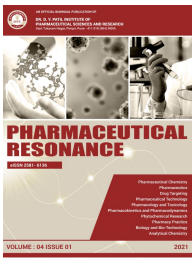
REVIEW ARTICLE

PRONIOSOMES: MODERN DRUG DELIVERY SYSTEM



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ABSTRACT : Drug delivery using nanotechnology is showing progressive changes by playing a vital role in developing new dosage forms. One of the technologies developed by using nanoforms is the vesicular drug delivery system. Such advancement in nano-vesicular drug delivery is niosomes and proniosomes. Proniosomes are a dry formulation of water-soluble carrier particles coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes. Provesicular systems, such as proniosomes which is one of the advancement in nanotechnology, minimize problems of the vesicular system such as aggregation, fusion and leakage of drug and provide additional convenience in transportation, distribution, storage and dosing. Conventional vesicular systems such as liposomes and niosomes face stability related difficulty. This new emerging concept has demonstrated the potential in improving oral bioavailability, targeting drugs to the specific site, It permeation of drugs across the stratum corneum. It prolongs the existence of the drug in systemic circulation and finally reduces the toxicity.

Keywords : *Proniosomes, Niosomes, Transdermal, Coacervation.*

INTRODUCTION:

In recent times no single delivery systems fulfill all the criteria, but an attempt has made through novel approaches. Many novel approaches emerged covering various routes of administration to achieve their controlled or target drug delivery. The primary aim of novel drug delivery is the maintain the constant and effective drug level in the body and minimizing the side effects. Localizes the drug action by targeting the drug delivery by using drug carriers.

Vesicular systems have been receiving a lot of interest as a carrier for advanced drug delivery. Encapsulation of drug prolongs the duration of action and reduces toxicity. Colloidal liposomes and noisomes have advantages over conventional dosage form. In this system, particles act as drug reservoirs and carry both hydrophilic and hydrophobic drug. The vesicles in a dispersed aqueous system may suffer from some chemical problems associated with degradation by hydrolysis or oxidation; also physical problems as sedimentation, aggregation, or fusion of liposomes during storage. A Novel approach; was adopted in dealing with these problems to develop the proliposomes and to develop Niosomes using non-ionic surfactants alternatives to phospholipids in preparing vesicles.

Niosomes exhibit chemical stability during storage, but the problem is physical stability. The latest approach in the field is vesicular delivery is to combine the two previously mentioned techniques by extending the pro-vesicular approach to niosomes through the formation of 'proniosomes', which converted to niosomes upon hydration. Niosomes are non-ionic surfactant vesicles that can entrap a solute in a manner analogous to liposomes. They are osmotically active and are stable on their own, while also increasing the stability of the entrapped drugs. Niosomes possess an infrastructure consisting of hydrophilic and hydrophobic moieties together. The particle size ranges from 10nm-100nm.[1-5]

Proniosomes Overview [2]

Proniosomes are vesicular system in which the vesicles made up of non-ionic based surfactants, cholesterol and other additives. Proniosomes prepared by dissolving the surfactant in a minimal amount of an

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acceptable solvent, namely ethanol and then hydration with the least amount of water to form a gel. These structures are liquid crystalline compact niosomes hybrids that can be converted into niosomes immediately upon hydration or used in topical/ transdermal applications. The use of proniosome gel in topical/dermal delivery does not require hydration before application. It can be applied as such or loaded on a base material of emulsion, gel, ointment before application. Base helps in the application and dilution of active material on the skin. Proniosomes used to enhance drug delivery in addition to conventional niosomes.

They are becoming popular due to their semisolid/ liquid crystalline compact nature when compared to niosome dispersion. Proniosomal gels are generally present in transparent, translucent or white semisolid gel texture that makes them physically stable during storage and transport. The dissolution of most surfactants in water leads to the formation of lyotropic liquid crystals rather than the micellar solution. The lamellar phase shows sheets of surfactants arranged in bilayer form, whereas the hexagonal cylindrical units packed in a hexagonal fashion. The cubic phase consists of a curved bio continuous lipid bilayer extending in three dimensions, separating two congruent networks of water channels. Liquid crystals are attractive because of the transparency and high viscosity.

The addition of water leads to interaction between water and polar groups of the surfactant results in swelling of bilayers. Solvent concentration increased above a limited value. Bilayers tend to form random spherical structures, i.e., multilamellar, multivesicular structures. The beauty of these proniosomes lies in their ability to rearrange as stable niosomal suspension on hydration with water.

Structure of Proniosomes [3]

These are microscopic lamellar structure. It combines a non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class of cholesterol followed by hydration in the aqueous media. The surfactant molecule directs itself such that the hydrophilic end of the non-ionic surfactant orients outward, while the hydrophobic end is in the opposite direction to form the bilayer. Like liposomes, proniosomes also made of the bilayer. In proniosomes, this bilayer made up of a non-ionic surface-active agent. Proniosomes are unilamellar or multilamellar.

Advantages of Proniosomes [4]

- Avoiding the problem of physical stability like aggregation, fusion, leaking,
- Avoiding hydration of encapsulated drugs is limiting the shelf-life of the dispersion.
- Proniosomes are water-soluble carrier particles coated with surfactant and can be hydrated to form niosomal dispersion immediately before use brief agitation with the hot aqueous medium. It has added convenience of transportation, distribution, storage. Designing would be dry niosomes promising industrial product.
- Furthermore, unacceptable solvents avoided in proniosomal formulations. The systems may be directly formulated into transdermal patches and don't require the dispersion of vesicles into the polymeric matrix.
- The storage makes proniosomes a versatile delivery system with potential with a wide range of active compounds.

Disadvantages

- **Demerits Of Liposomes Include**: Liposomes require special precautions and conditions for formulation and preparation
- Complex method for routine and large scale production.
- Less chemical stability.
- High cost.

1. **Demerits of niosomes include physical instability:**

- Aggregation.
- Fusion.
- Leaking of the entrapped drug.
- Sedimentation

Types of Proniosomes5

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

A. Dry Granular Proniosome: According to the type of carrier, they again divided as sorbitol based proniosomes.

B. Maltodextrin Based Proniosomes:

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

Components of Proniosomes[6]

The essential and most common components for the delivery system are as follows.

Surfactants:

Surfactants are the surface-active agents that usually an organic compound that is amphiphilic (having both hydrophobic and hydrophilic groups). Therefore, a

surfactant molecule contains both a water-insoluble and a water-soluble (hydrophilic) component. They have a variety of functions includes acting as solubilizers, wetting agents, emulsifiers and permeability enhancers. The most common non-ionic amphiphiles used for vesicle formation are alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids.

1. Carrier materials:

In formulation, carrier permits flexibility depending on the ratio of surfactant and other components incorporated. In addition to this, it increases the surface area and hence efficient loading. The carriers should be safe, effective and non-toxic, free-flowing, poor solubility in the loaded mixture solution and good water solubility for ease of hydration. The Material and its role in the preparation of proniosomes mentioned in Table 1.

1. Slurry method: [7, 8]

Proniosomes prepared by addition of the carrier and the entire surfactant solution in a round-bottomed flask that fitted to the rotary flash evaporator, a vacuum was applied to form a dry and free-flowing powder. Finally, the formulation should store in a tightly closed container under refrigeration in light. The time required for proniosomes production is independent of the ratio of surfactant solution to the carrier material and appears to be stable.

The proniosomal powder formed is collected and sealed in containers and stored at 4°C. Proniosomes prepared by the developed slurry method using maltodextrin as a carrier. The required volume of surfactant and cholesterol stock solution per gram of maltodextrin and drug should be dissolved in the solvent in a 100 ml round bottom flask containing the carrier (maltodextrin). Additional chloroform can be added to form slurry in case of lower surfactant loading. The flask has to be attached to a rotary flash evaporator to evaporator solvent at 50- 60 rpm at a temperature of45-2°C and a reduced pressure of 600mm Hg until the mass in the flask had become container under refrigeration in light.

Advantages of Slurry Method

1. Maltodextrin is easily soluble in water and used as carrier material in the formulation; they were easily coated by simply adding surfactant in an organic solvent to dry Maltodextrin.
2. Due to the uniform coating, it protects the active ingredient and the surfactants from hydrolysis and oxidation.
3. The higher surface area results in thinner surfactant coating that makes the rehydration process efficient.

Disadvantages of slurry method:

1. The method is time-consuming and involves specialized equipment with vacuum and nitrogen gas.
2. The thin-film approach allows only for a predetermined lot sizes. So material often wasted, so small quantities and small dose batch can be a tedious one.

Coacervation phase separation method: [8, 9]

Proniosomal gels can be prepared by this method which comprises surfactant, lipid and drug in a wide-mouthed glass vial along with a small amount of alcohol in it. The mixture is warmed-over water bath at 60-70°C for 5min until the surfactant mixture dissolved completely. Then the little aqueous phase is added to the above vial and warmed still a clear solution is formed then converted into proniosomal gel on cooling. After hydration of proniosomes, they converted to uniformly sized niosomes.

Advantages of coacervation phase separation method :

1. The method is simple and without time consumable so it does require any specialized equipment.
2. Specially adapted for gel preparation
3. Small dose formulation can be prepared on a lab-scale.

3. Slow spray coating method: [10-13]

Table 1: Materials and their role in the preparation of proniosomes

Sr. No	Material	Example	Role
1	Surfactant	Span 20, 40, 60,80, 85, Tween 20, 40, 80	Formation of vesicles
2	Stabilizers	Cholesterol, lecithin	To prevent leakage of drug Formulation
3	Carriers	Maltodextrin, Sorbitol	Provides flexibility in surfactant and other Component ratio.

In this method, the surfactant is added to an organic solvent and sprayed onto the carrier. Then the solvent is evaporated. This process repeated until the desired surfactant loading achieved because the carrier is soluble in the organic solvent. As the carrier dissolved, hydration of this coating allows the formation of a multilamellar vesicle.

These niosomes have uniform size distribution and similar to those produced by conventional methods. A 100 ml round bottom flask containing the desired amount of carrier can be attached to a rotary flash evaporator. A mixture of surfactant and cholesterol should be prepared and introduced into a round bottom flask on a rotary evaporator by sequential spraying of aliquots onto the carrier's surface. The evaporator has to be evacuated and the rotating flask can be rotated in a water bath under vacuum at 65-70 o C for 15-20 min. This process has to be prepared until all of the surfactant solutions had been applied. The evaporation should be continued until the powder becomes completely dry.

Advantage of the slow spray coating method:

1. It's a simple method suitable for the hydrophobic drug without concerns of instability or susceptibility of active pharmaceutical ingredient to hydrolysis.

Disadvantages of slow spray coating method:

1. The method is time-consuming and involves specialized equipment with vacuum and nitrogen Gas.
2. The thin-film approach allows only for a predetermined lot sizes. So material often wasted minute quantities; a small dose batch can be a tedious one.

Mechanism of Action: [14-16]

The exact mechanism of penetration of drug in the vesicles through the skin not yet explored, penetration will depend on the nature and type of the drug used, vesicles formed and hydration temperature for the conversion of proniosomes to Niosomes. The lipids used in the preparation of proniosomes, act as a carrier that will form depot at the site of action and hence sustains the action. The rate-limiting step in the penetration of the drug through the transdermal drug delivery is the lipid (ceramides) part of the stratum corneum, which packed tightly as a bilayer by hydrogen bonding. The hydrogen bonding will strengthen and stabilize the lipid bilayer and as a result, will impart the barrier property of the stratum corneum.

Proniosomes will hydrate to niosomes when applied to the skin. This increases the concentration gradient and hence increases the diffusion pressure for the driving of the drug through the stratum corneum.

Factors Affecting the Formulation Proniosomes [17]

Various processing and formulation variables affect the proniosomes characteristics. They include surfactant chain length, cholesterol content, drug concentration, total lipid concentration, a charge of lipids, pH of the dispersion medium and type of alcohol used in the preparation.

1) Surfactant chain length

Spans are commonly used in the preparation of proniosomes. Spans have the same head group and different alkyl chain. By increasing the alkyl chain length leads to higher entrapment efficiency. The entrapment efficiency follows the trend such as Span 60

(C18)>Span 40(C16)>Span 20 (C12)>Span 80 (C18). Span 60 and Span 80 have the same head groups but Span80 has an unsaturated alkyl chain. The introduction of double bonds into the paraffin chains causes a marked enhancement of the permeability of liposomes, possibly explaining the lower entrapment efficiency of the Span 80 formulation.

2) Cholesterol content

Cholesterol increases or decreases the percentage encapsulation efficiency depending on either the type of the surfactant or its concentration within the formula.

3) pH of the hydration medium

The percentage encapsulation efficiency of niosomes prepared by hydration of proniosomal gels of Span 60/ cholesterol (9:1) was found to be greatly affected by the pH of the hydrating medium. For example, the fraction of flurbiprofen encapsulated was increased to about 1.5 times as the ph decreased from pH 8 to 5.5. The increase in the percentage encapsulation efficiency of flurbiprofen by decreasing the pH could be attributed to the presence of the ignitable carboxylic group in its chemical structure. Decreasing the pH could increase the proportions of the unionized species of flurbiprofen, which have higher partitioning to the bilayer lipid phase compared to the ionized species.

4) Total lipid concentration

The percentage encapsulation efficiency of flurbiprofen was increased as the lipid concentration was increased from 25 to 200 mol/ml, respectively. The increase in percentage encapsulation efficiency of flurbiprofen as a function of total lipid concentration was linear. On the other hand, the amount of flurbiprofen entrapped was decreased on increasing the lipid concentration from25 to 200mol/ml, respectively. This leads to the fact that the fraction of lipid taking part in encapsulation decreases as the concentration of

lipid increases.

5) Drug concentration

Increasing flurbiprofen concentration from 25 to 75 mg/mol lipids in the proniosomes prepared from Span 60/cholesterol (9:1), showed an increase in both percentage encapsulation efficiency and the amount of drug encapsulated per mol total lipids upon hydration and formation of niosomes.

6) Charge of the lipids

Incorporation of either diacetyl phosphate (DCP) which induces negative charge or stearylamine (SA) which induces positive charge decreased the percentage encapsulation efficiency of flurbiprofen into niosomal vesicles.

Characterization of Proniosomes

1. Vesicle morphology:[18]

Vesicle morphology involves the measurement of size and shape of proniosomal vesicles. Size of proniosomal vesicles can be measured by dynamic light scattering method in two conditions: without agitation and with agitation. Hydration without agitation results in largest vesicle size. Scanning electron microscopy (SEM) can also be used for the measurement of vesicle size and shape. Determination of vesicle size is important for the topical application of vesicles. Size of captopril vesicles was found after agitation of dispersion as energy applied in agitation resulted in the breakage of the larger vesicles to small vesicles. The size of captopril vesicles was found 11.38-25.06 mm (without agitation) and 4.14-8.36 mm (with agitation). Hence, it can be concluded that increasing hydrophobicity of the surfactant monomer leads to a smaller size vesicle, since surface energy decreases with increasing the hydrophobicity. The size distribution of niosomes with tweens was significantly lower than with span surfactants. The vesicle size analysis of Indomethacin niosomes showed that vesicles were discrete and separate with no aggregation or agglomeration. The diameter Indomethacin niosomes was found to be in the rage of 10-15 mm. Haloperidol proniosomes with lower HLB values seemed to be mostly spherical and discrete with sharp boundaries having smooth and rigid surfaces. The main difference between deformable and rigid vesicles was found due to fluidity of the lipid bilayers of the deformable vesicles.

2. Shape and surface morphology:[19]

Surface morphology means roundness, smoothness and formation of aggregation. It was studied by scanning electron microscopy, optical microscopy, and transmission electron microscopy.

3. Scanning electron microscopy:[20, 21]

The surface morphology and size distribution of proniosomes were sprinkled onto the double-sided tape that was affixed on aluminum stubs. The aluminum stub was placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips Netherlands). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 tor, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).

4. Optical microscopy: [22]

The Niosomes were mounted on glass slides and viewed under a microscope (Medilux- 207RII, Kyowa -Getner, Ambala, India) with magnification of 1200X for morphological observation after suitable dilution. The photomicrograph of the preparation also obtained from the microscope by using a digital SLR camera.

5. Angle of repose: [23-26]

The angle of repose of dry proniosomes powder was measured by a funnel method. The Proniosomes powder was poured into a funnel which was fixed at a position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows down from the funnel to form a cone on the surface and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

Encapsulation Efficiency:

The encapsulation efficiency of proniosomes is determined after separation of the unentrapped drug.

(1) Separation of unentrapped drug is done by the following techniques: [27]

(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.

(2) Determination of entrapment efficiency of proniosomes:

The vesicles obtained after removal of unentrapped drug by dialysis is then resuspended in 30% v/v of

PEG 200 and 1 ml of 0.1% v/v triton x-100 solution was added to solubilize vesicles the resulted clear solution is then filtered and analyzed for drug content. The percentage of drug entrapped is

Calculated by using the following formula :

$$\text{Perentage Entrapment} = \frac{\text{Amount of drug entrapped}}{\text{Total amount of drug}} * 100$$

Methods for the characterization of proniosomes: [28]

Parameter used for characterization of proniosomes mentioned in Table 2.

Applications of Proniosomes [29]

1. Non-Steroidal Anti-Inflammatory drug:

Ketorolac, a potent non-steroidal anti-inflammatory drug, is formulated as a proniosome gel using spans, tweens, lecithin and cholesterol with ethanol as a solvent. Each of prepared proniosomes formulation shows significantly improved drug permeation in case of transdermal drug delivery system.

2. Hypertension-

Fabricated proniosomes using different non-ionic surfactants, such as Span 20, Span 40, Span60, Span 80, Tween20, Tween 40 and Tween 80 for transdermal drug delivery system of losartan potassium. Proniosomal formulation more effective in hypertension.

3. Skin disorders -

Developed a proniosomal gel for transdermal drug delivery of chlorpheniraminem maleate (CPM).The system was formulated with Span 40 and evaluated for the effect of composition of formulation and having high penetration property.

4. Hormonal insufficiencies -

A proniosome based transdermal drug delivery system of levonorgestrel (LN) was developed and extensively characterized both in-vitro and in -vivo. The proniosomal structure was liquid crystalline compact niosomes hybrid which could be converted into niosomes upon hydration. The system was evaluated in-vitro for drug loading, rate of hydration (spontaneity), vesicle size, poly dispersity, entrapment efficiency and drug diffusion with high skin permeability across rat skin.

5. Antibacterial therapy -

Amphotericin-b proliposomes could be stored for 9 months without significant changes indistribution of vesicle size and for 6 months without loss of pharmacological activity.

6. Carriers for Haemoglobin -

Proniosomes derived niosomes can be used as carriers for hemoglobin within the blood.

7. Used in Cardiac disorders :

Proniosomal carrier system for captopril for the treatment of hypertension (high blood pressure) that is capable of efficiently delivers in entrapped drug over an extended period of time. The roles 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 in dexand low water solubility.

Current Researches in Proniosomes Drug delivery System[30]

Proniosomes gel:

In the past few decades, considerable attention has been focused on the development of new drug delivery system. Many novel approaches emerged covering various routes of administration, to achieve either

Table 2: Characterization parameter of Proniosomes

Parameter	Instrument / Method Used
Vesicle morphology	Scanning electron microscopy, Laser microscopy.
Shape and surface Morphology	Optical microscopy, Scanning microscopy, Transmission microscopy.
Angle of repose	Funnel method
Encapsulation efficiency	Diode array spectrophotometer, Centrifugation method, Dialysis method.
Drug release kinetic data analysis	Higuchi's model, Peppa's model
In-vitro methods for assessment drug release from proniosomes	Dialysis tubing, Reverse dialysis, Franz diffusion cell.
In-vitro permeation study	Franz diffusion cell, Keshary chien diffusion cell
Zeta potential analysis	Zeta potential probe model

controlled or targeted delivery. The prime aim of novel drug delivery is maintenance of the constant and effective drug level in the body and minimizing the side-effects and it also localizes the drug action by targeting the drug delivery by using drug carriers. Topical/ Transdermal delivery systems, when compared with conventional formulations, generally show a better control of blood levels, a reduced incidence of systemic toxicity, no hepatic first-pass metabolism and a higher compliance. A continuous interest toward the dermal and transdermal products can be seen, offering several advantages. Niosomes are capable of entrapping hydrophilic and hydrophobic solutes. Many disadvantages associated with Niosomes have overcome by the help of proniosomes. Proniosomes, hydrated by agitation in hot water for a short period of time, have been proposed for a number of potential therapeutic applications, e.g. as carriers of anti-inflammatory drugs. Meloxicam (MLX) is a nonselective, nonsteroidal anti-inflammatory drug (NSAID) with preferential inhibition of cyclo-oxygenase-2 (COX-2) over COX-1.MLX does not have documented cardiovascular toxicity at doses of less or equal to 15 mg/day which are recommended for the treatment of rheumatoid arthritis and osteoarthritis. However, when orally administered, nonselective NSAIDs may adversely affect the gastrointestinal tract and can even reduce the life expectancy of patients with rheumatoid arthritis. Transdermal delivery of MLX would avoid major gastrointestinal side effects and provide steady plasma levels from a single dose. In addition, it has been demonstrated that NSAIDs promote local analgesia when administered locally through the skin. Therefore, alternative non-invasive mode of delivery of the drug is needed.

Preparation of Proniosome gel

Proniosome can be prepared by various methods. In one method proniosome are prepared by slurry method using Malto dextrin as a carrier. In this method Maltodextrin powder is added to round bottom flask and the entire volume of surfactant solution is added directly to the flask. The flask is attached to the rotary evaporator and vacuum is applied until the powder appears to bedry and free flowing. Then the flask is removed from the evaporator and is kept under vacuum overnight [34]. Then proniosome powder is stored in sealed container at 4°c.

In another Spray coated method, proniosome can be prepared by spraying the surfactant mixture containing span, cholesterol and diacetyl phosphate in to the round bottom flask on the rotary evaporator by sequential spraying of aliquot on to the surface of Sorbitol powder. During the spraying period, the rate of application is controlled so that the powder beds of Sorbitol do not become overly wet. The evaporator is than evacuated and rotating flask is lowered into water bath at 65 to 70oc and flask is rotated under vacuum for 15 to 20 min or until Sorbitolis appeared to be dries. This process is repeated until all of the surfactant solution has been applied. After addition of the final aliquot, evaporation is continued until the powder is completely dried (about 20-30 min). The material is further dried in desiccators under vacuum at room temperature overnight. Thus, a dry preparation is obtained; this dry preparation is referred to as 'proniosome' and is used for preparation and for further study on powder properties. Proniosome derived niosome dispersion is obtained by hydrating proniosome preparation with80°C distilled water and vortex mixing for 2 min.

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

Applications

(1) Drug Targeting[31-32]

One of the most useful aspects of proniosomes is their ability to target drugs. Proniosomes can be used to target drugs to the reticule-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 noisome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to 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 carrier 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. Many cells also possess carbohydrates determinates, and this can be exploited by niosomes to direct carrier system to particular cells.

(2) Anti-neoplastic treatment[33-34]

Most antineoplastic drugs cause severe side effects. Proniosomes can alter the metabolism; prolong circulation and half-life of the drug, thus decreasing the side effects of the drugs. Proniosomal 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.

(3) Treatment of Leishmanasis[35]

Leishmanasis 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 (antimonial), which in higher concentrations can cause cardiac, liver and kidney damage. Use of proniosomes 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.

(4) Delivery of peptide drugs[36]

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of proniosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an in-vitro study, oral delivery of a Vasopressin derivative entrapped in proniosomes showed that entrapment of the drug significantly increased the stability of the peptide.

(5) Uses in studying immune response[37]

Proniosomes are used in studying immune response due to their immunological selectivity, low toxicity and greater stability. Proniosome are being used to study the nature of the immune response provoked by antigens.

(6) Niosomes as carriers for haemoglobin[38]

Proniosomes can be used as carriers for hemoglobin within the blood. The proniosomal vesicle is permeable to oxygen and hence can act as a carrier for hemoglobin in anemic patients.

(7) Transdermal drug delivery systems[39-41]

One of the most useful aspects of proniosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing proniosomal technology is widely used in cosmetics; In fact, it was one of the first uses of the niosomes. Topical use of proniosome 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 proniosomal technology is also being researched. The proniosome (along with liposomes and transferomes) can be utilized for topical immunization using tetanus toxoid. However, the current technology in proniosomes allows only a weak immune response, and thus more research to be done in this field.

(8) Sustained release

The role of liver as a depot for methotrexate after proniosomes is taken up by the liver cells. Sustained release action of proniosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via proniosomal encapsulation.

(9) Localized drug action[42-43]

Drug delivery through proniosomes 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 proniosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity. The evolution of proniosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has promise in cancer chemotherapy and anti-leishmanial therapy. Some example of Proniosomes as a carrier of various drug molecules mentioned in Table 3.

Future Trends[44]

There is a strong need for exploring the proniosomal delivery systems for cosmetics, herbal actives and nutraceutical. Use of proniosome in the cosmetic formulation will lead to prolongation, better absorption along with many advantages. To get the desired characteristics of a particular proniosome gel formulation, it is important to select the surfactant of suitable HLB in the formulation of proniosome gel. Studies on proniosome gel formulation indicate that it has become a useful dosage form for drug permeation into the skin, especially due to their simple, scaling-up production procedure and ability to modulate drug delivery across the skin. Hence, a more extensive study should be undertaken to find out the optimal proniosome formulation for drug/cosmetic permeation into the skin

Current researches in proniosomes as a drug delivery system:

Proniosomes as a drug carrier for Candesartan cilexetil[45]

Candesartan is an angiotensin II receptor antagonist widely used in treatment of hypertension and characterized by its good efficacy and lesser side effect compared to other angiotensin II receptor antagonist. The Proniosomal carrier system for Candesartan cilexetil was developed for the treatment of hypertension as it was capable of efficiently delivering entrapped drug overan extended period of time. Candesartan proniosomal gel was formulated by Coacervation phase separation method. Through study it was found that transdermal Proniosomal gels showed controlled drug release properties.

Table 3: Proniosomes as a carrier of various drug molecules

Sr. No	Drug	Category	Result
1	Tenoxicam	NSAID	The proniosomal gel proved superior to oral marketed tablets in anti-inflammatory properties.
2	Guggul	Herbal	Proved superior to the NSAIDs existing in the market.
3	Carvedilol	Anti-hypertensive	Proniosomal gel for improved transdermal delivery were investigated using various surfactant
4	Valsartan	Anti- hypertensive	The encapsulation efficiency of span 60 was superior to span 40
5	Celecoxib	NSAIDs	The proniosomal formulation improved the extent of absorption then conventional capsules.
6	Hydrocortisone	NSAIDs	The application of hydrocortisone in the form of proniosome leads to prolonged action.
7	Griseofulvin	Antifungal	Result indicate that the optimize PNG formulation of griseofluvin have better skin permeation potential then plain drug solution in water
8	Losarton potassium	Antihypertensive	The result show increase in bioavilability as compared to oral dose
9	Piroxicam	NSAIDs	The result shows that proniosomal based transdermal drug delivery system of piroxicam were promising carrier for delivery of piroxicam.
10	Flubiprofen	NSAIDs	The result indicate that the entrapment efficiency followed the trend span 60> span 40> span 20> span 80

Candesartan cilexetil Proniosomal containing lecithin, cholesterol and in combination of surfactant like span 20,40,60 shows sustained release of drug over a period of 24hrs for the management of hypertension. Skin compatibility which is the primary requirement for good local formulation was found that the ph. of range 5.24-7.[40] suited the skin ph., indicating skin compatibility. Thus it was concluded that proniosomal formulation of Candesartan cilexetil holds an immense potential for the development of topical antihypertensive agent comparable to conventional oral antihypertensive agent.

Proniosomes for effective topical delivery of clotrimazole [45]

Clotrimazole is a broad spectrum imidazole used in treatment of infection caused by Candida species, aspergillus species. The oral formulation of clotrimazole have very low bioavailability (5%-10%) because of poor solubility of the drug(0.49µg/ml) and are highly prone to drug interaction which makes this drug a suitable candidate for topical application. Since both hydrophilic and lipophilic substances can be embedded in proniosomal vesicles thus they are expected to offer a special advantage for clotrimazole which is lipophilic with relative hydrophobicity. Through the study it was found that proniosomal gel of clotrimazole was prepared by using span and tweens as surfactant, cholesterol and soya lecithin. The outcomes of microbiological activity studies showed greater potential of vesicular system in inhibiting the growth of Candida albicans with a higher zone of inhibition up to 24h. The enhanced antifungal activity of clotrimazole may be attributed to enhanced penetration of vesicles containing clotrimazole through fungal cell walls to inhibit ergo sterol synthesis. The proniosomal gel formulation contains ethanol and surfactant. Ethanol exhibit better anticandidal activity as it kills organisms by denaturing their proteins and dissolving their lipid apart from skin fluidization and penetration. Thus these studies showed promising results hence delivering of clotrimazole through proniosomal gel proved to be promising carrier due to their simple production and simplistic scale up.

Proniosomal based transdermal delivery of Ondansetron hydrochloride [46]

Ondansetron hydrochloride is a potent highly selective, competitive antagonist at the 5-ht receptors Its short biological half-life (3-5hours) and low bioavailability (45-50%) due to hepatic first pass metabolism makes it an appropriate candidate for sustained release ondansetron hydrochloride loaded proniosomal gel formulation was prepared using optimum ratio of lecithin and cholesterol (9:1) with span 40 as surfactant demonstrated good result. The proniosomal formulation prepared using span as surfactant in the ratio 9:1 gave better results in terms of %entrapment efficiency, vesicle size and vesicle count. Thus proniosomes derived niosomes appear to be better than proliposomes and plain drug level.

Proniosomal gel of Flurbiprofen[47]

Flurbiprofen are non-steroidal anti-inflammatory drug is used for the relief of pain and inflammation associated with rheumatoid arthritis and osteoarthritis. It's more potent than ibuprofen but has more gastric side effects like peptic ulceration and severe gastrointestinal bleeding may occurs. The plasma half-life of flurbiprofen is 4-6 hours. Hence repeated administration of high dose (100mg: three times a day) is required for effective management of rheumatoid arthritis and osteoarthritis. To overcome the problem like gastric side effect, short half-life and low bioavailability was solved by formulating it into proniosomal gel. Proniosomes was prepared by Coacervation-phase separation method. Formation of vesicle mainly depends on the concentration of cholesterol and surfactant ratio. Thus from the study it was concluded that the proniosomal gel possess higher entrapment efficiency and utilizes alcohol, which itself act as a penetration enhancer. Thus proniosomes proved to be promising carrier for the topical administration due to enhanced delivery of the drugs through the skin.

Proniosomes Based Drug Delivery for Phytochemicals

a) Proniosomes encapsulated Curcumin for transdermal administration [48]

Curcuminoids are oleoresin, derived from the ethanolic extraction of turmeric. Curcuminhas wide range of therapeutic effects such as anti-inflammatory, anti-bacterial, antifungal, anticancer, antispasmodic, antioxidant. Curcumin indicates its poor solubility in acidic medium and consequently low absorption from the GIT which lead to ultimately poor bioavailability by oral absorption. By the means of transdermal drug delivery system all these can be avoided and therapeutic efficacy of Curcumin can be improved. Proniosomal systems of Curcumin made with SPAN80 exhibited good physiological and release properties and can easily be prepared. Curcumin is lipid soluble so dissolved in cholesterol and dispersed uniformly throughout the composition. The cholesterol content in the vesicles increased the incorporation of the drug in vesicles also increased. Cholesterol increased the rigidity of proniosomal membrane. The encapsulation efficiency increases when the concentration of span-80was increased.

Gugulipid - loaded proniosomal gel[49]

Gugulipid is an ethyl acetate extract of guggul resin, obtained from Commiphora wightii. Gugulipid is a potent hypolipidemic agent. Apart from its hypolipidemic activity, a large number of therapeutic activities like antimicrobial, anti-helminthic, anti-inflammatory, antiarthritic and antioxidant activity. Proniosomal gel of Gugulipid was prepared employing span 40 and it provided with vesicles of larger size, with higher entrapment efficiency and least rate of leakage of the drug. The entrapment efficiency of Gugulipid in proniosomal gel conducted across semi-permeable membrane revealed the initial faster release followed by slow sustained release of the drug for 8hr. thus proniosomal formulations of Gugulipid holds an immense potential for development of topical herbal anti-inflammatory formulation.

Patents in the field of Proniosomes[50]

1. Cosmetic and pharmaceutical compositions containing niosomes and a water-soluble polyamide and a process for preparing this composition US Patent 4830854.
2. Immuno targeting of non-ionic surfactant vesicles US Patent 20070172520.
3. Non-ionic surfactant emulsion vehicles and their use for deposition of drug into and across skin US Patent 5720948.

Conclusion

Proniosomal gel systems are widely accepted by the researchers and academicians in recent days because of its ability to deliver the drug to the desired organs and giving desired activity with less amount of drug with fewer side effects. Proniosomes are thought to be better module of drug delivery as compared to liposome sand niosomes due to various factors like cost, stability etc. These systems have been found to be more stable during sterilization and storage than niosomes. The use of proniosomal carrier results in delivery of high concentration of active agent(s), regulated by composition and their physical characteristics. Proniosomes have been tested to encapsulate lipophilic as well as hydrophilic drug molecules. Various types of drug deliveries can be possible using proniosomes based niosomes like targeting, ophthalmic, topical, parenteral, peroral vaccine etc. Among all vesicular systems niosomes has special importance because of its rich quality in different factors like stability, cost, encapsulation

capacity, etc. But its importance is limited by its physical instability. This problem can be effectively reduced by the proniosomes concept which was proved by many researchers. As a result of this proniosomes will become prominent drug delivery systems in this novel drug delivery system.

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