug useless regardless of its therapeutic potential. The use of modern pharmaceutical carriers to improve the potency of many medications in vivo (14). Unlike liposomes, vesicles of niosomes are also capable of both water-soluble and insoluble drugs being trapped. In the case of liposomes, bilayer formation in niosomes consists of non-ionic surfactant uncharged single chain, while double-liposomal structures. Non-ionic surfactant vesicles as colloidal drug carriers have remarkable advantages that make them superior to other traditional and vesicular delivery systems (12). These vesicular systems also provide a continuous release of drugs in order to extend their action (13). Due to their improvement in guided, directed drug delivery, design of drug Nano carriers has received tremendous interest among various nanomaterials (8). Vesicle design uses simple procedures with low quantities of pharmaceutically appropriate materials which further emphasize their economic advantage (17). Their role in immunology, membrane biology, diagnostic techniques and, most recently, genetic engineering has been assessed (16).

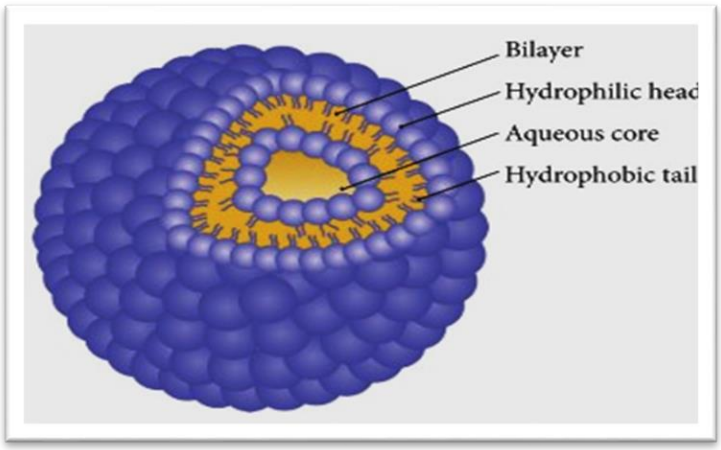

Figure No 1: Structure of Niosome

Niosome Advantages (28)

1. Compared with other vesicles used in drug delivery, they are economically inexpensive.

2. All water-soluble and insoluble drugs can be stuck.

3. These are more stable than liposomes because they are quickly oxidized by the phospholipid present in the liposomes.

4. During surfactant handling and processing, they do not require any special conditions.

5. These are stable and osmotically active, which is why they are used in the delivery of ophthalmic drugs.

6. These are biodegradable, biocompatible, and non-immunogenic and improve poorly absorbed drugs ' oral bioavailability.

7. They can modulate drug penetration in the body. The niosomal vesicles will serve as a depot and release the drug in a controlled way.

8. We have recently been studied to target specific tissues for drug delivery and can modulate the drug's ADME.

Niosomes v / s liposome:

Unlike liposomes, niosomes are functionally identical, both can be used in a guided, directed and sustained drug delivery process, the property of both depends on bilayer components and preparation methods, and both improve bioavailability and decrease the body clearance, the major distinguish between liposomes and niosomes are mention in Table 1(7).

Table 1: Difference between Liposome and Noisome

Liposomes	**Niosomes**
More expensive	Less expensive
Phospholipids are prone to unstable due to oxidative Degradation.	Non-ionic surfactants are stable than phospholipid.
Required special condition for storage, handling and purification of phospholipids.	Do not required special condition for such formulations as Compare to liposomes.
Phospholipids can be charged or neutral.	Non-ionic surfactants are uncharged.

Components of Niosomes:

1. Non-ionic surfactants

In these non-ionic surfactant contains both hydrophilic head and hydrophobic tail are present. The major of non-ionic surfactants used are Span (20, 40, 60, 65, 80, and 85)Tween (20,40,65,80,85), Brij (52,58,35,30), Sorbitan ester, Ester alkyl amide. Definitions of different classes of non-ionic surfactant are as below:

A) Ether connected surfactant

These are ether-connected surfactants contain water-soluble and insoluble molecules linked by polyoxyethylene alkyl ethers, ether to the general formula (CnEOm), where n; i.e. the number of carbon atoms varies between 12 and 18 m; i.e. the number of oxyethylene units varies between 3 and 7.

Examples

(a) Alkyl ethers glucoside: octyl glucoside, glucoside deacyl, glucoside lauryl.

(b) Triton X-100

(c) Polyoxyethylene glycol alkyl phenol ethers: Nonoxynol-9

(d) Other ethers: glucosyl, Brij, polyglycerol alkyl ether (22).

B) Surfactant-connected esters

Alkyl esters such as Sorbitan fatty acid esters (Span) and polyoxyethylene Sorbitan fatty acid esters (Tween) are commonly used in cosmetics and foods, as well as in oral, parenteral and topical pharmaceutical formulations (1).

Examples: glyceryl laurate, strings, polysorbate (22).

C) Amides

Alkyl glucosides and galactosidase incorporating spacers of amino acids. The alkyl groups are C12 to C22 hydrocarbons partially or completely saturated and some new amide compounds have fluorocarbon chains (23).

D) Fatty acid and amino acid compounds

These are long-chain fatty acids and moieties of amino acids are also used in the preparation of certain niosomes (2). When fatty acids are used, the moiety of amino acids is amphiphilic. Hydrophobic alkyl side chains form the vesicles, while fatty acids form closed vesicles called "Ufasomes" (24).

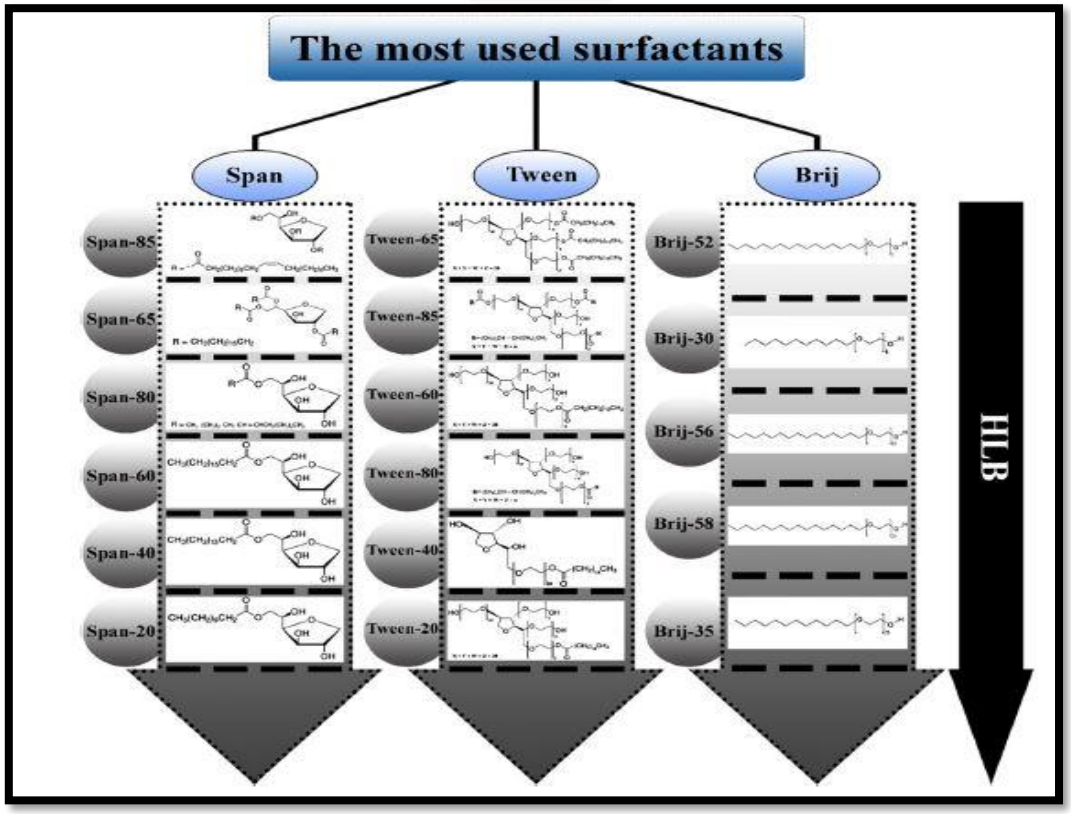

Figure 2: Mostly Used Nonionic Surfactants.

2. Cholesterol (bilayer membrane stabilizer):

It offers rigidity, fluidity and permeability to cell membranes and vesicle membranes that are not supplied by the surfactants alone (they are fairly brittle otherwise) and thus integrates cholesterol into the bilayers of the artificial vesicle in order to increase their organized condition (14). Cholesterol may be included in bilayers, but it does not itself shape bilayers (22). It overcomes the vesicle aggregation by including molecules that stabilize the system against the creation of aggregates through repulsive steric or electrostatic forces that lead to the transition in niosome systems from the gel to the liquid phase. As a result, the niosome in nature becomes less leaky (2).

3. Other additives:

Other additives include charge inducers which increase surface charge density and prevent vesicles flocculation, aggregation and fusion. Both positively and negatively charged molecules are used for induction of charge in niosomes. Stearyl amine (SA) and Dicetyl phosphate (DCP) induces negative or positive charge on membrane and thereby help to stabilize the formulation (6).

Niosome preparation method:

1. Ether injection process

This method provides a means of generating nonionic surfactant vesicles by gradually injecting a surfactant solution dissolved in diethyl ether into warm water at 60 ° C. The surfactant mixture in ether is inserted into an aqueous material solution via a 14-gage needle. Ether vaporization leads to single-layered vesicles being formed. The diameter of the vesicle ranges between 50 and 1000 nm, depending on the conditions used (12).

2. Thin film hydration method

Surfactant and other vesicles that form ingredients such as cholesterol are combined and mixture dissolved in a round bottom flask in a volatile organic solvent such as diethyl ether, chloroform or methanol. The organic solvent is extracted at room temperature (20 ° C) using a rotary evaporator, thus depositing a thin layer of solid mixture on the flask surface. The dried surfactant film can be rehydrated at 60 ° C with moderate agitation resulting in Multilamellar Niosome formation (20).

3. Sonication

In the aqueous phase, the mixture of surfactant cholesterol is dispersed. The dispersed phase is sonicated at 60 ° C for 10 minutes to produce multilamellar vesicles (MLV), further increase in sonic time producing unilamellar vesicles (24).

4. Micro fluidization

The process of micro fluidization is based on the principle of submerged stream. In this system, the drug and the fluidized surfactant streams interact at ultra-high speeds within the interaction chamber in precisely defined micro channels. The impingement of high speed and the energy involved contributes to niosomes being created. This approach provides greater accuracy, smaller size, unilamellar vesicles, and high niosome formulation reproducibility (25).

5. Reverse phase evaporation method

A mixture of ether and chloroform (1:1) prepares the cholesterol and surfactant solution. To this, the drug's aqueous solution is added and sonicated at 4-5 ° C temperature. Upon adding phosphate buffer saline (PBS), the resulting solution is further sonicated resulting in gel formation. The temperature is then increased to 40 ° C and the pressure to extract the solvent is increasing. The PBS is re-added and heated to produce niosomes at 60 ° C for 10 min. (18).

6. Membrane extrusion method

By extrusion through a polycarbonate membrane, niosomes were prepared using C16 G2, a chemically determined non-ionic surfactant. Such studies show not only the effect of amount of extrusion on the length of the vesicles, but also the impact of volume on drug encapsulation (20).

7. Bubble method

The processing of liposomes and niosomes in one step without the use of organic solvents is a ground breaking technique. The bubbling unit is a round-bottomed flask with three necks to regulate the water bath temperature. Water-cooled reflux and thermometer were put through the third neck in the first and second supply of neck and nitrogen. In this buffer, cholesterol and surfactant are dispersed together (pH 7.4) at 70 ° C, dispersion combined with a high shear homogenizer for 15 seconds and then instantly "bubbled" with nitrogen gas at 70 ° C (26).

Niosome types:

Niosomes are categorized according to the number of bilayer, size and preparation process.

Multilamellar diameter: 0.5 μm to 10 μm.

Larger unilamellar diameter: 0.1 μm to 1 μm.

Small unilamellar: diameter 25-500 nm

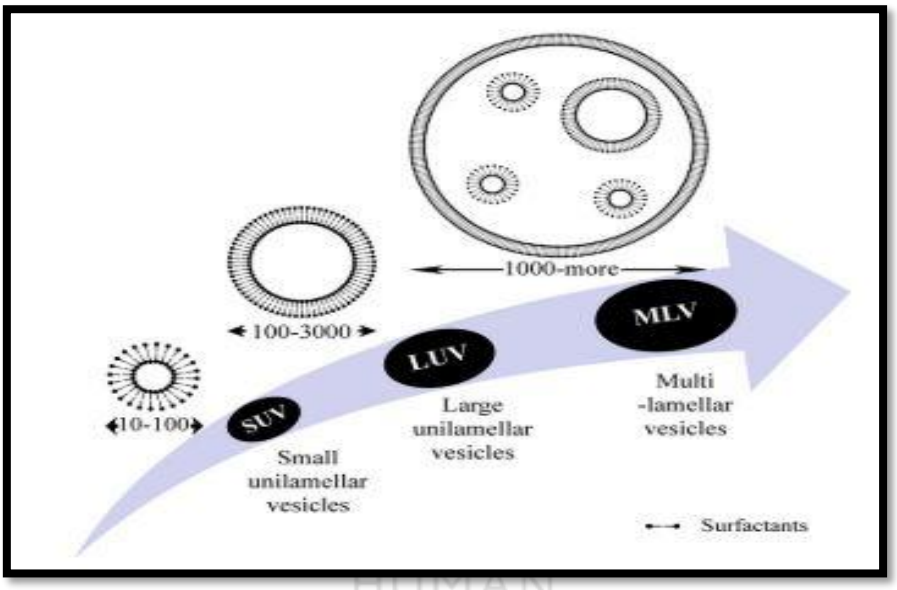

Figure 3: Types of Niosome

Increases in Niosomes:

1. Proniosomes

A dry material known as proniosomes can be hydrated immediately prior to use to create aqueous niosome dispersions and preparations (28). Hydration results in aqueous niosome dispersion. Proniosomes de- creates the problem of aggregation, leakage and fusion associated with niosomal formulations. (2) The proniosomal powder may be processed to produce beads, tablets or capsules in order to provide convenient unit dosing (14).

2. Bola surfactant containing niosomes

Two hydrophilic heads are bound by one or two long lipophilic spacers. Bola-niosomes display appropriate tolerability in both in-vitro and in-vivo and are made of alpha omega-hexadecyl bis-(1-aza-18-crown-6) (Bola-surfactant)-Span 80-cholesterol (2:3:1 molar ratio).

3. Aspasomes

Aspasomes are the aqueous vesicles formed by a mixture of ascorbic palmitate, cholesterol and di-acetyl phosphate (28). Aspasomes are prepared by film hydration method followed by sonication.

4. In Carbopol Gel Niosomes

Niosomes used medication, spans and cholesterol are pre-painted. The resulting niosomes were then incorporated into the base of carbopol-934 gel (1% w / w) containing propylene glycol (10% w / w) and glycerol (30% w / w). For diffusion cells, the use of human corpse, for vitro diffusion studies of such niosomal gel, flat product gel and branded gel. The mean flux value and co-efficient of diffusion for niosomal gel was found to be 5 to 7 times lower compared to flat drug gels. However, the inhibition of paw edema caused by carrageenan (i.e. 66.68? 5.19 percent) was higher as a com- pared to flat gel by niosome formulation (2).

5. Elastic Niosomes

These elastic or ultra-deformable liposomes, Transferosomes, demonstrated the ability to penetrate intact skin while carrying drug therapeutic concentrations (1).

6. Polyhedral niosomes

Polyhedral niosomes formed by mixtures of hexadecyl diglycerol ether (C16G2): cholesterol: polyoxyethylene 24 cholesteryl ether (Solulan C24) have previously been shown to form spherical, tubular, polyhedral and disc-like vesicles depending on the molar ratio (22).

Separation of untrapped drug :(21)

Different techniques can be used to extract untrapped solution from the vesicles, including:

A. Dialysis

In a dialysis tubing against phosphate buffer or regular saline or glucose solution, the aqueous niosomal dispersion is dialyzed.

B. Gel Filtration

Gel filtration of niosomal dispersion through a Sephadex-G-50 column and phosphate buffered saline or regular saline elution is used to extract untrapped material.

C. Centrifugation

Centrifugation of the niosomal suspension and isolation of the supernatant. The pellet is cleaned and then resuspended in order to obtain a drug-free niosomal suspension.

Niosomal Characterization:

1. Niosomal morphology

Morphological niosomal analysis was performed by negative staining transmission electron microscopy. A drop of the niosomal formulation was placed on a carbon-coated copper grid and the excess specimen was collected with filter paper. A fall of 2% (w / v) of PTA (phosphor-tungstic acid solution) was then added to the carbon grid and left for 2 min. Once the excess staining agent was extracted with filter paper, the specimen was air-dried and with the transmission electron microscope the thin film of stained niosomes was observed (13).

2. Vesicle size

Dynamic Light Scattering (DLS) and Laser Doppler Velocimetry (LDV) were used to calculate the hydrodynamic diameter and zeta potential of both Niosomes and nioplexes using Zeta sizer Nano ZS (Malvern Instrument, UK). Z-average has obtained particle size recorded as hydrodynamic diameter (15).

3. Bilayer formation

Bilayer Formation Assembly of non-ionic surfactants forming a bilayer vesicle is characterized by X-cross formation under microscopy of light polarization (10).

4. Lamellae Number

This is calculated by the use of nuclear magnetic resonance (NMR) spectroscopy, small-angle X-ray scattering and electron microscopy (10).

5. Bilayer Rigidity and Homogeneity

The rigidity of the bilayer affects the bio distribution and biodegradation of Niosomes. In homogeneity, both within niosome structures themselves and in dispersion between niosomes can occur and can be defined by. P-NMR, calorimetry differential scanning (DSC) and techniques of FT-IR transform-infra red spectroscopy. Previously, the enter fluorescence.

6. Entrapment efficiency

Entrapment efficiency (EE percent) is defined as the niosome trapped portion of the drug used. Unencapsulated free medicine can be removed from the niosomal solution with centrifugal dialysis or gel chromatography. With the addition of 0.1 percent of Triton X-100or methanol to niosomal suspension, niosomes can be destroyed. A spectrophotometer or high-performance liquid chromatography (HPLC) will assess the charged and free drug concentration (Seleci et al. 2016).

$$\%EE = [\text{Total Drug} - \text{Drug in supernatant Total Drug}] \times 100$$

7. In vitro drug release

A method of in-vitro release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in a 250ml buffer solution in a 250ml beaker with constant shaking at 25 ° C or 37 ° C. The buffer is analyzed for the drug content at different time intervals using an appropriate test method (20).

8. Stability study

Niosomal stability can be assessed by determining mean vesicle size, distribution of size, and efficiency of trapping at different temperatures over several months of storage. Niosomes are sampled at regular intervals during storage and the percentage of the drug kept in the niosomes is analyzed using UV spectroscopy or HPLC methods (25).

Table 2: Methods for Evaluation of Niosomes.

Evaluation Parameter	Methods
Morphology	SEM, TEM, freeze fracture technique
Size Distribution ,PDI	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

Niosome applications:

1) Oral route delivery

A research involving 100 nm of methotrexate C16 G3 niosomes first demonstrated the oral delivery of drugs using niosomal formulations. Compared to the free drug administration, significantly higher concentrations of methotrexate were observed in the blood, liver, and brain of PKW mice administered orally a niosomal formulation. Therefore, with these niosomal formulations, it appears that there is increased drug absorption. (27). recently, in one study, mixed niosomes have been prepared for oral delivery of Candesartan Cilexetil as a prototype of a poorly water-soluble medication. In vitro drug release from niosomes improved compared to free Candesartan Cilexetil after niosomal treatment (11).

2) Cosmetic delivery

L'Oréal first developed and patented niosomes in the 1970s and 80s, and Lancôme launched the first brand' Niosome' in 1987. Niosomes enhance the stability of trapped products, demonstrate significantly improved bioavailability of many poorly absorbed ingredients, and show increased skin penetration (28).

3) Ophthalmic drug delivery

Specific ocular drug delivery systems such as niosomes for delivery of brimonidine tartrate in glaucoma management are investigated to reduce the problems associated with traditional eye

drops. Niosomes contain nonionic surfactants that have been treated with gentamycin sulfate as a drug that are non-antigenic and non-toxic to the skin. Vyas et al. reported a 2.48-fold increase in timolol maleate's ocular bioavailability in the form of a niosome relative to timolol maleate. The Carbopol or Chitosan coated timolol maleate niosome has only half the desired effect.

4) Nasal and pulmonary Delivery

The therapeutic value of pulmonary administration may surpass that of oral or parenteral administration in inflammatory diseases, infections, or respiratory tract cancer as the affected area is directly reached by the medication. In diseases marked by hypersecretion of bronchial mucus, lipophilic substances such as corticosteroids, which are found within the cytoplasm of bronchial epithelial cells, are greatly impeded from reaching their receptors. Niosomes have been used to solve this problem (14). Drug delivery seems to be quite important in the nasal and pulmonary routes. Yes, the large alveolar region's surface area attracts formulation scientists to promote vesicular delivery for it.

5) Transdermal Delivery

Thanks to their exceptional characteristics such as increased drug penetration, continued drug release, increased drug stability and the ability to carry both hydrophilic and lipophilic drugs, NSV is becoming common. Some of the drugs developed as niosomes include enoxacin, tretinoin, terbinafine, ibuprofen, meloxicam, lopinavir and erythromycin. Cholesterol increased or decreased the effectiveness of niosomes in trapping depending on either the type of surfactant used or its concentration within the formulae. Increasing concentration of total lipid or drug also increases the efficiency of trapping as in the case of flurbiprofen into niosomes. The absorption of benzyl peroxide into niosomes showed prolonged release of the drug, increased drug retention in the skin and improved permeation throughout the skin after encapsulation Because of its protective effects on the skin, including the ability to inhibit melanin synthesis by inhibiting tyrosinase expression, high intake of drugs in human epidermal immortal keratinocytes.

6) Brain targeted drug delivery

Marco Bragagni et al. developed a targeted niosomal formula with glucose-derivative N-palmitoylglucosamine (NPG) niosomal vesicles consisting of Span: cholesterol: Solulan: NPG

(50:40:10:10 mol ratio) vesicles with thin layer evaporation, for the preparation of doxorubicin-loaded NPG-niosomes (mean size 161±4 nm, encapsulation efficacy 57.8±1.8) After 6 months of storage at room temperature, the zeta potential or trap efficiency was observed, suggesting good stability. Intravenous administration to NPG-niosomal formulation rats made it possible to reduce drug accumulation in the heart and to maintain it longer in the flow of the blood compared to commercial formulation. In fact, a concentration of2.9±0.4 μg / g w in the brain.

7) Diagnostic imaging with Niosomes

A study in the literature details the analysis of these devices as therapeutic agents in addition to the use of niosomes as different drug carriers. C16 G3 and C16C12G7 niosomes containing cholesterol and stearylamine that encapsulate the radio-opaque agent iopromide have been found to rely on intravenous administration in the kidneys (27).

8) Immunological Applications

Skin vaccination may be particularly advantageous as the immune-competent Langerhans cells (LCs) are found in abundance along the transdermal penetration pathways and these cells are specifically aligned along the minute pores through which pathogens are likely to invade the body. LCs are found in close proximity to stratum corneum and are the underlying network of immune cells. Antigen was found to bind epidermal LCs cutaneous and then process it. We migrate from the epidermis to lymphatic vessels and eventually to urban lymph nodes by bearing concentrated antigen. Studied tetanus toxoid delivery via noisome, Transferosomes and liposome and found maximum response after 42 days after transdermal route immunization with these vehicles. Niosomes demonstrated better immune response than liposomes, immune response of transdermal TT vaccination using niosomes was substantially (pb0.05) comparable after secondary immunization to that obtained by intramuscular injection of the same AATT dose.

9) Gene Delivery

Gene therapy for the CNS is a major challenge in many neurodegenerative diseases to introduce normal gene copies and correct mutant gene defects. To adapt this promising technology to routine clinical practice, however, there is a need for safe and effective gene carrier systems. Non-viral vectors have several significant advantages relative to the viral vector. We are easier and cheaper to manufacture, for example, and these vectors do not have pre-existing immunity.

Therefore, they are not made from pathogens and therefore have less safety concerns. Nevertheless, their efficacy in transfection is lower than their counterparts based on viruses.

10) Anti-neoplastic Therapy

There are many side effects in the anti-cancer (anti-neoplastic) drugs. Where niosomes can be used to change the half-life of the drugs; prolong the distribution and alter the metabolism, thereby helping to reduce the side effects of the drugs. Niosomes contain other beneficial properties in which they decrease the time taken for cancer cell proliferation due to the long-term presence of the drug through slow removal (9) Niosomes composed of a non-ionic methotrexate encapsulating surfactant, cholesterol and diacetyl phosphate (MTX) result in increased absorption from the gastrointestinal tract following oral ingestion. Excessive use of MTX in the liver following intravenous administration of niosomes compared to MTX, orally or intravenously administered (24).

Table 3: Marketed Niosomal Products

Brand Name	**Company Name**	**Applications**
Beyond Paradise	Estee Launder Companies	After shave lotion
Prototype #37-C Lancôme	L-Oreal Paris	Anti-aging cream
White Shoulders	White Shoulders	Cologne spray
Or lane – Lip color And Lipsticks	Or lane	Lip gloss
Suractif	Lancaster	Night cream
Jean Paul Gautier	Jean Paul Gautier	Toilette spray
Love In Paris	Nina Ricchi	Deodorant spray
Realities	Liz Claiborne	Shower gel
Blane Parfait	Givenchy	Brightening spot corrector
Foundation And Complexation	Lancôme	Flash retouches brush on corrector
Britney Spears	Britney Spears	Curious correct, dual ended perfume and pink lip gloss, body soufflé.

CONCLUSION

The vesicular distribution has just strengthened the other drug delivery vehicles since the last decade. There's been a huge amount of research done in this area. All the aspects of the formulation of niosomal preparations are given in a sequential manner with copula elements and some acrid facts regarding drug delivery. Okay, it is worth saying that it is still very much in its infancy yet it shows great promise in the fields of cancer and therapies for infectious diseases. The program is well developed for cosmetic products which are mentioned in this. Manuscript as well. This definitely has potential avenues in the drug delivery field for future research.

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