**ABSTRACT**

The aim of the drug delivery system is deliver the therapeutic agent into the desired site of action. The transdermal route is most important but the stratum corneum acts as barrier which is present on the top of the epidermis and also acts as the rate limiting membrane of penetration of drugs. Vesicular drug delivery system such as niosomes and liposomes are promising systems to cross this permeation barrier. The provesicular niosomes is the colloid carrier in the early stage of developed it may need to exploit more in field of drug delivery. They are non-toxic and non-immunogenic bilayer that be changed to niosomes once applied to skin by absorption of water and interacts with the strong hydrogen bond of stratum corneum and loosens it, thereby permitting the diffusion of drug into the skin. The provesicular system is the new emerging concept and it provides the solution to gel of the stability and also provides the higher entrapment efficiency over conventional systems. This review provides a very important summary of preparation, formulation, characterization and application of proniosome gel as a drug carrier.

**KEYWORDS:** Provesicular systems, proniosomal gel, non-ionic surfactant, penetration, entrapment efficiency, transdermal.

**INTRODUCTION**

In the past few decades, reasonable attention has been centered on the improvement of novel drug delivery system. Several novel approaches emerged covering numerous routes of administration, to attain either controlled or targeted delivery. The prime aim of novel drug
delivery is maintenance of the constant and effective drug level within the body and minimizing the side-effects and it additionally localizes the drug action by targeting the drug delivery by drug carriers.\textsuperscript{[2]} Penetration improvement with special formulation approaches is principally supported the usage of mixture carriers. Mixture carriers have attracted the most interest as a result of they're promising systems having localized impact. These carrier, accumulate in horny layer or alternative higher skin layers aren't expected to penetrate into viable skin.\textsuperscript{[3]}

The proniosomes are promising drug carriers because they are possess the greater chemical stability and lack of many disadvantages associated with liposomes and also niosomes. It has additional advantages with niosomes are low toxicity due to non-ionic nature, no requirement of special precautions and conditions for formulation and preparation. Niosomes have shown advantages as drug carriers. Such as low price and chemical stability as compared to liposomes however they're related to downside associated with physical stability like fusion, aggregation, physical phenomenon and discharge and storage. Proniosomes are dry formulations of damper coated carrier vesicles which may be measured out specialist and rehydrated by short-term agitation in quandary the ensuing niosomes are very just like standard niosomes and a lot of uniform size. This proniosomes are minimizing the trouble problem dry, free flowing product that is a lot of stable throughout storage and sterilization and it’s extra blessings of simple of transfer, distribution, measure and storage build proniosomes a saying versatile delivery system.\textsuperscript{[4]}

**Advantages of Proniosomes**\textsuperscript{[4,5,6]}

1. Avoiding the problems of physical stability such as fusion, aggregation, sedimentation, and leakage on storage.
2. Avoiding hydration of encapsulated drugs which is limiting the shelf-life of the dispersion.
3. Uses acceptable solvents in the preparation.
4. It can entrap both hydrophilic and hydrophobic drugs.
5. Hydration is much easier than the long shaking process requiring in the case of liposome and niosomes.
6. Ease of storage and handling i.e. Requires no special conditions for storage and handling.
7. Drug delivery improves bioavailability and minimum side effects.
TYPES OF PRONIOSOMES\textsuperscript{[7,8]}

The types of proniosomes are as follows.

1. Liquid crystalline proniosomes.
2. Dry granular proniosome.

**Liquid crystalline proniosomes:** When surfactant molecules are made in contact with water there are three ways in which the lipophilic chains of surfactants are being transformed into a disordered liquid state. The followings are the three ways.

1) Addition of solvents.
2) Increasing temperature at Kraft’s point.
3) Using both temperature and solvents.

Liquid crystalline proniosomes and proniosomal gel acts as a reservoir for the transdermal drug delivery system. This method avoids the use of pharmaceutically unacceptable solvent and it is easy to scaleup.

Advantage of Liquid crystalline proniosomes.

1. As a penetration enhancer.
2. Higher entrapment efficiency
3. No disruption of membrane.
4. Stability

**2. Dry granular proniosome:** In this type of proniosomes the water soluble carriers are coating with sorbitol and maltodextrin resultant into the dry formulation. Hence the according to the type of carrier and method of preparation the dry granular proniosomes further classified into.

1. Sorbitol based proniosomes.
2. Maltodextrin based proniosomes.

**1. Sorbitol based proniosomes:** The sorbitol based pronisomes are dry formulations, which mainly involves the sorbitol as acarrier. These are made by spraying surfactant mixture prepared in organic solvent into sorbitol powder and then evaporating the surfactant. Since the surfactant coating into the carrier is very thin and hydration of this coating allows the multilamellar vesicles to forms as the carrier dissolves. In the sorbitol based proniosomes size distribution in very uniform. When there is the active ingredient is the susceptible to the
hydrolysis then this type of proniosomes are used. This type of proniosomes are prepared by slow spraying method.

2. Maltodextrin based proniosomes: This type of proniosomes are recently developed and has potential application in delivery of hydrophilic or amphiphilic drugs. These are prepared by fast slurry method. Maltodextrin is a polysaccharide easily soluble in water and is used as a carrier material in formulation. The better of these formulations used to hollow particle with high surface area.

**Action of Proniosomes:** Proniosomes show their action after they are converted to niosomes on hydration.

\[ \text{Proniosomes} \xrightarrow{\text{hydration}} \text{Niosomes} \]

The hydration may occur either by the skin or by the addition of aqueous solvents. Proniosomes can entrap both hydrophilic as well as lipophilic drugs.

**Formulation Aspects of Proniosome**

**Surfactants**[^9]: A wide range of surfactants are available they considered the important structural component. The selection of surfactants should be done on the basis of Hydrophilic Lipophilic balance (HLB). The HLB in between 4 to 8 was found to be compatible with vesicles formulation. Surfactants are the surface active agent usually organic compounds that are having both hydrophobic and hydrophilic groups. Therefore, a surfactant molecule contains both a water insoluble and a water soluble component. The most common non-ionic amphiphiles used for vesicle formation are alkyl ethers (Brij30, Brij56), Sorbitan fatty acid esters (span 20, 40, 60.), Polyoxymethylene fatty acid esters (Tween 20, 40, 60, 80). Transition temperature of surfactants affects on the entrapment of drug in vesicles. Spans have highest phase transition temperature provides the highest entrapment for the drug. The surfactant likespan 40 and span 60 produces vesicles of larger size with higher entrapment of drug. The drug leaking from the vesicles is reduced due to high phase transition temperature and low permeability. Tween is low encapsulation efficiency as compared to span because of the larger size of vesicles and less lipophilic nature of tween. When span is used it also increases the lipophilicity of drug. The relationship between the structure of the surfactant containing the size of hydrophilic head group, and length of lipophilic alkyl chain in the ability to form vesicles is described in following equation.

[^9]: Desai et al.
Critical Packing Parameter (CPP) Of Surfactants.

\[ CPP = \frac{V}{L_c} \times A_0 \]

Where,
CPP=critical processing parameter.
V =volume of hydrophobic group.
Lc= critical hydrocarbon chain length.
A0=Area of the hydrophilic head group.

A CPP between 0.5 and 1 indicates that the surfactant is likely to form vesicles. A CPP value below 0.5 indicates a large contribution from the hydrophilic head group area and is said to give spherical micelles and a CPP of above 1 indicates a large contribution from the hydrophobic group volume should produce inverted micelles.

Hence,
CPP \lt 0.5 micelles form.
CPP = (0.5-1.0) spherical vesicles form.
CPP \gt 1 inverted micelles form.

**Cholesterol:** Cholesterol is essential component of vesicles. Cholesterol is integral part of biological membrane where it influences several membrane properties such as aggregation, ion permeability, fusion process size and shape.\(^9\) Incorporation of cholesterol influences the transition temperature vesicle stability and permeability. Concentration of cholesterol plays an important role in entrapment of drug in vesicles. When the concentration of cholesterol increases then the entrapment efficiency increases but further increases the concentration of cholesterol then it decreases the entrapment efficiency because the cholesterol molecule enters with drug into the vesicular bilayer structure then it destroy and decreases the
entrapment efficiency. Cholesterol imparts the hydrophobicity to the formulation and affects on the vesicle size.\textsuperscript{[10]}

**Lecithin:** Phosphotidyl choline is the major component of lecithin. The name basically depends upon their source of origin such as soya lecithin from soya beans and egg lecithin from egg yolk. Phosphotidylcholine has low solubility in water. Incorporation of lecithin in proniosomes may act as permeation enhancer, prevents the leakage of drug and also acts as the enhanced the percent drug entrapment due to high phase transition temperature. The vesicles composed of soya lecithin are of larger size than vesicle composed of egg lecithin due to difference in the intrinsinc components. On the basis of penetration capability the soya lecithin is considered as a good candidate as it contains unsaturated fatty acids, oleic and linoleic acid while egg lecithin contains fatty acids.\textsuperscript{[11]}

**Solvent:** Selection of the solvent is the important aspect because it affects on the drug permeation and the vesicle size. It is reported that the ethanol gives vesicles of larger size as compared to other alcohol due to the slow phase separation and more solubility in the water. Vesicles shaped from totally different alcohols measure of various sizes and that they follow the order: ethanol > propanol > butanol > Isopropanol. wherever as isopropyl alcohol shows the upper penetration due to branched structure that act as co chemical agent and loosen the bilayer packing ensuing into the raised release of drug.\textsuperscript{[12]}

**Aqueous phase:** Phosphate buffer 7.4, 0.1% glycerol and warm water are mainly used aqueous phase for proniosomes. pH of the hydrating medium also play main role in entrapment efficiency. The aqueous medium may influence the tactness of proniosomes, thus affecting their entrapment efficiency.

**Formation of Niosomes From Proniosomes:** The addition of liquid phase into proniosomes to make the niosomes with short-time agitation at a temperature larger than the mean transition phase temperature of the surfactant.\textsuperscript{[13]}

\[ T > T_m \]

Where,

\[ T = \text{Temperature} \]
\[ T_m = \text{mean phase transition temperature.} \]
Formation of Niosomes from Proniosomes

Method of preparation of Proniosomal gel: Proniosomal formulations may be prepared by the following methods,

1. Coacervation phase separation method.
2. Slurry method.

1. Coacervation phase separation method: Proniosomal gel was prepared by a coacervation-phase separation technique. Accurately weighed amounts of surfactant, lecithin, cholesterol and drug were taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol was added to it. After warming, all the ingredients were mixed well with a glass rod; the open end of the glass bottle was covered with a lid to prevent the loss of solvent from it and warmed over water bath at 60-70°C for about 5 min until the surfactant mixture was dissolved completely. Then the aqueous phase (phosphate buffer saline pH 7.4) was added and warmed on a water bath till a clear solution was formed which was converted into Proniosomal gel on cooling. The gel thus obtained was preserved within the same glass bottle in dark conditions for characterization.[14]
2. **Slurry Method:** In this method Proniosomes are prepared with the maltodextrin as the by a slurry method in contrast to the slow spray–coating method. The sorbitol carrier in the original proniosomes is soluble in solvent used to deposit surfactant, so preparation is tedious and the sorbitol interfered with encapsulation of model drug. The time needed to yield the proniosomes by this simple technique is self-determining of surface-active agent to carrier material within the slurry technique, maltodextrin powder is additional to a round shaped bottom flask and also the entire volume of surface-active agent is directly added to the flask. Then this flask is attached to a rotary evaporator to evaporate the chloroform at 60-70 rpm, a temperature of 43 °C – 47 °C, and decreases the pressure 600 mmHg until the powder becomes to be dry and free flowing. The flask is removed from the evaporator and kept under vacuum overnight. Proniosomes powder is stored in sealed containers at 4 °C.[15]

3. **Slow Spray Coating Method:** The round bottom flask having the capacity 100 ml then this flask addition of some amount carrier and then it attached to the rotary flask evaporator. A mixture of surfactants and cholesterol should be prepared and introduced into round bottom flask on rotary evaporator by sequential spraying of aliquots onto carrier’s surface. The evaporator has to be evacuated and rotating flask can be rotated in water bath under vacuum at 65-70°C for 15 – 20 min. This process has to be repeated until all of the surfactant solution had been applied. The evaporation should be continued until the powder becomes completely dry.[11]

**Proniosomal gel and transdermal drug delivery system:** Transdermal therapeutic systems are the recently developed devices, which are non invasive to skin as compared to other routes. Although the skin, particularly the stratum corneum presents a barrier for the various types of transdermal therapeutic systems are utilized for long term continuous infusion of therapeutic agents, including antihypertensive, antifungal, analgesics, steroids and contraceptivedrugs. Various types of transdermal drug delivery system include liposomes, erythrosomes, liposomes, niosomes, ethosomes, and proniosomes.[16]

Proniosomal gel is used as a carrier for the transdermal delivery system. The proniosomal gel is directly can be formulated into the reservoir type transdermal patch. The proniosomes are the some potential applications within the delivery of hydrophobic as well as hydrophilic drugs. Transdermal drug delivery has been recognized as an alternative route to oral delivery.[17] Proniosomal based transdermal drug delivery system of many drugs
has been formulated as alternative to the oral route mainly for the NSAID, hormones delivery for the effective contraception. A. Chandra and P.K Sharma formulated the proniosomal gel loaded reservoir type transdermal patch of Piroxicam for the treatment of various musculoskeletal disorder like osteoarthritis, rheumatoid arthritis etc.\textsuperscript{[18]}

**Evaluation of proniosomal gel**

1. **Vesicle morphology**: Determination of vesicle size is important for the topical application of proniosomal formulation. Vesicle morphology involves the measurement of size and shape of proniosomal vesicles. Size of proniosomal vesicles can be measured by dynamic light scattering method. Scanning electron microscopy (SEM) without agitation and with agitation. Hydration without agitation results in largest vesicle size while hydration of vesicles with agitation results in the formation of smaller vesicles. Increase in the hydrophobicity of surfactant decrease the surface free energy and reduces the vesicle size.\textsuperscript{[19]}

2. **Entrapment efficiency**: Separation of unentrapped drug is completed by the subsequent techniques.

   a. **Dialysis**: The aqueous niosomal dispersion is dialyzed tubing against suitable dissolution medium at room temperature then samples are withdrawn from the medium at suitable time interval centrifuged and analyzed for drug content using UV spectroscopy.

   b. **Gel filtration**: The free drug is removed by gel filtration of niosomal dispersion through a sephadex G50 column and separated with suitable mobile phase and analyzed with analytical techniques.

   c. **Centrifugation**: The niosomal suspension is centrifuged and the surfactant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug.

**Determination of entrapment efficiency of proniosomes**: Proniosomal was centrifuged at 25,000rpm at 250C for 30 min to separate untrapped drug as supernatant. Supernatant was separated, filtered and sufficiently diluted with methanol to determine the concentration of untrapped drug spectrophotometrically. The percentage of drug encapsulation was calculated by.

\[
EE (%) = \left(\frac{t-f}{t}\right) \times 100
\]
Where,

t = concentration of total drug,

f = concentration of free drug,

Encapsulation efficiency of proniosomal gel is depends on the types of surfactants used. Proniosomes formed from Span 60, Span 40, Span20, and Span 80 was found to be high encapsulation efficiency compared with proniosomes prepared from tweens (Tween 20, Tween 80). Span 60 have higher encapsulation efficiency due to the longer saturated alkyl chain compared to that of span 40, span 20 and span 80. Most of the surfactants used to make nonionic surfactant vesicles such as spans have a low aqueous solubility. However, freely soluble nonionic surfactants such as Tween can form the micelles on hydration in the presence of cholesterol. Tween containing formulations also able to entrap efficiently. However the encapsulation efficiency was relatively low compared to those composed of Span. This is because the vesicles can be successfully formed by Tween only in the presence of excess cholesterol.

3. Shape and surface morphology: After hydration of proniosomes formation of numerous niosomes then this resultant solution transferred to the bottom of a small stoppered glass tube and spread uniformly. One ml saline or phosphate buffer was added carefully along the walls of the test tube and kept aside without agitation. After 15-20 min a drop of aqueous layer was withdrawn and placed on Neubaur’s chamber. The number of niosomes eluted from proniosomes was counted. Spontaneity studies showed that niosomes containing isopropanol and butanol were formed more spontaneously than niosomes containing propanol and ethanol perhaps due to faster phase separation of isopropanol and butanol due to their lower solubility in water.

4. In-vitro Drug Release From Proniosomal Vesicles: In-vitro drug release and skin permeation studies for proniosomes can be determined by following different techniques:

a) Franz diffusion Cell.
b) Dialysis Tubing.
C) Reverse Dilsysis.

5. In vivo studies: In vivo studies can be carried out by using different grades of animals i.e. rats, mice, rabbits and guinea pig. The goat abdominal skin may also use for the ex vivo evaluation of the topical formulations.
Applications of Proniosomes

1. **Transdermal drug delivery systems:** One of the best helpful aspects of proniosomes is that they greatly enhance the uptake of drug through the skin. Transdermal drug delivery utilizing proniosomal technology is widely employed in cosmetics; if truth, it was the primary uses of the niosomes. Topical use of proniosome entrapped antibiotics to treat acne disease. The penetration of the drug through the skin is greatly improved as compared to un-entrapped drug. Recently transdermal vaccines utilizing proniosomal technology is additionally being researched. The proniosome (along with liposomes and transferomes) will be utilized for topical immunization response tetanus oxoid. However, the present technology in proniosomes permits weak immunologic response and so a lot of research to be carried out this field.

2. **Drug Targeting:** One of the most helpful aspects of proniosomes is their ability to focus on drug. Proniosomes will be used to target drug to the reticulo-endothelial system. The reticulo-endothelium system (RES) preferentially takes up proniosomes vesicles. The uptake of proniosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosomes for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize the liver and spleen. This localization of the drugs can also be used for treating parasitic infections of the liver. Proniosomes can also be utilized for targeting drugs to organs other than the RES. A carriers system (such as antibodies) can be attached to proniosomes (as immunoglobin bind readily to the lipid surface of the noisome) to target them to specific organs.

3. **In Cardiac Disorder:** Proniosomal carrier system of lisnopril for the treatment of high blood pressure that's capable to delivery of lisnopril for extended amount of time. The potential of proniosomes as a carrier for the transdermal drug delivery system for lisnopril was investigated by encapsulating the drug in numerous formulations of Proniosomal gel containing numerous ratios of surface-active agent, cholesterol, and lecithin.

4. **Proniosomes as a carrier:** Proniosomes are used as a carrier for delivery of peptide drugs and haemoglobin within the blood. They are also used in studying immune response due to their immunological selectivity, low toxicity and greater stability. The proniosomes are also used as a carrier system in cardiac disorders, hormonal therapy, NSAIDS and antibacterial therapy.
5. **Anti-neoplastic Treatment:** The antineoplastic drugs are having the side effects. The niosomes are the change the metabolism; extend circulation and half life of the drug, thus reducing the side effects of the drugs. Niosomal entrapment of Doxorubicin as well as Methotrexate (separate study) exhibited helpful effects over the unentrapped drugs, such as reduced rate of proliferation of the tumor and higher plasma levels among slower elimination.

6. **Antibacterial Therapy:** 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 phospholipids.

7. **Uses in studying Immune Response:** Proniosomes are used in studying the immune response due to their immunological selectivity, low toxicity and high stability.

8. **Cosmeceuticals application of proniosomes:** 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 essential to deliver into the skin as an example, increased time of application sometimes results in higher activity. Proniosomal gel can be used as actual delivery systems for cosmetics and Cosmeceuticals due to their distinctive 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. The delivery system not specially enhances the delivery of active therapeutic agent through skin however moreover controls the rate of release. Proniosomal gel carriersystem entraps not only hydrophilic but hydrophobic agents also. There is excessive possibility for cosmetic agents to be include in the proniosomal gel delivery system. Nowadays a large numeral of cosmetic preparations available in the market are using niosomes and liposomes as a carrier for delivery of actives. These cosmetic formulations can be used for topical/transdermal applications for numerous functions. Proniosomes gel has an attraction towards biological membranes which helps in improving the penetration of actives through skin. A short-term
compilation associated to wide range of actives with therapeutic agents and cosmetic agents are which have been reported to be used for many applications.

9. Delivery of peptide drugs: Oral peptide drug delivery has long been faced with a of bypassing the enzymes which having the potency of breakdown the peptide. In a study, oral delivery of a vasopressin entrapped in proniosomes showed highest entrapment of the drug and significant increase within the stability of the incorporated peptide.

10. Sustained Release: The role of liver as a depot for methotrexate afterward niosomes is taken up by liver cells. Sustained release exploit of niosomal can be useful to drugs with low therapeutic index and low water solubility subsequently those could be maintained in the circulation through niosomal encapsulation.

CONCLUSION
From above, this can be concluded that Proniosomes can be used as efficient carrier for numerous classes of drugs. They are known to avoid many of the problems associated with either the aqueous niosome dispersion as problems of physical stability such as aggregation, fusion, and leakage. They provide additional convenience of transportation, distribution, storage and dosing. The proniosomes are drug delivery system as well as it improve the rate of penetration through the skin barrier.

REFERENCE