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AN OVERVIEW ON TRENDS AND DEVELOPMENT OF NIOSOMES AS DRUG DELIVERY

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ABSTRACT

Niosomes or non ionic surfactant are microscopic lamellar structures which may be unilamellar or multilamellar. These are amphiphillic in nature, hence capable of entrapping both hydrophilic and lipophilic drugs for their controlled delivery. Niosomes are formulated by hydration of the lipid by the aqueous phase which may be either single surfactant or a mixture of surfactant with cholesterol. Stability of niosomes is greater as compared with other novel drug delivery techniques. Niosomes are widely used for delivery of many drugs especially in treatment of life threatening diseases, site specific targeting can be achieved with niosomes, and they are also used in diagnostic imaging purpose. This study is based upon the recent advances by which niosomes can be formulated and their application in controlled and effective delivery of various drugs. 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 thoughts 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, parenteral, etc.

INTRODUCTION

At present no available drug delivery system achieves the site specific delivery with controlled release kinetics of drug in predictable manner. Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc. Among different carriers liposomes and niosomes are well documented drug delivery. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with nontarget tissue. Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of nonionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate.

Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, numbers of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc.[1,2,3,4]

Advantages of Niosomes [5, 6, 7]

- The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages: - ·The vesicle suspension is water–base vehicle.
- This offers high patient compliance in comparison with oily dosage forms. ·They 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. Other advantages of niosomes include: They are osmotically active and stable, as well as they increase the stability of entrapped drug. Handling and storage of surfactants requires no special conditions. 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.

Comparison of Niosomes Vs Liposomes-[8,9,10]

a) Niosomes are now widely studied as an alternative to liposome's, which exhibit certain disadvantages such as they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids are variable.

b) Differences in characteristics exist between liposome's and niosomes, especially since niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposome's are prepared from double-chain phospholipids (neutral or charged) Handjani-Vila *et al* 6 were first to report the formation of vesicular system on hydration of mixture of cholesterol and a single-alkyl chain non-ionic surfactant.

c) Niosomes behave *in-vivo* like liposome's, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. Encapsulation of various anti neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, increasing the anti-tumour efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. They can be expected to target the drug to its desired site of action and/or to control its release.

d) As with liposome's, the properties of Niosomes depends both on the composition of the bilayer and on method of their production. It was observed by Baillie *et al*10 that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation and thus entrapment efficiency. As the concentration of cholesterol increases, entrapment efficiency decreases.

e) The entrapment efficiency increases with increase in the concentration and lipophilicity of surfactant. Chandraprakash *et al*12 made Methotrexate loaded nonionic surfactant vesicles using

lipophilic surfactants like Span 40, Span 60 and Span 80 and found that Span 60 (HLB = 4.7) gave highest percent entrapment while Span 85 (HLB = 9.8) gave least entrapment. They also observed that as HLB value of surfactant decreased, the mean size was reduced.

Types of Niosome: [11, 12]

Niosomes can be divided into three groups on the basis of their vesicles size:

(i) Small Unilamellar Vesicles (SUV, Size=0.025-0.05 µm)

(ii) Multilamellar Vesicles (MLV, Size=>0.05 µm)

(iii) Large Unilamellar Vesicles (LUV, Size=>0.10 µm)

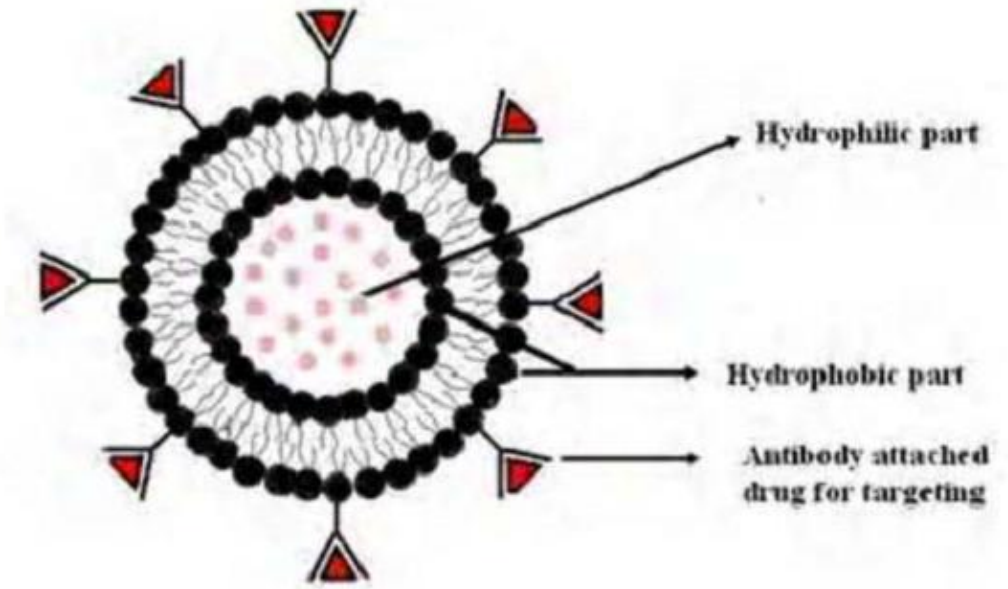

Fig. 1: Niosome Structure

Methods of Preparation:[13,14,15,16,17]

1.Ether injection method

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

2. 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 film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.

3. Sonication

A typical method of production of the vesicles is by sonication of solution as described by Cable. 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**.**

4. Micro fluidization

Micro fluidization 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 greater uniformity, smaller size and better reproducibility of niosomes formed**.**

5. 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 solution and the resultant suspension extruded through polycarbonate membranes, which are placed in series for upto 8 passages. It is a good method for controlling niosome size.

6. Reverse Phase Evaporation Technique (REV)

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.

7. Ether injection method

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

8. 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 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.

9. The "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.

10. 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". The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation. T=Temperature. Tm = mean phase transition temperature. Blazek-Walsh A.I. *et al* [18] have 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.

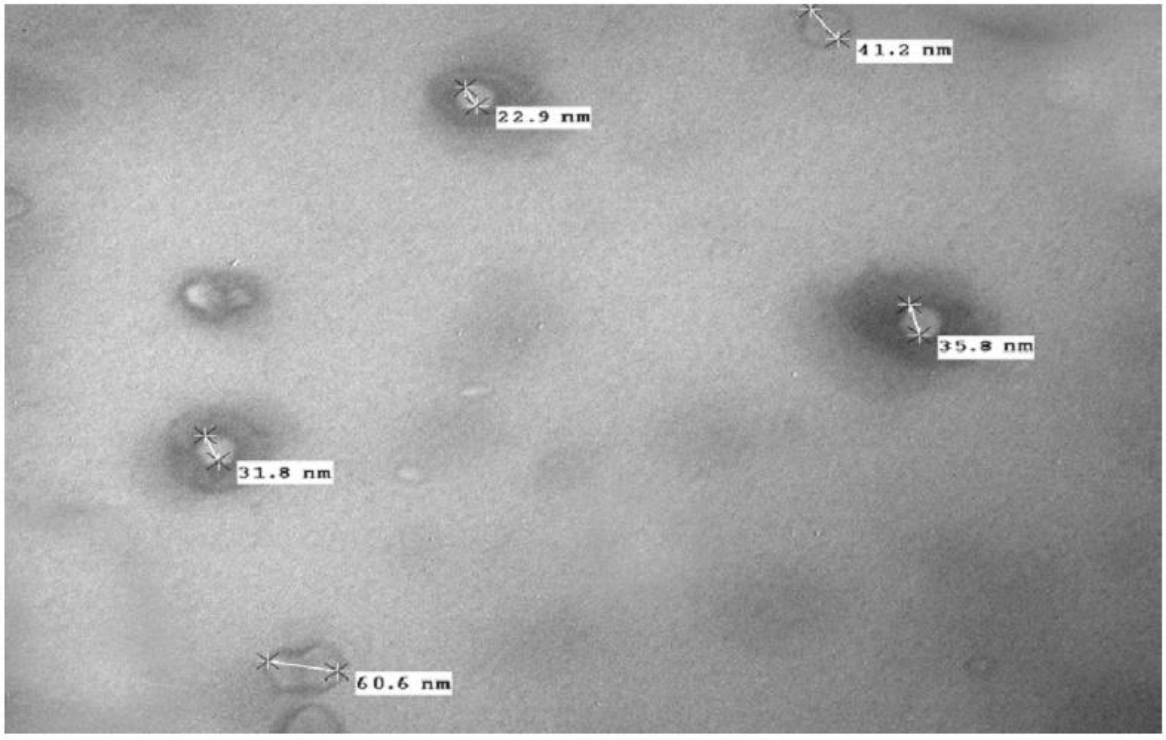

Fig.2:Transmission Electron Micrograph (TEM) of the Niosomes

Evaluation of Niosomes :[18,19,20,21]

Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is separated by dialysis centrifugation and gel filtration. The drug remain entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzed resultant solution by appropriate assay method using following equation.

Particle size analysis

Particle size analysis can be done by scanning electronic microscopy (SEM) using JEOL JSM-T330A scanning microscope brass stab. The stabs can be place briefly in a drier and then can be coat with gold in an ion sputter. Pictures of niosomes can be taken by random scanning of the stub and count. The diameter of niosomes can be measured from the photomicrographs of each batch.

In-vitro release study

Human cadaver skin (HCS) was obtained from ventral part of forearm of 35 years old male corpse and was stored at 4°C. HCS membrane was spread and punches it at approximately 3 cm2 area. Trimmed away the excessfat and sliced to 500□m thickness using a Daw's derma tone. These slices were hydrated in pH 7.4 PBS for 24 hrs prior to use. The HCS were attached to Khesary cell (K.C., filled with 100 ml of PBS) and add 10 mg niosomal suspension on it. Finally, cell was immersed into the receptor compartment. The dermal surface was just flush to the surface of permeation fluid (PBS), which was maintain at 37°C 0.50° C and stirred magnetically at 50 r.p.m., aliquots were withdraw and replaced with the same volume of fresh buffer, at every sampling points and analyzed by U. V. Spectrophotometer method at 294 nm.

Stability study

All niosomal formulations were subjected to stability studies by storering at 4°C, 25°C and 37°C in thermostatic oven for the period of three months. After one month, drug content of all the formulations were checked by method discussed previously in entrapped efficiency parameter. *In-vitro* release studies of selected formulations were also carried out.

Application of Niosomes: **(22,23 24,25,26,27)**

A. Niosomes as Drug Carriers

A number of workers have reported the preparation, characterization and use of niosomes as drug carriers. Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes. The niosomal encapsulation of Methotrexate and Doxorubicin increases drug delivery to the tumor and tumoricidal activity of the drug. Doxorubicin niosomes possessing muramic acid and triglycerol surfaces were not taken up significantly by liver. The triglycerol niosomes accumulated in the tumor and muramic acid vesicles accumulated in the spleen. Those vesicles with polyoxyethylene surface were rapidly taken up by the liver and accumulated to a lesser extent in tumor. Baillie *et al* investigated the encapsulation and retention of entrapped solute 5,6-carboxy fluorescence (CF) in niosomes. They observed that stable vesicles could not be formed in the absence of cholesterol but were more permeable to entrapped solute. The physical characteristics of the vesicles were found to be dependent on the method of production. Chandraprakash *et al* reported the formation and pharmacokinetic evaluation of Methotrexate niosomes in tumor bearing mice.

Cable *et al* modified the surface of niosome by incorporating polyethylene alkyl ether in the bilayered structure. They compared the release pattern and plasma level of Doxorubucin in niosomes and Doxorubucin mixed with empty niosomes and observed a sustained and higher plasma level of doxorubicin from niosomes in mice. D' Souza *et al* studied absorption of Ciprofloxacin and Norfloxacin when administered as niosome encapsulated inclusion complexes. Raja Naresh *et al* reported the antiinflammatory activity of niosome encapsulated Diclofenac sodium in arthritic rats. It was found that the niosomal formulation prepared by employing a 1:1 combination of Tween 85 elicited a better consistent anti-inflammatory activity for more that 72 hrs after administration of single dose. Carter *et al* reported that multiple dosing with sodium stibogluconate loaded Niosomes was found to be effective against parasites in the liver, spleen and bone marrow as compared to simple solution of sodium stibogluconate. Namdeo *et al* reported the formulation and evaluation of Indomethacin loaded Niosomes and showed that therapeutic effectiveness increased and simultaneously toxic side effect reduced as compared with free Indomethacin in paw edema bearing rats. Parthasarthi *et al* prepared niosomes of vincristine sulfate which had lesser toxicity and improved anticancer activity. Jagtap and Inamdar prepared niosomes of Pentoxifylline and studied the *in-vivo* bronchodilatory activity in guinea pigs. The entrapment efficiency was found to be 9.26 ± 1.93% giving a sustained release of drug over a period of 24 hrs. Azmin *et al* reported the preparation and oral as well as intravenous administration of Methotrexate loaded niosomes in mice. They observed significant prolongation of plasma levels and high uptake of Methotrexate in liver from niosomes as compared to free drug solution.

B. 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.

Anti-cancer drug

Daunorubicin HCl

Niosomal daunorubicin hydrochloride exhibited an enhanced antitumor 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. Doxorubicinloaded 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 methotreaxate is high compared to drug solution.

Bleomycin

Niosomal formulation of bleomycin containing 47.5% cholesterol exhibits higher level drug in the lever, spleen and tumour as compared to plan drug solution in tumorbearing mice . There is no significant difference in drug concentration with niosomal formulation in lung as compared to plan drug solution.10Also; 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 (Parthasarathi G et al., 1994). Also, niosomal formulation of carboplatin exhibits higher tumoricidal efficacy in S-180 lung carcinoma-bearing mice as compared to plan drug solution and also less bone marrow toxic effect.

Anti-infective agents

Sodium stibogluconate is a choice drug for treatment of visceral leshmaniasis is a protozoan infection ofreticuloendothelial 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.

C. Diagnostic imaging with Niosomes

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

D. 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. Alsarra et al., studied transdermal delivery pro-niosomal 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.

E. 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 use, 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 presents 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 thoughts 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, parentral, etc.

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