



Received on 21 August, 2012; received in revised form 04 October, 2012; accepted 20 November, 2012

PRNIOSONES AS A DRUG CARRIER: A REVIEW

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Keywords:

Proniosomes, Characterization, Medical Applications

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QUICK RESPONSE CODE



IJPSR:
ICV (2011)- 5.07

Website:
www.ijpsr.com

ABSTRACT

Nanotechnology is an advancing technology expected to bring revolutionary changes in the field of life sciences including drug delivery, diagnostics, nutraceuticals and biomedical for implants and prosthesis. The advance in nanotechnology helps in preparing newer formulations. One of the advancement in nanotechnology is the preparation of proniosomes. A comprehensive research has done on proniosomes as a drug carrier for transdermal delivery in last few years. 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 focus of this review is to bring out different aspects related to proniosomes preparation, characterization, entrapment efficiency, *in vitro* drug release, applications and merits.

INTRODUCTION: The transdermal route is widely used now days as it is convenient over the conventional dosage forms. Transdermal route bypasses the GI tract hence avoiding the gastric irritation, reduces number of doses, improved patient compliance, enhanced bioavailability and can maintain suitable plasma concentration¹.

Controlled release dosage forms are widely used in now a days. It has a prolonged action formulations which gives continues release of their active ingredients at a predetermined rate and for a predetermined time.

The vital objective for the development of controlled release dosage forms is to prolong the extended duration of action and thus gives assurance for higher patient compliance. There are four types of controlled drug delivery systems;

1. Rate Pre-programmed DDS
2. Activation modulated DDS
3. Feedback regulated DDS
4. Site targeted DDS²

Today, number of novel approaches has emerged covering various routes of administration, to achieve either controlled or targeted delivery¹. Vesicular drug delivery is one of the approaches which encapsulate the drug eg. Liposomes, niosomes, transferosomes, pharmacosomes, and proovesicles like proliposomes and proniosomes¹. Vesicular system like Liposomes² or Niosomes³ has specific advantages while avoiding demerits associated with conventional dosage forms because the particulate carriers can act as drug reservoirs, but these particulate carriers has disadvantages rather than advantages.

To overcome these disadvantages vesicular system of proniosomes are arrived. Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation with hot aqueous medium. These proniosomes has additional convenience of the transportation, distribution, storage and designing would be dry niosomes a promising industrial product^{4,5}.

Hence, dry niosomes can be prepared which are often called as proniosomes and it avoids many problems associated with niosomes like physical stability. Proniosomes can be hydrated immediately before use to give niosomal dispersion.

Proniosomes are dry, free flowing granular product which upon hydration gives multi lamellar niosomal dispersion. This Proniosomal drug delivery have attracted towards transdermal drug delivery because surfactants themselves act as penetration enhancers and are biodegradable, non-toxic, amphiphilic, possess property of encapsulation and they can entrap both hydrophilic and lipophilic drugs⁶ as shown in **Fig. 1**.

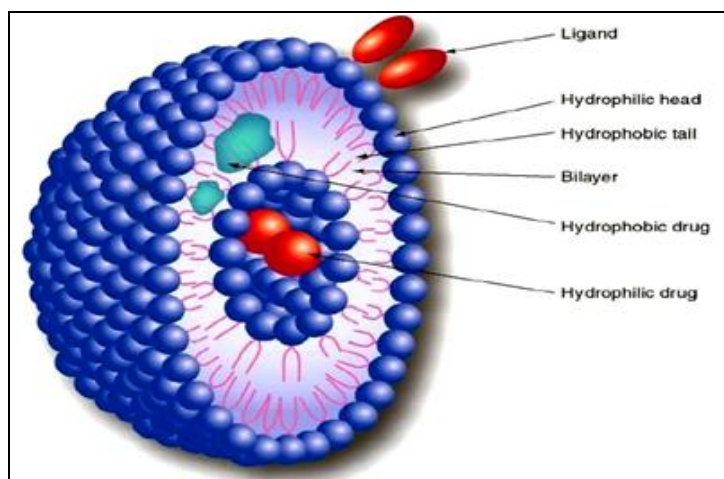


FIGURE 1: REPRESENTATION OF PRONIOSOMES

Structure of Proniosomes: Proniosomes are present in transparent, translucent or semisolid gel structure because of limited solvent presence and these are mixture of liquid crystals like lamellar, hexagonal, and cubic as shown in (**Fig. 2**). Here lamellar phase shows sheets of surfactants arranged in bilayer, hexagonal phase shows cylindrical compact structure arranged in hexagonal fashion whereas cubic phase consist of curved continuous lipid bilayer extending to three dimensions. While formulating this gel, in the beginning, less viscous composition is formed in some

cases but addition of water leads to interaction between water and polar group of surfactant resulting swelling of bilayer. If amount of solvent is increased further, then a spherical structure is formed i.e., multi-lamellar, multi-vesicular. This leads to complete hydration thereby formation of Niosomes^{7,8}.

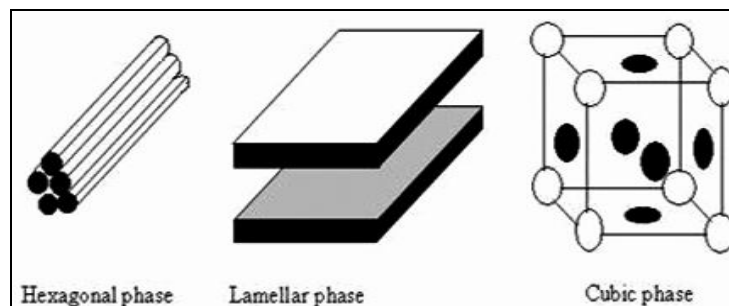


FIGURE 2: SCHEMATIC REPRESENTATION OF VARIOUS LIQUID CRYSTALLINE PHASES

Advantages of Proniosomes over the Niosomes⁹⁻¹²:

- Avoiding problem of physical stability like aggregation, fusion and leaking
- Avoiding hydrolysis of encapsulated drugs which limiting the shelf life of the dispersion

Mechanism of Drug Permeation of vesicles through skin:

- Absorption and fusion of vesicles onto skin surface leading to increase in thermodynamic activity gradient of the drug at interface, which act as driving force for absorption of lipophilic drugs across stratum corneum.
- Modification in the structure of stratum corneum is also type of interaction involves the ultra-structural changes in the intracellular lipid region of the skin and its deeper layers which is revealed by freeze fracture electron microscopy and small angle x-ray scattering.
- Bilayer present in niosomes act as rate limiting barrier for drugs.
- Proniosomes contains both non-ionic surfactants and phospholipids, both can act as penetration enhancers and useful in increasing penetrability of many drugs.
- The penetration enhancer's effect of vesicles leads to reduce stratum corneum barrier properties.

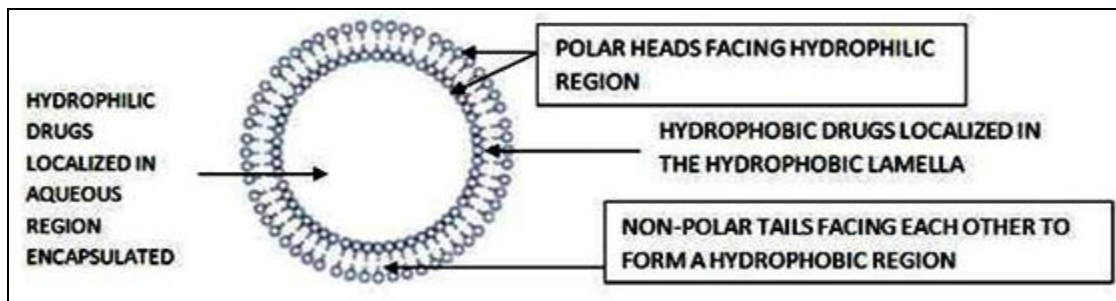


FIGURE 3: REGIONS OF DRUG PENETRATION IN PRONIOSOMES

Factors affecting penetration of Vesicles:

- Nature of drug
- Size and composition of vesicles
- Bio physical factors¹³

Proniosomes as Drug Carriers: The proniosomes are promising drug carriers, because they possess greater chemical stability and lack of many disadvantages associated with liposomes. It has additional merits with niosomes are low toxicity due to non-ionic nature, nor requirement of special precautions and conditions for formulation and preparation. Niosomes have shown advantages as drug carriers, such as low cost and chemical stability as compared to liposomes but they are associated with problems related to physical stability like fusion, aggregation, sedimentation and leakage and storage.

Proniosomes are dry formulations of surfactant-coated carrier vesicles which can be measured out as needed and rehydrated by brief agitation in hot water the resulting niosomes are very similar to conventional niosomes and more uniform size¹⁴. These proniosomes are minimizing the problems using dry, free flowing product which is more stable during storage and sterilization and it has additional merits of easy of transfer, distribution, measuring and storage make proniosomes a pronouncing versatile delivery system⁹.

Suitability of Drug to the Proniosomes: Different categories of drugs selections for proniosomes formation based upon the below-mentioned points,

- Low Aqueous solubility drugs
- High dosage frequency drugs

- Low half-life
- Controlled drug delivery suitable drugs
- Higher adverse drug reactions drugs¹⁵

Preparation of Proniosomes: Proniosomes are prepared by two methods

1. Slurry method
2. Coacervation Phase Separation Method
3. Spray coated method

1. **Slurry Method**¹⁶: The slurry method is developed to produce proniosomes using maltodextrin as carrier. The time required to produce proniosomes. This method is independent ratio of surfactant solution to carrier material. The entire volume of surfactant solution is added to maltodextrin powder is rotary evaporator and vacuum applied until the powder appears to be dry and free flowing.
2. **Coacervation Phase Separation Method**¹⁷: This method is widely adopted to prepare Proniosomal gel. Precisely weighed amounts of surfactant, lipid and drug are taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol (0.5 ml) is added to it. After warming, all the ingredients are mixed well with a glass rod; the open end of the glass bottle is 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 is dissolved completely. Then the aqueous phase (0.1% glycerol solution) is added and warmed on a water bath till a clear solution was formed which is then converted into Proniosomal gel on cooling.

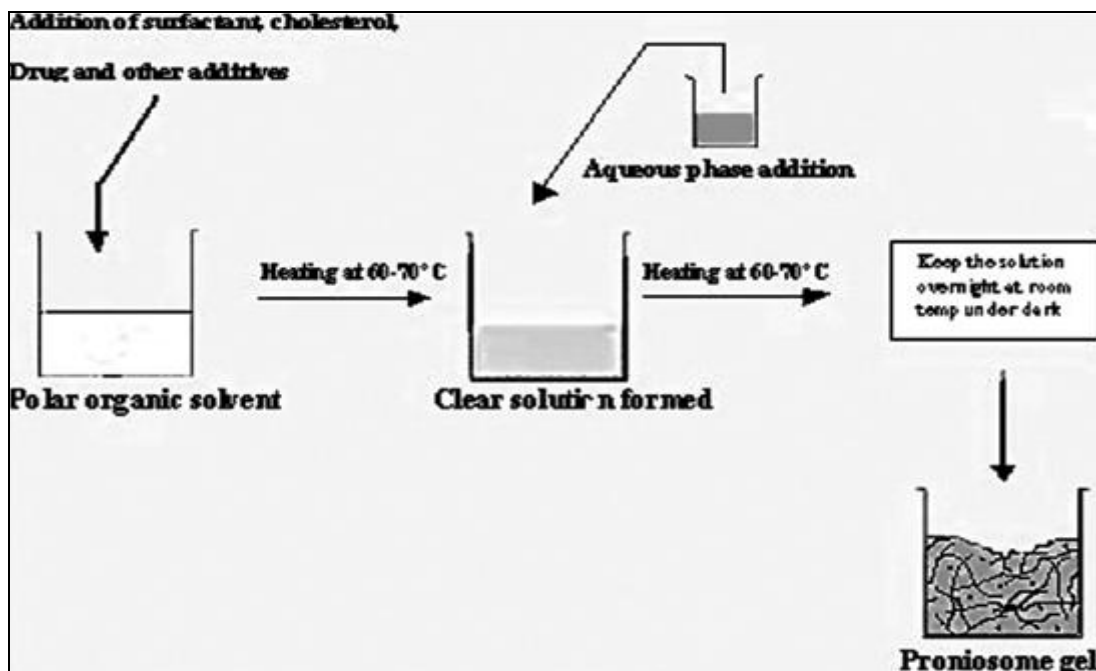


FIGURE 4. DIAGRAMMATIC REPRESENTATION FOR PREPARATION OF PRONIOSOMAL GEL BY COACERVATION PHASE SEPARATION TECHNIQUE

3. **Spray Coated Method**^{16,18}: Proniosomes are normally prepared by spraying surfactant in organic solvent into sorbitol powder and evaporating the solvent. It is necessary to repeat the process until the desired surfactant load has been achieved. The surfactant coating on the carrier is formed and a very thin layer and hydration of the coating allows multilamellar vesicles to form. By adding drug to the surfactant mixture prior to spraying the solution on to the sorbitol or aqueous solution.

Formation of Niosomes from Proniosomes by

Hydration: The niosomes can be prepared from the proniosomes by adding the aqueous phase with drug to the proniosomes with brief agitation at 80°C for 2 minutes to get niosomal suspension. It provides rapid reconstitution of niosomes with minimal residual carrier.

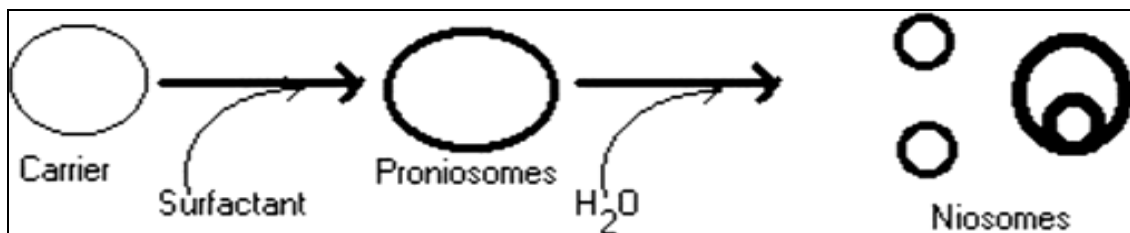


FIGURE 5: FORMATION OF NIOSOMES

Separation of free Untrapped Drug: The encapsulation efficiency of proniosomes is determined after separation of the untrapped drug using these techniques:

1. Dialysis
2. Gel filtration.
3. Centrifugation.

1. **Dialysis**¹⁹: The aqueous niosomal dispersion is dialysed tubing against suitable dissolution medium at room temperature. Then samples are withdrawn from the medium at suitable time interval centrifuged and analysed for drug content using UV spectroscopy.
2. **Gel Filtration**²⁰: The free drug is removed by gel filtration of niosomal dispersion through a sephadex G50 column and separated with suitable mobile phase and analysed with suitable analytical techniques.

3. **Centrifugation**²¹: The niosomal suspension is centrifuged and the surfactant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from untrapped drug.

In-vitro Drug Release from Proniosomal Vesicles: *In vitro* drug release and skin permeation studies for proniosomes were determined by different techniques like

1. Franz diffusion cell
 2. Dialysis tubing
 3. Reverse dialysis
1. **Franz Diffusion Cell**²²: Franz diffusion cell has a donor chamber fitted with a cellophane membrane. The proniosomes are placed in it and dialysed against a suitable dissolution medium at room temperature. The drug content is analysed using suitable method (UV Spectroscopy, HPLC) maintenance of sink conditions is essential.
 2. **Dialysis Tubing**²³: This apparatus has prewashed dialysis tubing which can be hermetically sealed. The proniosomes are placed in it and then dialysed against a suitable dissolution medium at a room temperature. The samples are withdrawn from the medium at suitable intervals. Centrifuged and analysed for drug content using suitable method (UV Spectroscopy, HPLC).
 3. **Reverse Dialysis**²³: In this apparatus a number of small dialysis tubes containing 1 ml of dissolution medium are placed. Then proniosomes then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method. But rapid release cannot be quantified using this method.

Characterisation of Proniosomes: Proniosomes are characterized for vesicle size, size distribution, shape and surface morphological studies.

1. **Measurement of Angle of Repose**^{16, 24}: 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.

2. **Scanning Electron Microscopy**^{10, 24}: Particle size of proniosomes is very important characteristic. The surface morphology (roundness, smoothness and formation of aggregates) and the size distribution of proniosomes were studied by Scanning Electron Microscopy (SEM). Proniosomes were sprinkled on to the double-sided tape that was affixed on aluminum stubs. The aluminum stub was placed in the vacuum chamber of a scanning electron. The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).
3. **Optical Microscopy**^{11, 16, 19}: The niosomes were mounted on glass slides and viewed under a microscope (Medilux-207R II Kyowa-Getner, Ambala, India) with a magnification of 1200X for morphological observation after suitable dilution. The photomicrograph of the preparation also obtained from the microscope by using a digital SL camera
4. **Measurement of Vesicle Size**^{16, 19}: The vesicle dispersions were diluted about 100 times in the same medium used for their preparation. Vesicle size was measured on a particle size analyzer (Laser diffraction particle size analyzer, Sympatec, Germany). The apparatus consists of a He-Ne laser beam of 632.8 nm focused with a minimum power of 5mW using a Fourier lens [R-5] to a point at the centre of multi element detector and a small volume sample holding cell (Su cell). The sample was stirred using a stirrer before determining the vesicle size. Hu C. and Rhodes in 1999 reported that the average particle size of proniosomes derived niosomes is approximately 6µm while that of conventional niosomes is about 14µm.
5. **Entrapment Efficiency**^{17, 25}: The vesicles obtained after removal of untrapped 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 analysed for drug content. The percentage of drug entrapped is calculated by using the following formula.

$$EE\% = \frac{\text{total drug-diffused drug}}{\text{total drug}} \times 100$$

In-vitro methods for the assessment of Drug Release from Proniosomes: *In vitro* drug release can be done by (Chen DB *et al.*, 2001);

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

1. **Dialysis Tubing:** Muller *et al.*, in 2002²³ studied *in vitro* drug release could be achieved by using dialysis tubing. The proniosomes is placed in prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and analysed for drug content using suitable method (U.V. Spectroscopy, HPLC etc.). The maintenance of sink condition is essential.

2. **Reverse Dialysis**²³: In this technique, a number of small dialysis as containing 1ml of dissolution medium are placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method; however the rapid release cannot be quantified using this method.

3. **Franz Diffusion Cell**^{22, 26}: The *in vitro* diffusion studies can be performed by using Franz diffusion cell. Proniosomes is placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The proniosomes is then dialyzed against a suitable dissolution medium at room temperature; the samples were withdrawn from the medium at suitable intervals and analysed for drug content using suitable method (U.V Spectroscopy, HPLC, etc). The maintenance of sink condition is essential.

Drug Release Kinetic Data Analysis²⁷: The release data obtained from various formulations were studied further for their fitness of data in different kinetic

models like Zero order, Higuchi's and Peppas's. In order to understand the kinetic and mechanism of drug release, the result of *in-vitro* drug release study of Niosome were fitted with various kinetic equation like zero order (**Equation 1**) as cumulative % release vs. time, Higuchi's model (**Equation 2**) as cumulative % drug release vs. square root of time. r^2 and k values were calculated for the linear curve obtained by regression analysis of the above plots.

$$C = k_0t \dots(1)$$

Where k_0 is the zero order rate constant expressed in units of concentration / time and t is time in hours.

$$Q = kHt^{1/2} \dots(2)$$

Where kH is Higuchi's square root of time kinetic drug release constant.

To understand the release mechanism *in-vitro* data was analyzed by Peppas's model (**Equation 3**) as log cumulative % drug release vs. log time and the exponent n was calculated through the slope of the straight line.

$$M_t / M_\infty = b t^n \dots(3)$$

Where M_t is amount of drug release at time t , M_∞ is the overall amount of the drug, b is constant, and n is the release exponent indicative of the drug release mechanism. If the exponent $n = 0.5$ or near, then the drug release mechanism is Fickian diffusion and if n have value near 1.0 then it is non-Fickian diffusion.

Osmotic shock^{28, 29}: The change in the vesicle size can be determined by osmotic studies. Niosomal formulations are incubated with hypotonic, isotonic, hypertonic solutions for 3 hours. Then the changes in the size of vesicles in the formulations are viewed under optical microscopy.

Stability studies¹⁹: To determine the stability of proniosomes, the optimized batch was stored in airtight sealed vials at different temperatures. Surface characteristics and percentage drug retained in proniosomes and proniosomes derived niosomes were selected as parameters for evaluation of the stability, since instability of the formulation would reflect in drug leakage and a decrease. In the percentage drug retained. the proniosomes were sample at

regular intervals of time (0, 1, 2 and 3 months), observed for color change, surface characteristics and tested for the percentage drug retained after being hydrated to form niosomes and analysed by suitable analytical methods (UV Spectroscopy, HPLC methods etc.)

Zeta Potential Analysis³⁰: Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted proniosomes derived niosome dispersion was determined using zeta potential analyzer based on Electrophoretic Light Scattering and Laser Doppler Velocimetry method (Zetaplus™, Brookhaven Instrument Corporation, New York, USA). The temperature was set at 25°C. Charge on vesicles and their mean Zeta Potential values with standard deviation of 5 measurements were obtained directly from the measurement.

Applications of Proniosomes: The application of niosomal technology is widely varied and can be used to treat a number of diseases. The following are the few uses of niosomes which are either proven or under research;

1. **Drug Targeting:** One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticulo-endothelial system. The reticulo-endothelial system⁴³ (RES) preferentially takes up niosome vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen⁵. This localization of drugs can also be used for treating parasitic infections of the liver. Niosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to niosomes (as immunoglobulin bind readily to the lipid surface of the niosome) to target them to specific organs⁴⁴. Many cells also possess the intrinsic ability to recognize and bind specific carbohydrate determinants and this can be exploited by niosomes to direct carrier system to particular cells.

2. **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 untrapped drugs, such as decreased rate of proliferation of the tumour and higher plasma levels accompanied by slower elimination.
3. **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 niosomes in tests conducted showed that it was possible to administer higher levels of the drug without the triggering of these effects and thus allowed greater efficacy in treatment.
4. **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 investigated²³. In an *in vitro* 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.
5. **Uses in Studying Immune Response:** (Brewer and Alexander in 1992) studied niosomes 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.
6. **Niosomes 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 haemoglobin in anaemic patients.

7. Transdermal Drug Delivery Systems Utilizing

Niosomes: 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 niosomes²⁵. 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 drug²⁶.

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 transferosomes) 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.

8. Other Applications:

- a. **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.
- b. **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. Antimonial encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence, decrease both in dose and toxicity. The evolution of niosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.

CONCLUSION: From the above article, it is concluded that the concept of incorporating the drug into niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Proniosomes serve as a promising carrier for various categories of drugs with improved physical and chemical stability, good bioavailability for poorly soluble drugs.

Proniosomes are good candidates for transdermal delivery of drugs due to non-toxicity and penetration enhancing effect of surfactant. This vesicular system is gaining lot of interest due to its controlled and sustained action. This carrier system is having immense opportunity in the area of transdermal delivery, cosmetics, nutraceuticals etc.

Proniosomal gel has tremendous drug delivery potential for anticancer, anti-infective agents. In future, this area might be focused for more entrapment efficiency and skin permeation with optimized concentration of surfactant and other formulation parameters. Thus, this area needs further exploration and research so as to bring out commercially available Proniosomal preparation.

Studies should be explored to assess the ability of different carrier materials to formulate proniosomes and the ability of proniosomes to deliver the drugs meant for administration through various routes.

ACKNOWLEDGEMENTS: The authors express their gratitude to the Management, Principal, Dean and Faculty members of Krupanidhi College of Pharmacy for their encouragement, support, and guidance for this Review.

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How to cite this article:

Indira U and Uma Shankar M.S: Proniosomes as a Drug Carrier: A Review. *Int J Pharm Sci Res.* 3(12); 4617-4625.