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REVIEW: FORMULATION AND EVALUATION OF NIOSOMES

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ABSTRACT
Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. The method of preparation of niosome is based on liposome technology. The basic process of preparation is the same i.e. hydration by aqueous phase of the lipid phase which may be either a pure surfactant or a mixture of surfactant with cholesterol. After preparing niosomal dispersion, unentrapped drug is separated by dialysis centrifugation or gel filtration. A method of in-vitro release rate study includes the use of dialysis tubing. Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. Niosomes are unilamellar or multilamellar vesicles formed from synthetic non-ionic surfactants. They are very similar to the liposomes. Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Niosomes have shown promise in the release studies and serve as a better option for drug delivery system. Target-specific drug-delivery systems for the administration of pharmaceutical compounds enable the localization of drugs to diseased sites. Various types of drug-delivery systems utilize carriers, such as immunoglobulins, serum proteins, synthetic polymers, liposomes, and microspheres. The vesicular system of niosomes, with their bilayer structure assembled by nonionic surfactants, is able to enhance the bioavailability of a drug to a predetermined area for a period. The amphiphilic nature of niosomes promotes their efficiency in encapsulating lipophilic or hydrophilic drugs. Other additives, such as cholesterol, can be used to maintain the rigidity of the niosomes' structure. This narrative review describes fundamental aspects of niosomes, including their structural components, methods of preparation, limitations, and current applications to various diseases.

KEYWORDS: Non ionic surfactant veicles, drug-delivery system, medical applications, methods of preparation, niosomes, structure.

INTRODUCTION
Niosomes are microscopic non-ionic surfactant vesicles attained by the hydration of synthetic non-ionic surfactant with or without inclusion of cholesterol.[1] They are akin to liposomes. Both Niosomes liposomes act as active carriers of both amphiphilic and lipophilic drugs.

Difference in the niosomal and liposomal system is that niosomal bilayer is formed by non-ionic surfactant where as liposomal bilayer made up of phospholipids.

Niosomes are formed by the self assembly of non-ionic surfactants in aqueous media as spherical, unilamellar, bilayered, multilamellar system and polyhedral structures depending on the method used to prepare and the inverse structure in case of non-aqueous solvent.

The orientation of the surfactant in niosome in hydrophilic ends exposed outwards while hydrophobic ends face each other forming bilayer of the surfactant.

The size of the niosomes ranges between 10 to 1000nm. Addition of cholesterol and a small quantity of anionic surfactant for instance dicetyl phosphate stabilizes the niosomal vesicles formed by the non-ionic surfactant.[2] Niosomes are suggested to be better than liposomes because of the higher chemical stability of surfactants than phospholipids which are easily hydrolyzed due to the ester bond and cost effective. Niosomes illustrate a promising drug delivery.[3] Various methods of administration of niosomal formulation include intramuscular,[4] intravenous,[5] peroral,[6] and transdermal.[7]

The concept of a drug-delivery system refers to a process of administering pharmaceutical compounds at a predetermined rate to achieve a therapeutic effect in humans or animals at a diseased site, and at the same time, reducing the concentration of the medication in surrounding tissues. Localized drug action enhances the efficacy of drug and reduces systemic toxic effects to tissues.[8]

Paul Ehrlich proposed the idea of targeted delivery directly to the diseased cell without damaging healthy cells in 1909, and this strategy has been known as the "magic bullet".[9] Since then, a number of drug carrier systems have emerged, including immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, and niosomes.[8]

Among these systems, liposomes and niosomes are well-documented vesicular drugdelivery systems.[10-13]

In general, a vesicular system is a drug-delivery platform that enables effective bioavailability of drugs through controlled release of therapeutic drugs for a prolonged period.[14–17]

The vesicles consist of bilayer amphiphilic molecules that surround an aqueous compartment.[15,18,19]

Niosomes are vesicles of nonionic surfactant (for example, alkyl ester and alkyl ether) and cholesterol that act as a carrier for amphiphilic and lipophilic drugs.

Niosomes improve the therapeutic performance of encapsulated drug molecules by protecting the drug from harsh biological environments, resulting in their delayed clearance.[22]

Advantages Of Niosomes

- The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages: -
- Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external nonaqueous phase.
- The vesicle suspension is water–based vehicle. This offers high patient compliance in comparison with oily dosage forms.
- Niosomes possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.
- The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
- The vesicles may act as a depot, releasing the drug in a controlled manner.
- They are osmotically active and stable, as well as they increase the stability of entrapped drug.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
- They can be made to reach the site of action by oral, parenteral as well as topical routes.
- The surfactants are biodegradable, biocompatible and non-immunogenic hence can be used safely in preparation of niosomes.
- They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.
- Handling and storage of surfactants requires no special conditions.

Structure of Niosomes

- Niosomes are spherical and consist of microscopic lamellar (unilamellar or multilamellar) structures (Figure 1). The bilayer is formed by nonionic surfactants, with or without cholesterol and a charge inducer.[23,24]
- Different types of surfactants at variable combinations and molar ratios are used to form niosomes.[25]
- Examples of surfactants include alkyl ethers, alkyl glyceryl ethers, sorbitan fatty acid esters, and polyoxyethylene fatty acid esters. Addition of cholesterol maintains the rigidity of the bilayer, resulting in less leaky niosomes.
- Meanwhile, charge inducers provide charge to the vesicles and increase vesicle size, increasing drug entrapment efficiency.
- Negative charge inducers, including dicetyl phosphate, dihexadecyl phosphate, and lipoamino acid, and positive charge inducers, including stearylamine and cetylpyridinium chloride, help to stabilize the vesicles.[26–29]

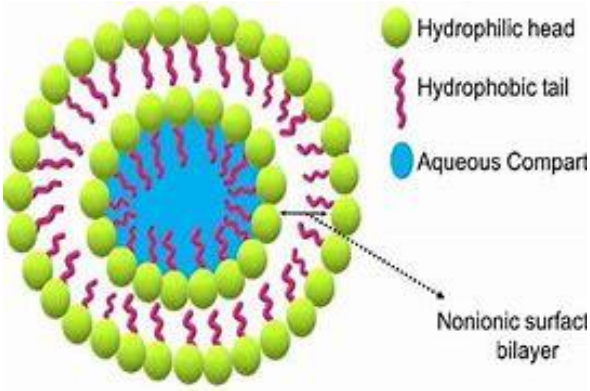

Figure 1: Structure of a noisome.

TYPES OF NIOSOME

The different types of niosomes are as follows:

- Multi lamellar vesicles (MLV)
- Large unilamellar vesicles (LUV)
- Small unilamellar vesicles (SUV).

Methods of preparation

1. Ether injection method

The ether injection method basically entails slowly injecting warm water maintained at 60°C with a surfactant solution dissolved in diethyl ether.

A 14-gauge needle is used to introduce the surfactant mixture in ether into the material's aqueous solution. Ether vapourization produces singlelayer vesicles. The niosomes produced range in diameter from 50 to 1000 nm depending on the parameters used.[30]

2. Hand shaking method (thin film hydration technique)

[31]In this procedure, the cholesterol and surfactant are dissolved in a round-bottomed flask using a volatile organic solvent (such as diethylether, chloroform, or methanol).

A rotary evaporator is used to extract the organic solvent at room temperature (20°C), leaving behind a thin coating of solid mixture that is deposited on the flask wall. Rehydrating the dried surfactant film with aqueous phase at 0 to 60 °C while gently stirring can result in the formation of multilamellar niosomes.

3. Sonication method

In this procedure, a 10-ml glass vial holding the surfactant/cholesterol mixture is filled with an aliquot of the drug solution in buffer. Using a titanium probe, niosomes are created by sonicating the liquid for three minutes at 60°C.

4. Micro fluidization method[32]

Micro fluidization is a more modern technique for producing unilamellar vesicles with a certain size distribution. This method is based on the submerged jet theory, which describes how two fluidized streams collide at very high speeds inside carefully designed microchannels inside an interaction chamber.

The energy delivered to the system remains in the region where niosomes form because the thin liquid sheet impingement is positioned along a single front. The result is the synthesis of more compact, reliable, and repeatable niosomes.

5. Multiple membrane extrusion method: A thin film is formed when a mixture of diacetyl phosphate, cholesterol, and surfactant in chloroform evaporates.

Aqueous drug polycarbonate membranes are used to hydrate the film. Through up to eight passages, the solution is extruded via these membranes. and the final result is the suspension that follows. It's a practical way to manage loud size.

6. Reverse Phase Evaporation Technique

[33]In this process, the cholesterol and surfactant are dissolved in a 1:1 ether and chloroform solution. This is combined with an aqueous phase that contains medicine, and the two stages are sonicated concurrently at 4-5°C. PBS, or phosphate buffered saline, is added once a clear gel has formed. which receives more sonication.

The organic phase is removed at 40 °C using low pressure. The resultant viscous noisome suspension is heated on a water bath at 60°C for 10 minutes, and then it is diluted with PBS to form niosomes.

7. Transmembrane pH gradient (inside acidic) Drug Uptake Process

A solution of surfactant and cholesterol is dissolved using chloroform. Next, as the solvent evaporates at a lower pressure, a thin layer forms on the wall of the flask with a circular bottom. This film is hydrated with 300mm citric acid (PH 4.00) via vertex mixing. Next, three rounds of sharing, freezing, and sonication are applied to the resultant multilamellar vesicles.

This niosomal suspension is mixed with an aqueous solution containing 10 mg/ml of the drug, and vortexes are formed. Next, 1M disodium phosphate is added to the sample to raise its pH to 7.0–7.2. This mixture is heated to 60 °C for 10 minutes in order to form niosomes.

8. The Bubble Method

[32]A three-necked flask with a spherical bottom that is submerged in water to control temperature is the bubbling unit.

The third neck receives nitrogen supplies, while the first and second necks have a thermometer and a reflux that is cooled by water.

Both cholesterol and surfactant are distributed concurrently in this buffer (PH 7.4). The dispersion is then quickly 'bubbled' at the same temperature with nitrogen gas to create niosomes after being blended for 15 seconds with a high shear homogenizer.[30,34]

FACTORS AFFECTING NIOSOMES FORMULATION

1. **Drug:** The drug's interaction with surfactant head groups raises the charge and mutual repulsion of the surfactant bilayers within niosomes, hence increasing the vesicle's size. Drugs are trapped in the lengthy PEG chains of polyoxymethylene glycol (PEG) coated vesicles, which inhibits their capacity to swell. The degree of entrapment is influenced by the medication's hydrophilic lipophilic equilibrium.[35]

2. **Amount and type of surfactant:** Because the surface free energy of HLB surfactants, such as Span 85 (HLB 1.8) to Span 20 (HLB 8.6), drops as the surfactant's hydrophobicity increases, the mean size of niosomes grows proportionately. The vesicles' bilayers can exist in either a liquid or gel state, contingent on many factors such as temperature, surfactant type, and the inclusion of

other components like cholesterol. Alkyl chains are present in the gel state in a well-organized form, while the bilayer structure is more disorganised in the liquid state.

The temperature at which the gel liquid phase change occurs describes the lipids and surfactants. The phase transition temperature of the surfactant influences entrapment efficiency, span 60 has a greater.

3. Cholesterol content and charge: The hydrodynamic diameter and niosome trapping efficiency were enhanced by cholesterol. Cholesterol generally has two effects: it increases the chain order of liquid state bilayers while also making the chain orders of gel state bilayers more disordered. At high concentrations of cholesterol, the gel state gives way to a liquid-ordered phase.

The resultant bilayers were stiffer due to a delayed rate of encapsulated material release caused by a higher cholesterol content in the bilayers. Charge has the tendency to increase the overall entrapped volume in multilamellar vesicle formations by lengthening the interlamellar distance between consecutive bilayers.

4. Methods of Preparation: The vesicles produced by the hand shaking approach have a diameter of 0.35–13 nm, which is larger than that of the ether injection method. One technique for producing tiny niosomes is reverse phase evaporation.

The micro fluidization process yields more uniformity and smaller vesicles. Drug entrapment and retention were improved in niosomes produced by the trans membrane pH gradient, an acidic drug absorption method.[36,37]

5. Resistance To Osmotic Stress: When niosomes are suspended in a hypertonic salt solution, their diameter decreases.

After a first slow release with slight vesicle enlargement in a hypotonic salt solution, a faster release could result from mechanically loosening the vesicles' structure under osmotic stress.[36,38,39]

Characteristics of Niosomes

- i. Vesicle diameter and morphology
- ii. Vesicle charge
- iii. Bilayer formation
- iv. Number of lamella
- v. Membrane rigidity and homogeneity
- vi. Drug loading and encapsulation efficiency
- vii. In-vitro drug release
- viii. Stability studies

i. Vesicle diameter

Niosomes are spherical in shape and the size range from 20nm to 50µm. Techniques used to determine the vesicle size and size distribution include light microscopy, coulter counter, and photon correlation microscopy and freeze fracture electron microscopy. Scanning electron microscopy, atomic force microscopy and cyto transmission electron microscopy are used to determine the shape and surface characteristics of the niosomes.[40]

ii. Vesicle charge

The vesicle surface charge plays a major role in the stability and behaviour of niosomes. Charged niosomes are found to be more stable than uncharged niosomes against aggregation and fusion. Surface potential of niosomes can be estimated by the zeta potential measured by micro electrophoresis or dynamic light scattering.[41] PH sensitive fluorophores can be used as an alternative method.

iii. Bilayer formation

Bilayer vesicle formation can be characterized by x-cross formation due to the assembly of non-ionic surfactants under light polarization microscopy.[42]

iv. Number of lamellae

Number of lamellae in vesicles is characterized by NMR spectroscopy, electron microscopy and small angle Xray scattering.[43]

v. Membrane rigidity and homogeneity

Membrane rigidity influences the bio distribution and bio degradation of niosomes. The bilayer rigidity of vesicles can be determined by the mobility of fluorescence probe as function of temperature. Membrane homogeneity can be identified by P-NMR, differential scanning calorimetry(DSC), fourier transform-infra red spectroscopy(FT-IR) and fluorescence resonance energy transfer(FRET).[44]

vi. Drug loading and encapsulation efficiency

Drug loading and encapsulation efficiency of niosomal dispersion is determined after the separation of unentrapped drug.

vii. In-vitro drug release

In-vitro drug release of niosomes can be characterized by the following methods[45]

1. Dialysis
2. Reverse dialysis
3. Franz diffusion cell

1) Dialysis: It is the simplest method used to determine the invitro release kinetics of the niosomal loaded drug. Dialysis tubing is used.

Niosomal suspension is placed in the dialysis sack which is hermetically sealed. Dialysis is carried out by placing the sack in 200ml of buffer solution with constant stirring at 25ºC or 27 ºC. Samples are withdrawn at regular intervals and drug content analysis is carried out by suitable method.

2) Reverse dialysis: 1 ml of dissolution medium is taken in a number of small dialysis tubes into which niosomes are added. Then the niosomes are displaced from the dissolution medium.

3) Franz diffusion:- Niosomes are dialyzed against suitable dissolution media through a cellophane membrane at room temperature in Franz diffusion cell.

The samples are withdrawn at regular intervals of time and analysis is carried out to determine the drug content. Now-a-days FRET is used to monitor the release of encapsulated matter in niosomes

viii. Stability of niosomes

Stability of niosomes is indicated by the constant particle size and constant concentration of entrapped drug. Stability of niosomes depends upon the concentration and type of surfactant, cholesterol.[46]
E.g.: Sonicated spherical niosomes are stable at room temperature. Sonicated polyhedral niosomes are instable at room temperature but stable at the temperature above the phase transition temperature.

Current applications of niosomes

Drug-delivery systems using niosomes through transdermal, parenteral, and ophthalmic routes are well studied.[47,48] Niosomal delivery via transdermal routes is able to overcome the slow penetration rate of conventional transdermal approaches.

The bioavailability and therapeutic efficacy of drugs such as diclofenac, flurbiprofen, and nimesulide increase by their incorporation into niosomal formulations.

For ophthalmic drug delivery, chitosan-coated niosomal formulation of timolol maleate exhibits a greater effect in reducing intraocular pressure compared with marketed formulations, with less cardiovascular side effects.[48] Because of their many desirable properties, niosomal formulations have been used in many other therapeutic applications, as discussed in the following sections.

Niosomal formulations have been used extensively in many other applications such as transdermal delivery. For example, 8-methoxypsoralen, a compound used in psoralen ultraviolet A therapy[49], had been formulated into niosomal vesicles and delivered topically to increase its local efficacy and safety.[50]

Another group of investigators has attempted to develop a niosomal gel formulation with acyclovir that has a superior topical bioavailability.[51]

Acyclovir is used in the treatment of herpes simplex, varicella zoster, and herpes zoster viral infections. Its usual route of oral administration is plagued by poor bioavailability and short elimination half life.[52]

Usual topical delivery is limited by the poor intrinsic permeation of acyclovir into the basal epidermis. A goal of topical delivery is that the drug is transported through the stratum corneum, thereby effectively reaching the target tissue.

The niosomal gel developed by Jacob et al. demonstrated successful delivery of acyclovir through topical administration. Niosomes could also potentially serve as gene delivery system.

Niosomes prepared by using cationic lipid N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride and the nonionic surfactant polysorbate 60, with or without lycopene, were used to encapsulate promoter of cytomegalovirus-enhanced green florescent protein (pCMSEGFP)-based plasmids.

The niosomes generated were then used in the transfection of ARPE-19 human retinal pigment epithelial cells. The higher transfection efficiency obtained indicates the potential use of this gene delivery system for various inherited retinal diseases.[53] Opanasopit et al. also investigated the use of niosomes using this approach.

They reported that cationic niosomes composed of Span 20, cholesterol, and spermine-based cationic lipids encapsulating pDNA encoding EGFP contributed to a high transfection efficiency of HeLa human cervical cells.[54] Other uses of niosomes include the treatment of glaucoma using dorzolamide niosomes[55], specific niosomal drug-delivery systems that target the liver[56] and induction of angiogenesis using growth factor-loaded nano-niosomal gel formulations.[57] Moghassemi et al.[58] formulated bovine serum albumin-loaded niosomes that have potential use in pharmaceutical and cosmetic applications.

Inflammation

Niosomal formulations of diclofenac sodium, nimesulide, and flurbiprofen exhibit greater anti-inflammatory activity than the free drugs.

Niosomal formulations of diclofenac diethylammonium, aceclofenac, meloxicam, and lornoxicam used for topical application also show good anti-inflammatory activity because of the penetration of niosomes into the deeper layers of the skin.[59–60]

Additionally, mefenamic acidloaded niosomes prepared by Kamboj et al.[61] demonstrated enhanced inhibition of inflammation in vivo.

Bacterial or fungal infections

Itraconazole is the drug of choice for treating fungal infections caused by Blastomyces dermatitidis, Histoplasma capsulatum, Paracoccidioides brasiliensis, and Coccidioides immitis.

It is used in the treatment of pseudallescheriasis, sporotrichosis, tinea corporis, tinea versicolor, and toenail onychomycosis. However, it has poor solubility and permeation that hinder its absorption through skin. Incorporation of the drug in niosomes enhanced its therapeutic efficacy, as evidenced by a study in which the itraconazole niosomes demonstrated greater antimycotic activity against Candida albicans than marketed formulations.[62]

Another potentially antifungal drug called diallyl disulfide was found to be entrapped in niosomes prepared efficiently using Span 80. When the niosomal diallyl disulfide was administered to C. albicans-infected mice, it cleared the fungal burden and increased the survival rate of the mice; the effect was better than the drug in free form.[63]

Fluconazole, which is commonly available in parental and oral dosage forms, is used in the treatment of cutaneous candidiasis. However, the drug is well known for its adverse effects such as taste disturbances and gastrointestinal irritation.

When the drug is given in an oral form, a high dose is usually required to reach therapeutic concentrations. Therefore, a topical formulation of the drug was developed.

Fluconazole-loaded niosomal gels were formulated as a topical ocular drug-delivery system for corneal fungal infections. Fluconazole was incorporated into poloxamer or chitosan niosomal gel, and the antifungal effects of the 2 gels were compared. Fluconazole in the poloxamer gel showed a better effect than it did in the chitosan gel.[64]

In another study, miconazole loaded in proniosomal vesicles was proven to be effective against Trichophyton rubrum in the treatment of tinea infections.[65]

Nisin is an antimicrobial agent used in food and pharmaceutical applications.[66] However, its effectiveness is limited because of its inaccessibility to an inner membrane of bacteria. Hence, ethylenediaminetetraacetic acid (EDTA) is used to improve the efficacy of nisin.[67]

Niosomes encapsulating both nisin and EDTA were evaluated for their antibacterial activity.

The encapsulated form of nisin and EDTA showed a better and longer-lasting effect in inhibiting Staphylococcus aureus than their free forms.[68] Gallidermin, an antibiotic that has effects similar to erythromycin or fusidic acid, is effective against endocarditis, abscesses, skin infections, and acne.[69]

When gallidermin is loaded in anionic niosomes and incorporated in gel, it accumulated in the skin with no risk of a systemic effect and displayed better antibacterial effects, particularly against Propionibacterium acnes and S. aureus.[70]

Niosomal cosmetics are already in market.

Examples of niosomal cosmetic preparations include: Estee Lauder - Beyond Paradise After Shave Lotion, White Shoulders Eau De Cologne Spray, Orlane Lip Gloss, Le Classique Eau De Toilette Spray, Love In Paris- Deodorant Spray, Liz Claiborne - Realities Shower Gel, Givenchy - Blanc Parfait - Day Care, Lancome- Foundation & Complexion, Britney Spears- Curious Coffret, Elene - Eye Care, Guinot - Night Care, Gatineau - Moderactive – Cleanser, Shiseido - Bio Performance - Night Care, Boss Soul After Shave, Amarige Eau De Toilette Spray, Chrome Eau De Toilette Spray, Golden Beauty After Sun Soothing Moisturiser, Guinot – Cleanser Gentle Face Exfoliating Cream.

Sustained Release Azmin et al suggested the role of liver as a depot for methotrexate after niosomes are taken up by the liver cells. Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation.

Localized Drug Action Drug delivery through niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects e.g. Antimonials encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity. The evolution of niosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.

CONCLUSIONS

Niosomes, a nonionic surfactant vesicular system, is a novel and efficient approach to drug delivery. With the incorporation of appropriate nonionic surfactant and cholesterol in the vesicular membrane, a wide range of drugs can be encapsulated. From the past few decades, there is a great revolution in development of novel drug delivery system. The technology of utilizing niosomes as promising drug delivery system is still in its infancy. Niosomes have shown a profound influence in targeting the particular organ and tissue. Niosomes can serve as better diagnostic agents, vaccine delivery system, tumour targeting agents, ophthalmic, nasal and transdermal delivery systems. Research has to be carried out extensively to have commercially available niosomal formulations. Drug incorporation in the niosomes to target the niosomes to the specific site is a promising drug delivery model. 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 multienvironmental structure. Niosomes are considered to be better candidates for drug delivery as compared to liposomes due to various factors like cost, stability etc. Niosomes are promising vehicles at least for lipophilic drugs. These advantages over the liposomes make it a better targetting agent. Ophthalmic, topical, parentral and various other routes are used for targetting the drug to the site of action for better efficacy.

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