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REVIEW ARTICLE

Proniosome & Niosome in Transdermal Application

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ABSTRACT

During the past decade formulation of vesicles as a tool to improve drug delivery. This has brought a revolution in the field of science which lead to the development of novel dosage forms such as niosomes, liposomes & proniosomes. Niosomes are non-ionic surfactant based multilamellar or unilamellar vesicles in which an aqueous solution of solute is enclosed by a membrane resulted from the oraganisation of surfactant macromolecule as bilayer. Proniosomes are recent development made in transdermal therapeautic system. Transdermal therapeautic system are the recently developed devices which are non-invasive to the skin as compared to other routes for drug administration. Proniosomes are drug formulation of water soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. They help in reducing physical instability such as leaking, fusion, aggregation & provide convenience in dosing, distribution, transportation & storage. The review focuses on different aspects of proniosomes & niosomes such as advantage, method of preparation, types, evaluation & clinical application in transdermal drug delivery.

KEYWORDS: Niosomes, Proniosomes, vesicles, administration, transdermal, clinical.

INTRODUCTION

Transdermal therapeutic systems are the recently developed devices, which are non invasive to skin as compared to other routes for administration of drugs. Although the skin, particularly the stratum corneum presents a barrier to most drug absorption, it provides a large (1-2 mtr) and accessible surface area for drug diffusion. Various types of transdermal therapeutic systems are utilized for long term continuous infusion of therapeutic agents, including antihypertensives, antifungal, analgesics, steroids and contraceptive drugs. Although transdermal delivery is currently limited to few drugs, it has achieved considerable commercial success. Some drugs which are used in transdermal delivery systems include nitroglycerine, scopolamine, estradiol, testosterone, nicotine, clonidine and estrogen-progestin combination into transdermal products.[(1)]

Niosomes:

Niosomes are non-ionic surfactants based multilamellar or unilamellar vesicles in which an aqueous solution of solute(s) is enclosed by a membrane resulted from the organization of surfactant macro-molecule as bilayer. Proniosomes are recent development made in transdermal therapeutic systems. These are niosomes possesses demerits like

1. Fusion
2. Aggregation
3. Sedimentation
4. Leakage on storage
5. Physical instability [(2)]

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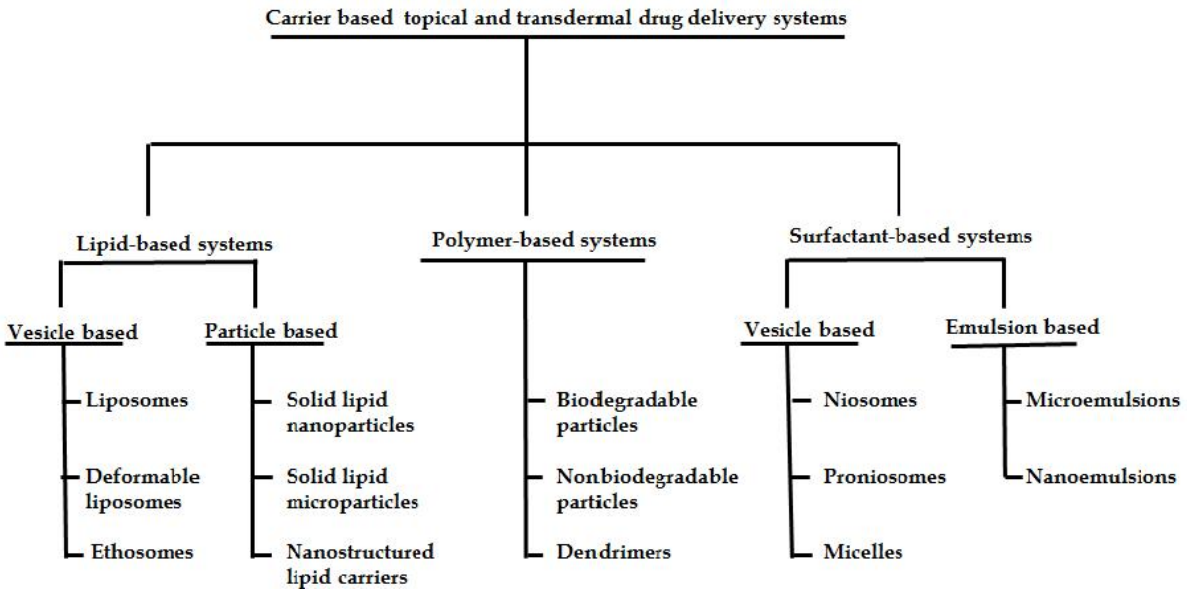

Proniosomes: Proniosomes are dry formulation of water-soluble carrier particles that are coated with surfactant and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. The resulting niosomes are very similar to conventional niosomes and more uniform in size.

Interaction Between skin and proniosomes:

There is a direct contact of proniosome formulation with skin after applies, so it is better to discuss the potential interactions between skin and vesicles formed in proniosome/niosome formulations. As we know that proniosomes or proniosomes derived niosomes are composed of non-ionic surfactants, and the vesicles are composed of these non-ionic surfactant only. So it is advisable to study the interactions between non-ionic surfactants and the skin. The non ionic surfactants are amphipathic molecules consisting of a hydrophobic (alkylated phenol derivatives, fatty acids, long chain linear alcohols, etc.) and a hydrophilic part (usually ethylene oxide chains of variable length). Nonionic surfactants are used widely in pharmaceuticals to increase their stability, solubility and permeation. There is a strong indication that the degree of interaction between vesicles and skin mainly depends on physicochemical properties of the surfactant molecules of which the niosomes or proniosomes are composed. Skin consists of a range of bioactive material like membrane phospholipids, proteins, amino acids, peptides, etc.

Surfactants are known to increase the permeability of vesicles and phospholipid membranes, causing low molecular mass compounds to leak. The interaction between biological membranes and non-ionic surfactant tested for phospholipid composition and rate of biosynthesis of major phospholipid components indicate no significant change in the phospholipid composition, where as biosynthesis and turnover rates of phospholipids were increased two to four times.[3

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Proniosomes: an Overview

Proniosomes are dry formulations of surfactant-coated carrier, which can be measured out as needed and rehydrated by brief agitation in hot water. These “proniosomes” minimize problems of niosomes physical stability such as aggregation, fusion and leaking and provided additional convenience in transportation, distribution, storage and dosing. Proniosome derived niosomes are superior to conventional niosomes in convenience of storage, transport and dosing. Stability of dry proniosomes is expected to be more stable than a pre-manufactured niosomal formulation. In release studies proniosomes appear to be equivalent to conventional niosomes. Size distributions of proniosome derived niosomes are somewhat better that those of conventional niosomes so the release performance in more critical cases turns out to be superior. [(4) (5)]

Proniosomes are dry powder, which makes further processing and packaging possible. The powder form provides optimal flexibility, unit dosing, in which the proniosome powder is provided in capsule could be beneficial. A proniosome formulation based on maltodextrin was recently developed that has potential applications in deliver of hydrophobic or amphiphilic drugs. The better of these formulations used a hollow particle with exceptionally high surface area. The principal advantage with this formulation was the amount of carrier required to support the surfactant could be easily adjusted and proniosomes with very high mass ratios of surfactant to carrier could be prepared. Because of the ease of production of proniosomes using the maltodextrin by slurry method, hydration of surfactant from proniosomes of a wide range of compositions can be studied. [(6) (7)]

COMPONENTS OF PRONIOSOMES

The essential components for the delivery system are as follows.

1. Surfactants:

Surfactants are the surface active agent usually organic compounds that are amphiphilic in nature (having both hydrophobic and hydrophilic groups). Therefore, a surfactant molecule contains both a water insoluble (lipophilic) and a water soluble (hydrophilic) component. They have variety of functions including acting as solubilizers, wetting agents, emulsifiers and permeability enhancers. [(8)]

The most common non-ionic amphiphiles used for vesicle formation are alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids (Table 1).

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Table 1: List of common non-ionic amphiphiles used in proniosome formulation

S.No.	Non-ionic Amphiphiles	Examples
1.	Alkyl ethers and alkyl glyceryl ethers	Polyoxyethylene 4 lauryl ether (Brij30) Polyoxyethylene cetyl ethers(Brij 52, 56, 58) Polyoxyethylenestearyl ethers (Brij 72, 76)
2.	Sorbitan fatty acid esters	Span 20, 40, 60, 80
3.	Polyoxyethylene fatty acid esters	Tween 20, 40, 60, 80

2. Carrier material:

The carrier when used in the proniosomes preparation permits the flexibility in the ratio of surfactant and other components that incorporated. In addition to this, it increases the surface area and hence efficient loading. The carriers should be safe and non-toxic, free flowing, poor solubility in the loaded mixture solution and good water solubility for ease of hydration.[9] [10] Commonly used carriers are listed below (Table 2).

Table 2: Carriers used for the preparation of Proniosomes

Sr. No.	Carrier materials investigated
1.	Maltodextrin
2.	Sorbitol
3.	Mannitol
4.	Spray dried lactose
5.	Glucose monohydrate
6.	Lactose monohydrate
7.	Sucrose stearate
8.	Lactose monohydrate
9.	Sucrose stearate

Egg lecithin probably due to the difference in the intrinsic composition [11] [12]

3. Solvent and Aqueous phase:

Alcohol used in Proniosome has a great effect on vesicle size and drug permeation rate. Vesicles formed from different alcohols are of different size and they follow the order: Ethanol > Propanol > Butanol > Isopropanol. Ethanol has greater solubility in water hence leads to

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formation of highest size of vesicles instead of isopropanol which forms smallest size of vesicle due to branched chain present. Phosphate buffer pH 7.4, 0.1% glycerol, hot water is used as aqueous phase in preparation of proniosomes.

4. Drug:

The drug selection criteria could be based on the following assumptions.

1. Low aqueous solubility of drugs.
2. High dosage frequency of drugs.
3. Short half life.
4. Controlled drug delivery suitable drugs.
5. Higher adverse drug reaction drugs.

2. FORMULATION CONSIDERATIONS

It is necessary to understand the role of basic formulation aspects of proniosomes before preparation which includes selection of surfactant, cholesterol concentration, the hydration medium, nature of encapsulated drug.

1. Selection of surfactant:

Surfactants can improve the solubility of some poorly soluble drugs. Selection of surfactants should be done on the basis of HLB value which is a good indicator of the vesicle forming ability of any surfactant. The formation of bilayer vesicles instead of micelles not only depends upon the HLB values of the surfactant but also on the chemical structure of component and the critical packing parameter. The HLB value of a surfactant plays a key role in controlling drug entrapment of the vesicle it forms. The critical packing parameter (CPP) is a geometric expression relating to hydrocarbon chain length (l) and volume (v) and the interfacial area occupied by the head group. CPP = v/ lc × a v = hydrophobic group volume lc = critical hydrophobic group length a = area of hydrophilic head group A CPP below 0.5 and 1 indicates that the surfactant is likely to form vesicles. A CPP of below 0.5 which indicates a large contribution from the hydrophilic head group area is said to give spherical micelles and a CPP of above 1 indicates a large contribution from hydrophobic group volume should produce inverted micelles. Non-ionic surfactant are the most common type of surfactant used in preparing the vesicles due to the superiority over other counterparts having good stability, compatibility and toxicity aspects. It was found that the HLB value in between 4 and 8 was found to be compatible with vesicle formation. The entrapment efficiency of bilayered vesicle also depends upon the phase transition temperature (Tc) of the surfactant [(13)]

2. Cholesterol concentration:

Cholesterol is an essential structural component of cell membrane and is required to establish proper membrane permeability and fluidity. It imparts rigidity to vesicles, which is very important under severe stress conditions. Cholesterol increases or decreases the percentage encapsulation efficiency depending on either the type of the surfactant or its concentration within the formulae. Cholesterol along with the addition of surfactant forms homogenous niosome dispersion rather than only a surfactant which forms a gel. Cholesterol is thus usually included in a 1:1 molar ratio in most formulations as it is known to abolish the gel to liquid phase transition of niosome systems resulting in niosomes that are less leaky. The amount of cholesterol to be added depends on the HLB value of the surfactants. As the HLB value increases above 10 it is necessary to increase the minimum amount of cholesterol to be added in order to compensate for

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the larger head groups. It was found that above a certain level of cholesterol, entrapment efficiency decreased possibly due to a decrease in volume diameter [14]

3. Hydration medium:

Phosphate buffer having various pH‟s are most widely used hydration medium for preparation of proniosome derived niosomes. The solubility of drug being encapsulated determines the actual pH of hydration medium. The temperature of hydration also plays an important role in governing the self assembly of non-ionic surfactant into vesicles and affects their shape and size. In case of proniosomal gel preparation, the hydrating temperature used to make niosomes should usually be above the gel to liquid phase transition temperature of the system. The proniosome derived niosomes are very similar to conventional niosomes and more uniform in size.

4. Nature of encapsulated drug:

The main factor in the consideration is the influence of an amphiphilic drug on vesicle formation. When drug was encapsulated in niosomes, aggregation occurred and was overcome by the addition of a steric stabilizer. When more drug is added the increase in its encapsulation could be the result of saturation of the medium. This suggests that the solubility of certain poorly soluble drugs can be increased by formulation in niosomes but only up to a certain limit above which drug precipitation will occur. Increase in drug concentration showed an increase in both percentage encapsulation efficiency and the amount of drug encapsulated per mole total lipids upon hydration and formation of niosomes [13]

3. ADVANTAGES OF PRONIOSOMES:

1. Avoiding the problem of physical stability like fusion, aggregation, sedimentation and leakage on storage.
2. Avoiding hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion.
3. Ease on storage and handling.
4. No difficulty in sterilization, transportation, distribution, storage uniformity of dose and scale up.
5. Drug delivery with improved bioavailability, reduced side effects.
6. Entrapment of both hydrophilic and hydrophobic drugs.
7. Shows controlled and sustained release of drugs due to depot formation.
8. Biodegradable, biocompatible and non immunogenic to the body .
9. Shape, size, composition, fluidity of niosomes drug can be controlled as and when required.

4. METHOD OF PREPARATION

Proniosome preparation mainly comprised of non-ionic surfactants, coating carriers and membrane stabilizers. The formulation may be prepared by following methods.

a. Slurry method:

Proniosomes can be prepared by addition of the carrier and the entire surfactant solution in a round bottomed flask which is fitted to rotary flash evaporator and vacuum was applied to form a dry and free flowing powder. Finally, the formulation should be stored in tightly closed container under refrigeration in light. The time required for proniosome production is independent of the ratio of surfactant solution to carrier material and appears to be stable. This method is advantageous because due to uniform coating on carrier it protects the active ingredients and surfactants from hydrolysis and oxidation. Along with that the higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient [12] [15].

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b. Slow spray coating method:

This method involves preparation of proniosomes by spraying surfactant in organic solvent onto the carrier and then evaporating the solvent. It is necessary to repeat the process until the desired surfactant loading has been achieved, because the carrier is soluble in the organic solvent. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves. The resulting niosomes have uniform size distribution similar to those produced by conventional methods. The main advantage of this method is to provide a means to formulate hydrophobic drugs in a lipid suspension with or without problem with instability of the suspension or susceptibility of active ingredient to hydrolysis. This method was reported to be tedious since the sorbitol carrier is soluble in the solvent used to deposit the surfactant. It is also found to interfere with the encapsulation of certain drugs [(15).]

c. Co - acervation phase separation method:

Proniosomal gels can be prepared by this method which comprises of surfactant, lipid and drug in a wide mouthed glass vial along with small amount of alcohol in it. The mixture is warmed over water bath at 60-700C for 5min until the surfactant mixture is dissolved completely. Then the aqueous phase is added to the above vial and warmed still a clear solution is formed which is then converted into proniosomal gel on cooling. After hydration of proniosomes they are converted to uniformly sized niosomes.[(16)]

5. TYPES OF PRONIOSOMES

Depending on the method of preparation, the proniosomes exists in two forms;

A) Dry granular proniosome:

According to the type of carrier these are again divided as

a) Sorbitol based proniosomes

Sorbitol based proniosomes is a dry formulation that involves sorbitol as a carrier. These are made by spraying surfactants mixture prepared in organic solvent on to the sorbitol powder and then evaporating the solvent. It is useful in case where the active ingredient is susceptible to hydrolysis.

b. Maltodextrin based proniosomes

Maltodextrin based proniosomes prepared by slurry method. Maltodextrin is a polysaccharide easily soluble in water and it is used as carrier material in formulation. Since its morphology is preserved, hollow blown maltodextrin particles can be used for significant gain in surface area. The higher surface area results in thinner surfactant coating, which makes the rehydration process efficient. Time required for this process is independent of the ratio of surfactant solution.

B) Liquid crystalline proniosomes

When the surfactant molecule are kept in contact with water, there are three ways through which lipophilic chains of surfactant can be transformed into a disordered, liquid state called lyotropic liquid crystalline state. These three ways are

- Increasing temperature at kraft point (Tc),
- Addition of solvent which dissolve lipids,
- Use of both temperature and solvent.

The liquid crystaliine proniosomes and proniosomal gel act as reservoir for transdermal delivery of drug [(17) (18)]

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Evaluation of the parameters of proniosomes

i. Drug Entrapment Efficiency:

DEE of the proniosomal dispersion can be estimated by separating the unentrapped drug by dialysis , centrifugation, or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50 % n-propanol or 0.1 % Triton X-100 and analyzing the resultant solution by appropriate assay method for the drug. The DEE can be calculated as follows:

$$DEE\ (\%) = [\text{Entrapped drug} / \text{Total drug}] \times 100$$

ii. Angle of repose

The angle of repose of dry proniosome powder is measured by a funnel method. In this method, the funnel is fixed at a position so that the 13 mm outlet orifice of the funnel is 10 cm above a level black surface. The powder is poured through the funnel to form a cone on the surface, and the angle of repose is then calculated by measuring the height of the cone and the diameter of its base.

iii. Vesicle size and vesicle size distribution

Drug permeability is dependent on vesicle size. Therefore, vesicle size vesicle size and vesicle size distribution of proniosomes are necessary. To determine average vesicle size and vesicle size distribution, instruments used mainly are:

a) Malvern Master sizer
b) Optical microscopy
c) Laser diffraction particle size analyzer;
d) Coulter submicron size analyzer.

iv. Vesicle shape and surface characterization

To determine vesicle shape and for surface characterization, instruments used are:

a) Optical microscopy;
b) Transmission electron microscopy (TEM)
c) Scanning electron microscopy (SEM)

v. Rate of hydration

To determine the rate of hydration Neubaur’s chamber is used

vi. Zeta potential

To analyze the colloidal properties of proniosomal formulations, zeta potential value determination is necessary. Zeta potential can be determined by Malvern Zetasizer .

vii. In-vitro Drug release from proniosomes

In vitro drug release from the proniosome can be evaluated by:

a) Dialysis tubing
b) Reverse dialysis
c) Using Franz diffusion cell

Dialysis Tubing: Muller et al., (2002) reported that the in vitro drug release could be achieved by using dialysis tubing. The proniosomes is first placed in prewashed dialysis tubing which can be hermetically sealed. Then proniosome suspension is dialyzed through dialysis sac against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium

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at suitable intervals, centrifuged and analyzed for drug content using suitable analytical method. The study requires sink condition to be maintained.

Reverse Dialysis: In this technique a number of small dialysis bags containing 1 ml of dissolution medium are kept in proniosomes. The proniosomes are then displaced into the dissolution medium. The drug release can be quantified with direct dilution of proniosome.
In vitro release study using Franz diffusion cell. The in vitro diffusion studies are generally performed by using Franz diffusion cell. Proniosomes are placed in the donor chamber of a Franz diffusion cell fitted with dialysis membrane or biological membranes. The entrapped drugs get permeated through the dialysis membrane from donor chamber to receptor chamber containing a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable analytical methods. In vitro drug release kinetics and mechanism: In order to understand the kinetic and mechanism of drug release, the result of in-vitro drug release study were fitted with various kinetic equations like: zero order, first order, Higuchi's model and Koresmeyer-Peppas Model.

Zero-order Kinetics: $F = Ko\ t$

where, F represents the fraction of drug released in time t, and Ko is the zero-order release constant.

First-order Kinetics: $\ln (1-F) = - K1\ t$

where, F represents the fraction of drug released in time t, and K1 is the first-order release constant.

Higuchi Model : $F = KH\ t1/2$

where, F represents the fraction of drug released in time t, and KH is the Higuchi dissolution constant.

Koresmeyer-Peppas Model: $F = Kp\ tn$

where, F represents the fraction of drug released in time t, and Kp is the Koresmeyer-Peppas release rate constant and n is the diffusion exponent.
The Korsmeyer-Peppas model was employed to determine the mechanism of drug release from the formulation. Type of diffusion can be categorized on the basis of diffusion exponent like: Fickian (non-steady) diffusional when n _ 0.5 and a case-II transport (zero-order) when n _ 1. And the in between 0.5 and 1 are indicative of non-Fickian, 'anomalous' release.

viii. Osmotic shock

This study is important to assess the change in vesicle size viewed under optical microscope after incubation with hypnotic, isotonic, hypotonic solutions for 3 hrs.

ix. Stability studies

Stability studies of proniosomal formulations were carried out by keeping at various temperature conditions like refrigeration temperature (2-8°C), room temperature (25 ± 0.5°C) and elevated temperature (45 ± 0.5°C) from a period of one month to three months. Drug content and variation in the average vesicle diameter were periodically monitored. ICH guidelines suggests stability studies for the dry proniosome powders meant for reconstitution that should be studied

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for accelerated stability at 40°C/75 % RH (relative humidity) as per international climatic zones and climatic conditions (WHO, 1996). According to ICH guidelines, for long term stability studies the temperature is 25°C/60 % RH for the countries in zone I and II and for the countries in Zone III and IV the temperature is 30°C/65 % RH. Product should be evaluated for appearance, colour, assay, pH, preservative content, particulate matter, sterility and pyrogenicity. [19]

Application of Proniosome:

1. **Drug targeting**

Proniosomes has the ability to target the drugs and can be used to target drugs to the reticulo-endothelial system (RES) because the RES preferentially takes up proniosome vesicles. The uptake of proniosomes is controlled by circulating serum factors called opsonins. These opsonins are useful marker substances for niosose clearance. Proniosomes target and localize the drug in higher concentration to treat tumors cells in animals especially in liver and spleen tumors and also can be used for parasitic infection of liver . It has been found that if a carrier system (such as antibodies) can be attached to proniosomes (as immunoglobulin bind readily to the lipid surface of the proniosome) to target them to specific organs.

2. **Antineoplastic treatment**

Antineoplastic drugs are generally known as cytotoxic drugs and it produces severe side effects. proniosome can reduce the side of these drugs by altering the metabolism through prolong circulation and half life of the drugs. Two separate studies showed that noisome containing doxorubicin and methotrexate gave beneficial effect over the unentrapped drug and also showed reduction in proliferation rate of tumor cells and achieving higher plasma level with slower elimination.

3. **Antiparasitic Treatment**

A leishmania parasite commonly infects liver and spleen and derivatives of antimony (antimonials) are primarily used for the treatment but higher concentrations of these are always harmful for our sensitive organs like heart, liver, kidney etc. Hunter et al., (1988) reported that the proniosome containing sodium stibogluconate showed greater efficacy in treatment as well as lower the side effects.

4. **Delivery of peptides**

Delivery of peptides has always been faced problems when administered through oral route due to presence of hydrolytic enzymes and a variety of pH system. Yoshida et al., (1992) investigated that peptides entrapped (vasopressin derivative) niosome for oral delivery showed greater stability of peptides as entrapped in proniosome .

5. **Proniosomes as carriers for haemoglobin**

Moser et al., (1989) conducted the study with taking noisome as a carrier for haemoglobin within the blood and suggested that the pronoisome vesicles can be used as carrier for haemoglobin in aneamic patients as pronoisome is permeable to oxygen.

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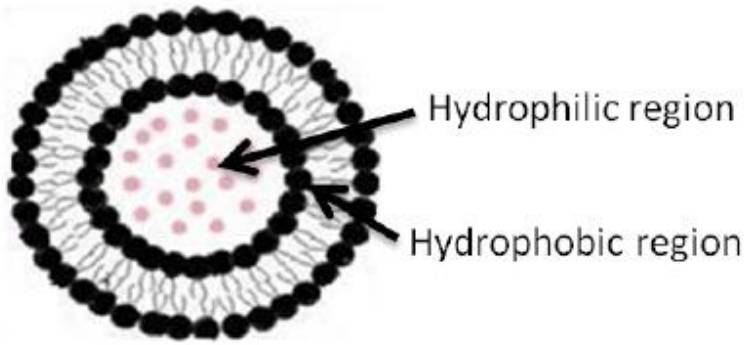
6. Proniosomes as transdermal drug delivery system

In recent time, proniosome has been received a great attention for delivering the drug substances via transdermal route as transdermal administration of drug avoids some drawbacks unlike oral route. Both hydrophilic and lipophilic drugs like: losartan potassium , chlorpheniramine maleate, levonorgestrel , flurbiprofen, ketoprofen , captopril , celecoxib , piroxicam , carvediol , methotrexate , doxorubicin have been found high permeation efficiency through the skin. Proniosomal preparation now has been used in cosmetics. [20]

Niosome : An overview

Niosomes are microscopic lamellar structures of size range between 10 to 1000 nm and constituted from non-ionic surfactant and cholesterol. Structurally, niosomes are similar to liposomes. Both are made up of bilayer, which is made up of non-ionic surfactant in the case of niosomes and phospholipids in case of liposomes. Both hydrophilic and hydrophobic drugs can be incorporated into niosomes. The niosomes are ampiphillic in nature, which allows entrapment of hydrophilic drug in the core cavity and hydrophobic drugs in the non-polar region present within the bilayer. [21]



Merits and demirits of niosomes

Following are the merits of niosomes:

1. They release the drug in sustained / controlled manner.
2. They enhance the bioavailability of drug, particularly, in ocular delivery system.
3. They have stable structure even in emulsion form.
4. They do not require special conditions such as low temperature or inert atmosphere.
5. They have ability to entrap both hydrophilic and hydrophobic drugs.
6. Niosomes are non-toxic, biodegradable, and non-immunogenic.
7. They are economic for large scale production.
8. They protect the drug from enzyme metabolism.

The niosomes suffer certain demerits, which include the following:

1. The aqueous suspensions of niosomes may undergo fusion, aggregation, leaking of entrapped drugs, and hydrolysis of encapsulated drugs, which lead to limited shelf life.
2. The methods of preparation of multilamellar vesicles such as extrusion, sonication, are time consuming and may require specialized equipments for processing. [22]

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Preparation of niosomes

Vesicles of niosomes are prepared using surfactants. The surfactants used in the preparation of niosomes include alkyl and dialkyl polyglycerol ethers, PEG–polyglycerol and dialkylpolyethylene ethers, dialkylpolyglycerol and polyoxyethylene ethers. Other bilayer forming amphiphilic substances are steroidal oxyethylene ethers, laurate ethers, alkyl galactosides, sorbitan monooleate and polyoxyethylated hydrogenated castor oil.

Different methods used for the preparation of niosomes are described below:

1. **Ether injection**

This method is essentially based slow injection of surfactant: cholestrol solution in ether through a suitable needle at approximately 0.25 mL/min into preheated aqueous phase maintained at 60^{o}c, where vaporization leads to formation of unilamellar vesicles.

2. **Hand shaking**

This is also known as thin film hydration technique. In this method, a mixture of surfactant and cholesterol are dissolved in volatile organic solvent such as diethyl ether, chloroform, methyl alcohol, in a round bottom flask. The organic solvent is removed by using rotary evaporator at room temperature, which leaves behind a thin layer of solid deposited on wall of the flask. After gentle agitation, the surfactant is rehydrated with aqueous phase at 0-60 C. This method forms multilamellar noisomes.

Thermo sensitive noisomes are prepared at 60 C by evaporating organic solvent and leaving a thin film of lipid of on the wall of rotary flask evaporator. The aqueous phase containing drug is added slowly by shaking at room temperature followed by sonication.

Fig.1: Flash evaporator

3. **Reverse phase evaporation**

The surfactant is dissolved in choloroform and phosphate buffer is added, followed by emulsification and sonication under reduced pressure.

4. **Bubbling of inert gas**

It is a novel technique for the preparation of niosomes and liposomes without use of organic solvents. The bubbling units consist of round bottom flask with three necks. The first neck is meant for water cooled reflux, the second neck is for thermometer, and the third neck is for nitrogen gas supply. Surfactant and cholesterol are dispersed together in buffer (pH 7.4) at 70^{o}c for 15 sec with high shearing homogenizer and immediatelynitrogen gas at 70^{o}c is bubbled, which forms vesicles.

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5. Sonication

Niosomes are prepared by using sonication method, in which mixture of surfactant and cholesterol is dispersed in aqueous phase in a vial. Then this dispersion is subjected to ultrasonic vibration for 30 min at 60^{o}c, which leads to formation of multilamellar vesicles.

6. Micro fluidization

It technique is based on submerged jet containing micro channels with interaction chamber in which two fluidized streams interact with each other at ultra velocities. The impingement of thin liquid sheet along with common front are arranged in such a way that the energy supplied for the formation of niosomes remains same.This forms unilamellar niosomes with better reproducibility and size uniformity.

7. Multiple membrane extrusion

Niosomes can be chemically prepared by extrusion through polycarbonate membrane (0.1 µm nucleophore) by using C16 G12. By this method, a desired size of the vesicles can be obtained.

Fig 2: Extruder

8. Transmembrane pH gradient drug uptake

Surfactant and cholesterol are dispersed into chloroform in a round bottom flask followed by solvent evaporation under reduced pressure leading to the formation of thin film on the wall of the flask. This film is hydrated with 300 mM citric acid by using vortex mixing. This forms multilamellar vesicles, which are frozen and sonicated to get niosomes. To this niosomal suspension, aqueous solution of drug containing is added and mixed by vortexing, after which, phosphate buffer treatment is done to maintain pH between 7.0 and 7.2 and the mixture is heated at 60^{o}c for 10 minutes to produce vesicles.

9. Formation of niosomes from proniosomes

Proniosome powder is filled in a screw capped vial, in which water or saline at 80 °C is added and mixed by vortexing, followed by agitation for 2 min results in the formation of niosomal suspension .

10. Aqueous dispersion

It is based on micro dispersion of surfactant in aqueous media containing active drug forentrapment or encapsulation.

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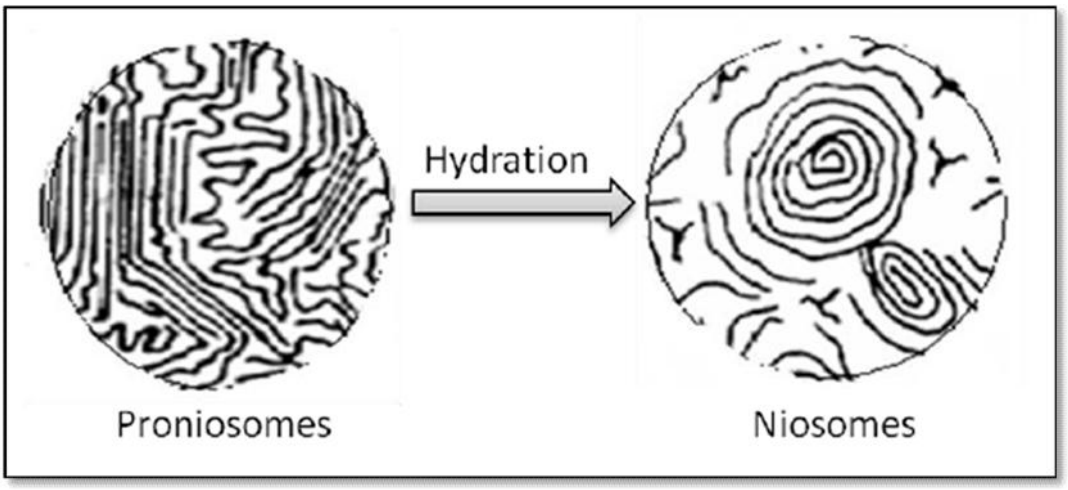
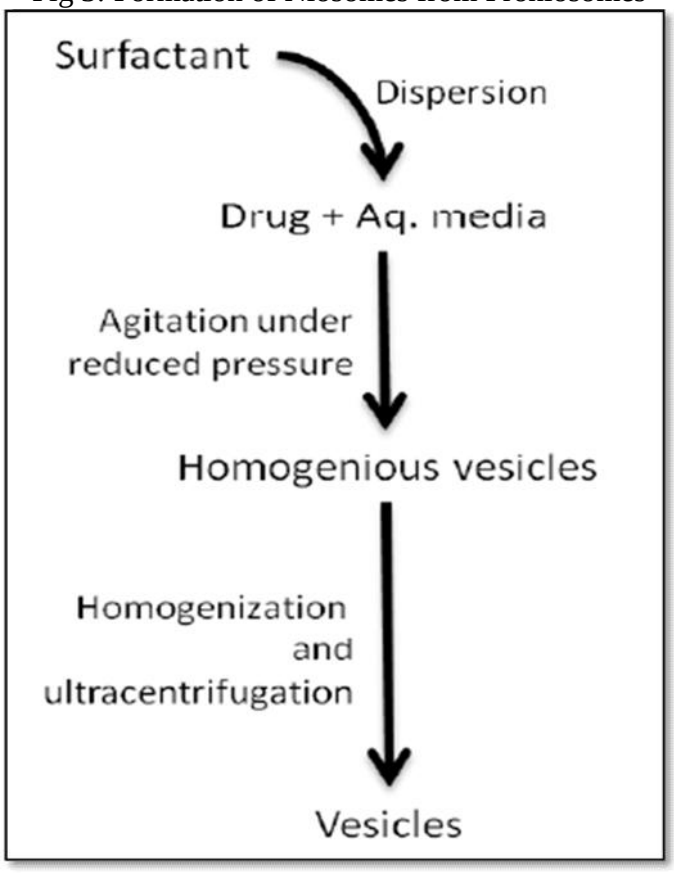


Fig 3: Formation of Niosomes from Proniosomes



Separation of unentrapped drug

The removal of unentrapped drug from the vesicles can be done by various techniques.

1. Dialysis: The aqueous niosomal dispersion is dialyzed using cellophane tubing against phosphate buffer or saline.

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2. Column chromatography: The free drug from niosomal dispersion can also be removed by passing through sephadex G50 column and eluting using phosphate buffer. The free drug gets retained on column and vesicles percolate down.
3. Centrifugation: The niosomal dispersion is subjected to centrifugation in water or saline, where niosomes get sedimented down and the supernatant containing free drug is separated.

Characterization of niosomes

The parameters for characterization of niosomes include size, shape, morphology and entrapment efficiency. The vesicles can be visualized by using freeze fracture electron microscopy; photon spectroscopy is used for determination of mean diameter of vesicles; electron microscopy is used for determination of morphological characters of vesicles; laser scattering is used for size distribution and mean diameter of niosomes. The entrapment efficiency is determined by using carboxy fluorescein as marker.Generally, carboxy fluorescein (CF) is used at 200 mM concentration for hydration. At this concentration inside the vesicles, it exhibits self quenching and does not give fluorescence. Another method is by disruption of vesicles using hydrophilic surfactants, which releases carboxy fluorescein and hence, fluorescence is observed.

Entrapment efficiency (%) =

(Amount of CF before disruption / amount of CF after disruption) ×100

a. In vitro drug release

In vitro drug release can be determined by the following methods:

1. Dialysis

Niosomes are placed in dialysis tubing, which would be hermetically sealed and dialyzed against a suitable dissolution medium at room temperature. Samples are withdrawn from medium at suitable intervals, centrifuged and analyzed for drug content by a suitable method.

2. Reverse dialysis

In this technique, niosomes are placed in a number of small dialysis tubes containing 1 mL of dissolution medium. The niosomes are then displaced from the dissolution medium.

3. Franz diffusion cell

In a Franz diffusion cell, the niosomes are dialyzed through a cellophane membrane against suitable dissolution medium at room temperature. The samples are withdrawn at suitable time intervals and analyzed for drug content.

b. Stability of niosomes

Stable niosomes suspension should have a constant concentration of entrapped drug and constant particle size. Stability of niosome is enhanced by entrapped drug. The stability is also dependent on concentration and type of surfactant used along with cholesterol content. For example, sonicated cholesterol rich spherical/tabular C16G2 niosomes are stable at room temperature, whereas, sonicated polyhedral niosomes are stable at temperatures above the phase transition temperature, but are instable at room temperature.

c. Toxicity of niosomes

The toxicity of CxEOy surfactants has been studied using cilio toxicity model on nasal mucosa. The results suggest that increase in alkyl chain length of surfactant leads to decrease in toxicity, whereas, increase in the polyoxyethylne chain length increases ciliotoxicity. It has been found that increase in alkyl chain length of surfactant leads to formation of gel, on the other hand as increase in polyoxyethylene chain length leads to formation of liquid state. By this study, it is

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clear that the liquid state is more toxic than gel state. In a toxicity study involving human keratocytes, it has been reported that the surfactant-linked-esters exhibit less toxicity than surfactant-linked-ethers. In another study, it has been reported that vincristine encapsulated in niosomes is less toxic than free drug.

d. Pharmacokinetics of Niosomes

The bioavailability of drug from niosomes is dependent on the extent of release of entrapped drug at target tissues. Liver is the only organ which has been extensively and quantitatively analyzed using physiological models for targeted drug availability. A three compartment physiological model has been used for studying kinetics of uptake and degradation of niosomes in liver. Based on this model, the measurable variables can be estimated as:

1. Percentage of injected intact niosomes that remained in liver.
2. Percentage of injected intact niosomes that remained in blood.
3. Percentage of injected intact niosomes that degraded in liver. (23)

Applications of niosomes:

1. Leishmaniasis therapy

Leishmaniasis is a disease caused by parasite genus Leishmania which invades the cells of the liver and spleen. Most Commonly prescribed drugs for the treatment are the derivatives of antimony – which, in higher concentrations – can cause liver, cardiac and kidney damage. Use of niosomes as a drug carrier showed that it is possible to administer the drug at high levels without the triggering the side effects, and thus showed greater efficacy in treatment.

2. Niosomes in oncology

Intravenous administration of noisome loaded with methotrexate, did not lead to increased accumulation of the drug in the liver compared to administration of free drug. This may be due to difference in the size of the niosomal vesicles used in the two studies or by a modification of the drug in the liver as compared to administration of free drug. It is clear that the charge, size, and hydrophilicity of the vesicles can change the distribution of encapsulated drug when administered intravenously. Also, drug accumulation in the tumor was found to increase when administered in cholesterol containing niosomes.

Niosomes containing doxorubicin prepared from C16 monoalkyl glycerol ether with cholesterol led to increased level of doxorubicin in tumor cells, lungs and serum, but not in spleen and liver. But, doxorubicin loaded niosomes without cholesterol exhibited reduced rate of tumor proliferation in mice. The life span of tumor bearing mice was increased. The cardio toxicity of doxorubicin was reduced with niosomal formulation. Also, in the form of niosomes, there was a change the general metabolic pathway of doxorubicin.

Niosomes containing bleomycin formulated using 47.5% cholesterol exhibited higher level of drug in the spleen, liver and tumor as compared to free drug solution when administered to tumor bearing mice. There was reduced accumulation of drug in kidney and gut in case of niosomal formulation. Niosomes containing vincristine exhibited higher tumoricidal efficacy as compared to free drug formulation. Niosomes with carboplatin also showed higher tumoricidal efficacy in S180 lung carcinoma-bearing mice as compared to free drug solution and decreased bone marrow toxic effects.

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3. Anti-inflammatory niosomes

Diclofenac sodium loaded niosomes with 70% cholesterol showed greater anti-inflammatory activity than free drug. Similarly, nimesulide and flurbiprofen loaded niosomes have exhibited greater anti-inflammation activity than free drug.

4. Niosomes in ophthalmic drug delivery

It is difficult to achieve good bioavailability of drug in ocular formulations due to the tear production, non productive absorption, impermeability of corneal epithelium and transient residence time. But, the bioavailability can be enhanced by use of vesicular systems such as niosomes.Bioadhesive-coated niosomes of acetazolamide prepared using span 60, cholesterolstearylamine or dicetyl phosphate have exhibited better efficacy in reducing the intraocular pressure than other ocular formulations. Chitosan-coated niosomal formulation of timolol maleate also showed higher efficacy in the reduction of intraocular pressure than other formulations.Such formulations also have reduced cardiovascular side effects.

5. Niosomes in transdermal drug delivery

Administration of drugs trough transdermal route has advantage of avoidance of first pass metabolism. But, it suffers a drawback of slow penetration of drugs through the skin. One of the approach to enhance the penetration rate is formulation of niosomes. Transdermal delivery ketorolac prepared as pro-niosomal formulation with span-60 exhibited a higher effect than the pro-niosomes prepared with tween-20.It has been reported that the therapeutic efficacy and bioavailability of drugs like flurbiprofen, diclofenac and nimesulide have been increased with niosomal formulations.

6. Niosomes for Diagnosis

Niosomes can be used as diagnostic agents. Conjugated niosomal formulations with gadobenate dimeglcemine with [N-palmitoyl-glucosamine] (NPG), PEG-4400, and both PEG and NPG significantly improved tumor targeting of encapsulated paramagnetic agent which was assessed with MR imaging. [24]

Formation of Niosomes from Proniosomes

The niosomes can be prepared from the proniosomes by adding the aqueous phase with the drug to the proniosomes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant.

$$T > Tm$$

Where,

T = Temperature

Tm = mean phase transition temperature

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.

Clinical Applications of Proniosomes:

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Approaches to stabilize niosomal drug delivery system without affecting its properties of merits have resulted in the development of the promising drug carrier, proniosomes. Proniosomes is dry formulation using suitable carrier coated with non ionic surfactants and can be converted into niosomes immediately before use by hydration. These proniosome-derived niosomes are as good as or even better than conventional niosomes. The application of proniosomal technology is widely varied and can be used to treat a number of diseases. The following are the few uses of proniosomes which are either proven or under research.

1. Drug Targeting:

One of the most useful aspects of proniosomes is their ability to target drugs. Proniosomes can be used to target drugs to the reticulo-endothelial system. The reticulo-endothelial system (RES) preferentially takes up proniosome vesicles. The uptake of proniosomes is controlled by circulating serum factors called opsonins. These opsonins mark the proniosome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of drugs can also be used for treating parasitic infections of the liver. Proiosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to proniosomes (as immunoglobulin bind readily to the lipid surface of the niosome) to target them to specific organs. Many cells also possess the intrinsic ability recognize and bind specific carbohydrate determinants, and this can be exploited by proniosomes to direct carrier system to particular cells.

1. Anti-neoplastic Treatment :

Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Niosomal entrapment of Doxorubicin and Methotrexate (in two separate studies) showed beneficial effects over the unentrapped drugs, such as decreased rate of proliferation of the tumor and higher plasma levels accompanied by slower elimination.

Podophyllotoxin-dipalmitoylphosphatidylcholine (PPT-DPPC) proliposomes (PPT-DPPC-PL) for improvement of the stability of PPT-DPPC liposome. Methods Freeze-drying method was used to prepare PPT-DPPC-PL, and the particle morphology, size range, encapsulation efficiency and stability of PPT-DPPC liposome were investigated. Results After hydration of PPTDPPC-PL, PPT-DPPC liposome appeared multivesicular under electron microscope and the particles were distributed homogenously with an average particle size of 1.45±0.38 μm. The encapsulation efficiency of PPT was 72.3%, and alters storage at 4 to 40 $^{\circ}$C for 6 months, the proliposome remained stable. Conclusion the prepared PPT-DPPC-PL particles by freeze-drying method are evenly distributed. The preparation method is relatively simple with higher embedding ratio and better stability.

2. Leishmaniasis :

Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen. Commonly prescribed drugs for the treatment are derivatives of antimony (antimonials), which in higher concentrations can cause cardiac, liver and kidney damage. Use of pronoisome in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of the side effects, and thus allowed greater efficacy in treatment.

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3. Delivery of Peptide Drugs: Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated.In an invitro study conducted by Yoshida et al, oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.

4. Uses in Studying Immune Response:
Proniosomes are used in studying immune response due to their immunological selectivity, low toxicity and greater stability. Niosomes are being used to study the nature of the immune response provoked by antigens.

5. Proniosomes as Carriers for Haemoglobin :
(Moser P. and Marchand Arvier M. in 1989) reported that niosomes can be used as carriers for haemoglobin within the blood. The niosomal vesicle is permeable to oxygen and hence can act as a carrier for hemoglobin in anemic patients.

6. Proniosomes used in Cardiac Disorders
Proniosomal carrier system for captopril for the treatment of hypertension that is capable of efficiently delivering entrapped drug over an extended period of time. The potential of proniosomes as a transdermal drug delivery system for captopril was nvestigated by encapsulating the drug in various formulations of proniosomal gel composed of various ratios of sorbitan fatty acid esters, cholesterol, lecithin prepared by coacervation-phase separation method. The formulated systems were characterized in vitro for size, vesicle count, drug entrapment, drug release profiles and vesicular stability at different storage conditions. Stability studies for proniosomal gel were carried out for 4 weeks. The current study was to investigate the feasibility of proniosomes as transdermal drug delivery system for losartan potassium. Different preparations of proniosomes were fabricated using different nonionic surfactants, such as Span 20, Span 40, Span 60, Span 80, Tween 20, Tween 40, and Tween 80. Different formulae were prepared and coded as PNG-1 (proniosomal gel-1) to PNG-7. The best in vitro skin permeation profile was obtained with proniosomal formulation PNG-2 in 24 h. The permeability parameters such as flux, permeability coefficient, and enhancement ratio were significant for PNG-2 compared with other formulations ($P < 0.05$). This optimized PNG-2 was fabricated in the form of transdermal patch using HPMC gel as a suitable base.

7. 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.

8. 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 niosome are taken up by mononuclear cells resulting in localization of drug,

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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.

9. Antibacterial threapy:

Amphotericin-b proliposomes could be stored for 9 months without significant changes in distribution of vesicle size and for 6 months without loss of pharmacological activity. Even though physical stability of the preparation can be increased, a vacuum or nitrogen atmosphere is still required during preparation and storage to prevent oxidation of phospholipid.

10. Cosmetics/Cosmeceuticals:

Proniosomal gels are generally present in transparent, translucent or white semisolid gel texture, which makes them physically stable during storage and transport. Due to the limited solvent system present, the proniosomes formed were the mixture of many phases of liquid crystal, viz. lamellar, hexagonal and cubic phase liquid crystals. Dissolution of most surfactants in water, leads to the formation of lyotropic liquid crystals rather than micellar solution. Lamellar phase shows sheets of surfactants arranged in bilayer form, whereas in hexagonal phase cylindrical units are packed in hexagonal fashion. Cubic phase consists of curved bio-continuous lipid bilayer extending in three dimensions, separating two congruent networks of water channels. These liquid crystals present an attractive appearance because of their, transparency and high viscosity, although in the beginning of its formation, a short range of less viscous compositions (so called liquid/gel compositions) appear in some cases . Addition of water leads to interaction between water and polar groups of the surfactant results in swelling of bilayer. Proniosomes exists in two forms, i.e. semisolid liquid crystal gel and dry granular powder, depending on their method of preparation. Out of these two forms, the proniosome gel is mainly used for topical/transdermal applications. Nowadays consumers are replacing cosmetics frequently with cosmeceuticals. Cosmeceuticals are skin care medicines which combine cosmetics and medicines. Many times consumer claims that their cosmetics are not effective this is true because the availability of the cosmetic agent is must at the site of action. The skin is a complex organ and allows entry of only selective components. So the formulation of a cosmetic/Cosmeceuticals is very important in terms of delivering the active agent at the site of action. The new drug delivery systems are required to deliver the actives into the skin. Applying a cosmetic/Cosmeceuticals in a certain way may change its activity. For example, increased time of application usually leads to higher activity. Occlusion (covering the product with something, as plastic or a medical membrane/hydrogel) usually increases activity. Proniosome gel can be used as-an effective delivery systems for cosmetics and Cosmeceuticals due to their unique properties. For applying therapeutic and cosmetic agents onto or through skin requires a non toxic, dermatologically acceptable carrier, which not only control the release of the agent for prolong action but also enhances the penetration to the skin layer . Proniosome gel is promising delivery systems for delivering the actives through skin via different formulations of drugs and cosmetics. The delivery system not only enhances the delivery of active agent through skin but also controls the rate of release. A wide variety of active agents of different therapeutic functions were formulated into proniosomal gel delivery system. Proniosomal gel carrier system entraps not only hydrophilic but hydrophobic agents also. There is great scope for cosmetic agents to be incorporate in the proniosomal gel delivery system.

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11. **Preparation of Vitamins:** To prepare vitamin A proliposomes and to enhance stability of vitamin A. Methods: Freeze drying method was used to prepare vitamin A proliposomes. The particle morphology, the size range, encapsulation efficiency and stability of vitamin A liposomes were studied. Results: After vitamin A proliposomes was hydrated, vitamin A liposomes with unilamellar vesicle was formed. The particles were distributed homogenously. The average particle size was 0.615 μm. The encapsulation efficiency of vitamin A was 98.5%.
12. **Significance of proniosomes over other liposomal vesicles in Transdermal drug delivery system and traditional drug delivery systems:**
    Adsorption and fusion of proniosomes on to the surface of skin leading to a high thermodynamic activity gradient of drug at the interface, which is the driving force for permeation of lipophilic drugs . The effects of proniosomes vesicles as the permeation enhancer reduce membrane barrier for drugs, stratum corneum in transdermal delivery. These were non thermoresponsive at 30°C and extremely viscous, hence if either the ambient temperature or the skin temperature were raised to 35°C, they were capable to release their encapsulated contents.

Following advantages of proniosomes can be illustrated In comparison to other transdermal & dermal delivery systems:

1. The proniosome minimizes these problems by using dry, free-flowing product, which is more stable during sterilization and storage.
2. Easy transfer, distribution, measuring, and storage make proniosomes a versatile delivery system with potential for use with a wide range of active compounds.
3. The great advantage offered by proniosomes is their ease of use and their hydration is much easier than the long shaking process required to hydrate surfactants in the conventional dry film method.
4. Furthermore, unacceptable solvents are avoided in proniosomal formulations. The systems may be directly formulated into transdermal patches and doesn't require the dispersion of vesicles into polymeric matrix.

Transdermal Drug Delivery Systems utilizing niosomes

a) One of the most useful aspects of niosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing niosomal technology is widely used in cosmetics; In fact, it was one of the first uses of the niosomes. Topical use of niosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to un-entrapped drug. Recently, transdermal vaccines utilizing niosomal technology is also being researched. A study conducted by P. N. Gupta et al has shown that niosomes (along with liposomes and transfersomes) can be utilized for topical immunization using tetanus toxoid. However, the current technology in niosomes allows only a weak immune response, and thus more research needs to be done in this field.
b) Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Niosomes of terbinafine hydrochloride was formulated by thin film hydration method using different ratios of non-ionic surfactants (Tween 20, 40, 60, and 80) and cholesterol with constant drug concentration. Niosomal preparations

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were tested for *in-vitro* antifungal activity using the strain *Aspergillus niger* and compared with pure drug solution (as standard). All the niosomal formulations showed gradual increase in zone of inhibition due to the controlled release of medicament. The studies revealed that gel containing total niosomes possess maximum zone of inhibition values (12mm) initially followed by sustained release (12mm-16mm) compared to gel containing drug entrapped niosomes, gel containing pure drug and marketed preparation. Proniosomal gels of flurbiprofen were developed using different spans with and without cholesterol. Niosomes were formed by hydrating proniosomes. Results indicated that the entrapment efficiency followed the trend Sp 60 (C18)>Sp 40 (C16)>Sp 20 (C12)>Sp 80 (C18). Cholesterol increased or decreased the entrapment efficiency depending on either the type of the surfactant used or its concentration within the formulae. Increasing total lipid or drug concentration also increased the entrapment efficiency of flurbiprofen into niosomes. Benzoyl peroxide was entrapped into niosomes by thin film hydration technique, and various process parameters were optimized by partial factorial design. The optimized niosomal formulation was incorporated into HPMC K15 gel and extensively characterized for percentage drug entrapment (PDE) and in vitro release performance. The present study demonstrated prolongation of drug release, increased drug retention into skin, and improved permeation across the skin after encapsulation of benzoyl peroxide into niosomal topical gel.

c) Entrapment of drug Erythromycin into niosomes showed prolongation of drug release, enhanced drug retention into skin and improved permeation across the skin after encapsulation.

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

d) In recent time, proniosome has been received a great attention for delivering the drug substances via transdermal route as transdermal administration of drug avoids some drawbacks unlike oral route. Both hydrophilic and lipophilic drugs like: losartan potassium, chlorpheniramine maleate levonorgestrel , flurbiprofen , ketoprofen, captopril , celecoxib, piroxicam, carvediol, methotrexate , doxorubicin have been found high permeation efficiency through the skin. Proniosomal preparation now has been used in cosmetics.

e) One of the most useful aspects of niosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing niosomal technology is widely used in cosmetics; In fact, it was one of the first uses of the niosomes. Topical use of niosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to un-entrapped drug. Recently, transdermal vaccines utilizing niosomal technology is also being researched.

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transdermal vaccines utilizing niosomal technology is also being researched. A study conducted by P. N. Gupta et al has shown that niosomes (along with liposomes and transfersomes) can be utilized for topical immunization using tetanus toxoid. However, the current technology in niosomes allows only a weak immune response, and thus more research needs to be done in this field [26]

CONCLUSION:

Niosomal drug delivery systems have been demonstrated to be promising controlled drug delivery systems for percutaneous administration. Niosomes also offer successful druglocalization in skin which are relatively non-toxic and stable. This advantage of niosomes has the potential of strengthening the efficacy of the drug accompanying with reducing its adverse effects associated with drug systemic absorption. Drug-associated challenges such as physical and chemical instability is also can be protected by vesicular carriers. Niosomes appeared to be a well preferred drug delivery system over liposome as niosomes being stable and cost-effective. Hence, many topical drugs may be developed using niosomal systems. But there are still some challenges in this area. Although some new approaches have been developed to overcome the problem of drug loading, it is still remain to be addressed. The researchers should be more alert in the selection of suitable surfactant for noisome preparation due to this fact that the type of surfactant is the main parameter affecting the formation of the vesicles, their toxicity and stability.

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