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A Review on Proniosomal Gel

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ABSTRACT

Topical administration is the most preferred route for local delivery of therapeutic agents due to its convenience and easy access. The specific challenge of designing a therapeutic system is to achieve an optimal concentration of a certain drug at its site of action for an appropriate time span. Vesicular drug delivery systems are novel means to increase the bioavailability of the enclosed drug with more advantages over than the conventional dosage forms. For transdermal delivery proniosomes were prepared as gel-like concentrated niosomes suitable for topical application. Proniosomes when applied onto the skin surface transform into niosomes due to the hydration by water from the skin which would provide an occlusive condition and offer a potential for drug delivery through the transdermal route. The gel property of Proniosomes maintaining better skin penetration and physicochemical properties. Both phospholipids and non-ionic surfactants in Proniosomes can act as penetration enhancers since it was found that some phospholipids are able to fluidize the stratum corneum lipid bilayers and disperse through them.

Keywords: Niosome, Proniosome, Proniosomal gel

INTRODUCTION

Proniosomal gel is a compact semi-solid liquid crystalline (gel) product of non-ionic surfactants easily prepared on dissolving the surfactant in a minimal amount of acceptable solvent and the least amount of aqueous phase.

Proniosomes are vesicular systems in which the vesicles are made up of non-ionic based surfactants, cholesterol, and other additives. Semisolid liquid crystal gel (proniosomes) ready by dissolving the surfactant in a minimal quantity of an acceptable solvent, namely ethanol, and then hydration with the slightest amount of water to form a gel. These structures are liquid crystalline dense niosomes hybrids that can be converted into niosomes upon hydration or used as such in the topical/transdermal applications. Proniosomal gels are generally present in transparent, translucent, or white semisolid gel texture, which makes them physically stable throughout storage and transport[1]. The surfactant molecule directs themselves such that the hydrophilic ends of the non-ionic surfactant face outward, while the hydrophobic ends are in the opposite direction to form the bilayer[2].

Proniosomal gel is a semi-solid, liquid crystalline gel that is used to deliver therapeutic drugs to the skin and through the skin. It is made of non-ionic surfactants, alcohol, lipids, and an aqueous phase and has a gel-like texture due to its low water content. Proniosomal gels are often transparent, translucent, or white in colour and are stable during storage and transport.

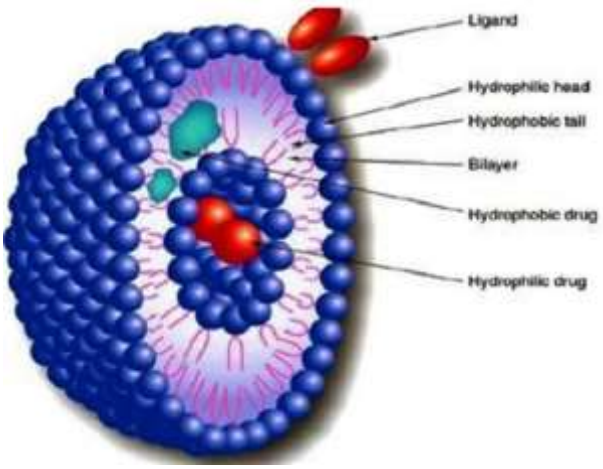

Figure 1: Structure of Proniosome

Proniosomal gels are prepared using a coacervation phase separation technique. The mixture is warmed in a water bath until the cholesterol dissolves, then hot distilled water is added until a clear or translucent solution forms. The mixture is then allowed to cool at room temperature until it turns into a gel. When applied topically, proniosomal gels are converted into niosomes by water in the skin. Proniosomes have several advantages over other vesicular systems, including:

No gelling agents: Proniosomes don't require gelling agents like other vesicular systems.

Less leaky: Proniosomes are less likely to leak drugs than niosomes.

More suitable for skin: Proniosomes' gel-like structure makes them better for applying to the skin.

Classification of proniosomes

In general, proniosomes were divided into the following types.

1. Semi-solid liquid crystal gel.

2. Dry granular powder.

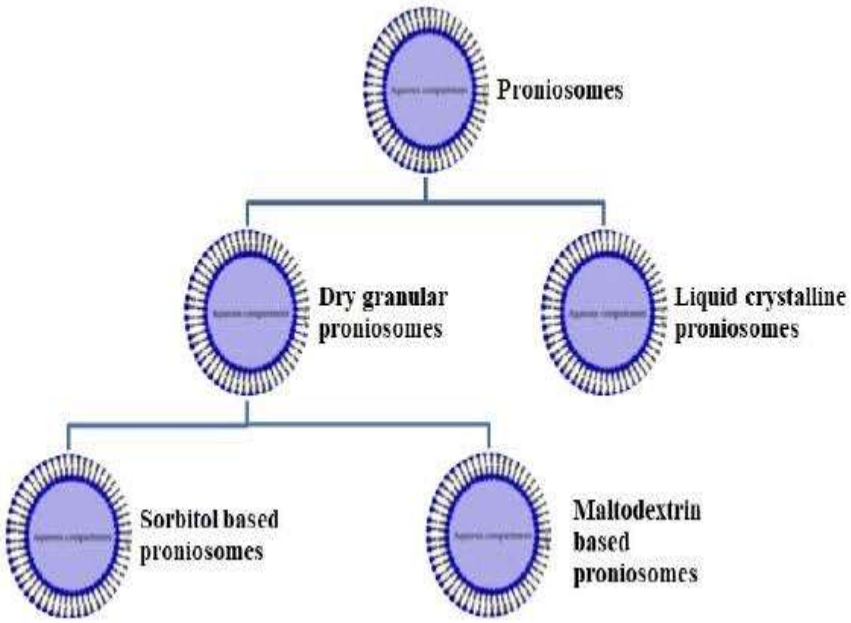

Figure 2: Types of Proniosomes

METHODS OF PREPARATION OF PRONIOSOMAL GEL

a. Coacervation phase separation.

b. Slow spray coating method.

c. Slurry method.

Coacervation phase separation

Appropriate amounts of proniosomal components mixed together with the drug were mixed with 2.5 ml of absolute ethanol in a clean and dry, wide-mouth glass tube. After mixing all the ingredients, the open end of the glass tube was covered with a lid to prevent loss of solvent from it and warmed in a water bath at 65 ± 3°C for ~5 min, until the surfactants were dissolved completely. Then, 1.6 ml of pH 7.4 phosphate buffer was added, and warming was continued on the water bath for ~2 min till a clear solution was observed.

The mixture was allowed to cool down at room temperature until the dispersion was converted to a proniosomal gel.

Slurry method

carrier material to a 250-ml flask and the entire volume of surfactant solution was added the flask to form the slurry. If the surfactant solution volume is less, then additional organic solvent can get slurry. The flask was attached to a rotary evaporator was applied until the free-flowing.

The flask was removed from the evaporator and kept under vacuum overnight. The proniosomes powder was stored in sealed containers at 4°C. The time required to produce proniosomes is independent of the ratio of surfactant solution to the carrier material and appears to be scalable.

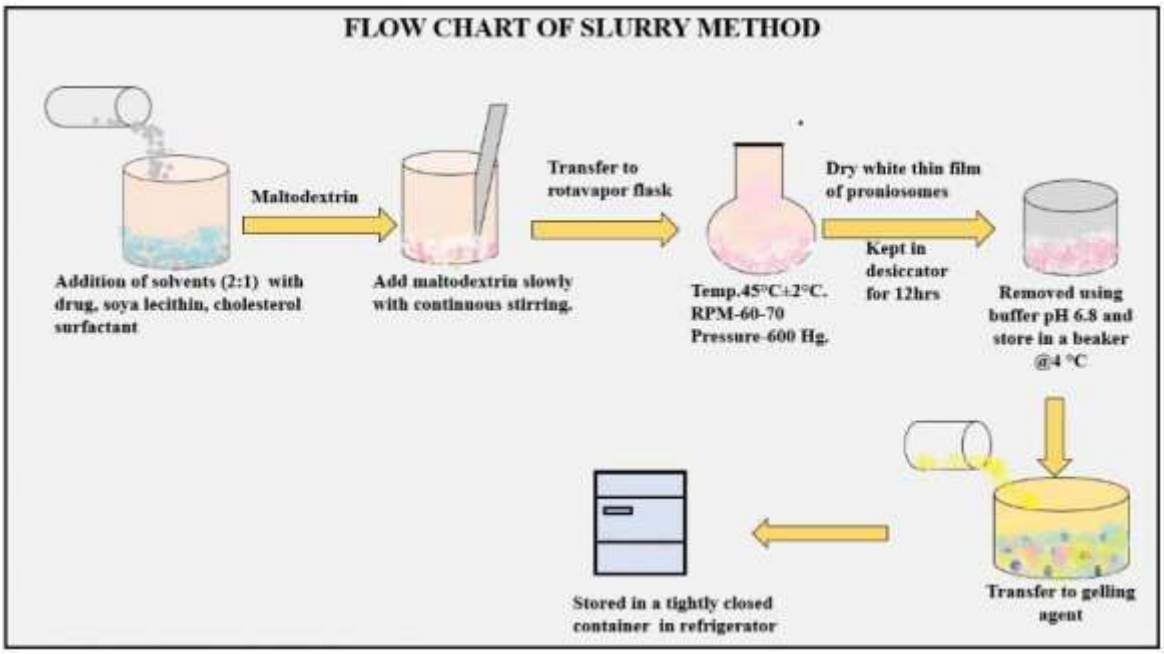

Figure 3: Flow chart of slurry method

Slow spray - coating method

This method involves preparation of proniosomes by spraying surfactant in an organic solvent onto carrier material and then evaporating the solvent. Since the carrier is soluble in the organic solvent, it repeats the process until the desired has been achieved.

The surfactant coating on the carrier is very thin, and hydration of this coating allows multilamellar when the carrier dissolves.

MECHANISM OF ACTION

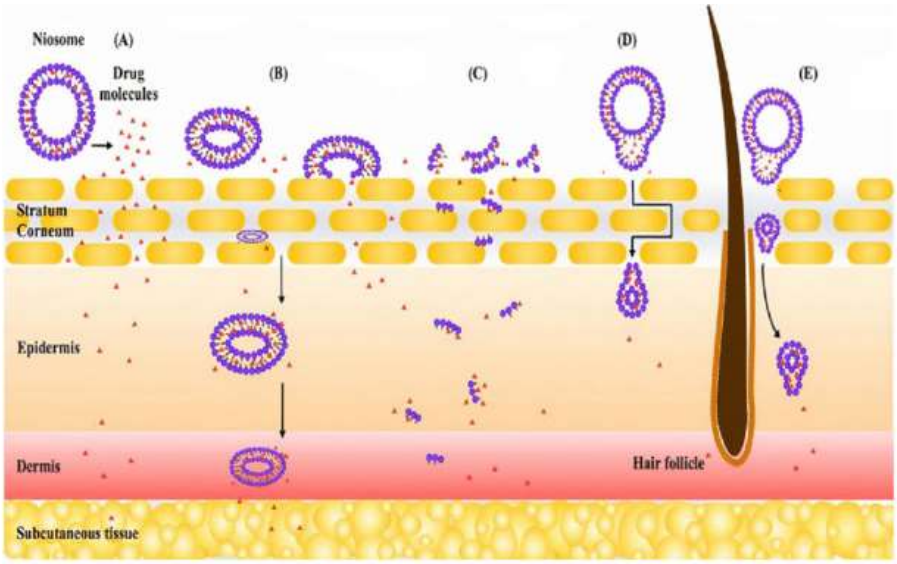

Figure 4: Mechanism of action

Mechanisms of action of niosomes and proniosomes for skin penetration in topical and transdermal drug delivery.

A. Release of drug molecules by niosomes.

B. Niosomes adsorption and fusion with stratum corneum.

C. Penetration of niosomes through intact sc.

D. Components of niosomes act as penetration enhancer and increase absorption of drug.

E .Penetration of niosomes through hair follicles or pilosebaceous units

FACTORS AFFECTING THE FORMULATION OF PRONIOSOME

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

ADVANTAGES OF PRONIOSOMAL GEL

Proniosomes have the potential for entrapping a wide range of active compounds. Easy for transportation, sterilization, distribution, storage, and dosing. Degradation by hydrolysis or oxidation problems is avoided. No special conditions required for storage and handling. Sedimentation, aggregation or leakage is not seen. Uses acceptable solvents in minimum quantity in the preparation. It shows controlled targeted and sustained release of drugs due to depot formation[3,4,5].

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 that are either proven or under research.

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 reticuloendothelial system. The reticuloendothelial system (RES) preferentially takes up noisome vesicles.

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

Delivery of Peptide Drugs: Oral peptide drug delivery has long been faced with the challenge of bypassing the enzymes which would breakdown the peptide. The use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated.

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 niosomes. Topical use of Niosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to the un-entrapped drug.

Sustained Release: 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.

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 Niosome are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity[6].

Cosmetics Formulation: Now a day's large numbers of cosmetic preparations available in the market are utilizing niosomes and liposomes as a carrier for the delivery of actives. Liposomes were prepared using unacceptable organic solvents, whose traces in the final preparation can cause harm to the skin. It is proved that proniosomes are as effective as noisome and liposomes, but their preparation, handling, storage, and transportation make them superior to others

NSAID Application: Non-steroidal anti-inflammatory drugs like Ketorolac tromethamine (KT) administered intramuscularly and orally in divided multiple doses for short-term management of postoperative pain[7].

EVALUATION OF PRONIOSOMAL GEL

Organoleptic properties

Proniosomal gels were characterized for appearance, color, and homogeneity by visual inspection.

Optical microscopy

One drop of the formed gel was spread on a glass slide and examined for the vesicle structure using ordinary light microscope with varied magnification powers (×10 and ×40). Photomicrographs were taken using a digital camera[8].

pH measurement

The pH of the gel was determined by digital pH meter (Model 420, ORION, USA). A sample of 0.1 g of gel was dissolved in 10 ml of distilled water and the electrode was then dipped into gel formulation and constant reading was noted[9].The readings were taken for an average of three times.

Determination of drug entrapment efficiency

A sample of 0.2 g of proniosomal gel was taken in a glass tube, and 10 ml of phosphate buffer (pH 7.4) was added. This aqueous suspension was sonicated in a sonicator bath (Rolex, India), followed by centrifugation at 9.000 rpm at 20°C for 30. The supernatant was collected and assayed by using ultraviolet (UV) method for unentrapped fluconazole content at 260 nm[10]. The percentage of drug encapsulation (entrapment efficiency percentage [EE%]) was calculated by the following equation:

EE% = (Total amount of drug − Unentrapped drug/Total amount of drug) ×100.

In vitro release study

The release of drug from proniosomal gels was determined using membrane diffusion technique. The proniosomal gel equivalent to 25 mg of drug was placed in a glass tube having a diameter 2.5 cm with an effective length of 8 cm that was previously covered with soaked osmosis cellulose membrane with a molecular weight cutoff 12,000 Daltons, which acts as a donor compartment. The glass tube was placed in a beaker containing 100 ml of phosphate buffer pH 5.5, which acts as a receptor compartment. The whole assembly was fixed in such a way that the lower end of the tube containing gel was just touched (1–2 mm deep) the surface of diffusion medium. The temperature of receptor medium maintained at 37°C ± 100°C, and the medium was agitated at 100 rpm speed using magnetic stirrer. Aliquots of 3 ml sample were withdrawn periodically and replaced with equal volume to maintain the volume constant of the receptor's phase. The collected samples were analyzed for the drug containing at 260 nm absorbance against a reagent using the UV spectrophotometer[11].

Particle size analysis of fluconazole proniosomes

The particle size (PS) and Polydispersity Index (PDI) of proniosomes were measured using a Zeta sizer 3000 PCS equipped with a 5-mW helium–neon laser with a wavelength output of 633 nm. Measurements were made at 25°C, angle 90, and runtime at least 180 s. (10) The proniosomal gels were appropriately diluted with distilled water before measurements. PDI was determined as a measure of homogeneity. Small values of PDI (<0.1) indicate a homogeneous population, while PDI values >0.3 indicate high heterogeneity[8].

Zeta potential analysis

Charge on drug-loaded vesicles surface was determined using zeta potential (ZP) analyzer Analysis time was kept for 60 s, and average ZP and charge on the proniosomes preparation after hydration with phosphate buffer saline pH 7.4 were determined at 25°C and three runs were carried out[12].

High-resolution transmission electron microscopy

The selected proniosomal gel was characterized for its shape by transmission electron microscopy using a 300-mesh carbon-coated copper grid and phosphotungstic acid (1%; w/v) as a negative stain. After being stained, the samples were allowed to dry at room temperature for 10 min for investigation[13].

Physical stability studies

The selected proniosomal gel was evaluated for their stability by storing and sealing in well-closed containers in the refrigerator at 4°C ± 1°C for 6 months. The stability study was performed according to different parameters, including physical appearance, %EE, PS, and ZP[14]. The changes of %EE, PS, and ZP against storage time were monitored.

Microbiological study of proniosomal gel

The *in vitro* antifungal efficacy of pronisomal gel was determined by performing agar-cup diffusion assay[15]. The assay was performed using cultures of *Candida albicans* (ATCC 60193) (0.1%), in Sabouraud dextrose agar. The strain was inoculated in sterile 0.85% NaCl tube in a ratio of 1:9. The culture was subjected to further dilution in a sterile 0.85% NaCl to get 106 CFU/ml. Sterile swab was dipped into the culture suspension and then placed on the edge of the agar plate and moved across to the other sides. Cups were made in the seeded agar plates of 6-mm diameter[16]. Cups were filled with 0.5 ml of the proniosomal gel and an equivalent weight of control and plain gel. The Petri dishes were then incubated at 37°C. The effectiveness of the prepared gel was compared with plain gel contains 0% of drug and the control. The zones of growth inhibition were measured for all the tested samples. Each type of samples was tested in triplicate. The inhibition zone of growth of *C. albicans* was measured in mm after 48 h and the mean inhibition zone was then calculated[17].

Statistical analysis

Statistical analysis of the results was performed using one-way analysis of variances to determine the significance of differences between groups; $P < 0.05$ was considered statistically significant.

CONCLUSION

Proniosomes have advantages of controlled and sustained release action, stability, and versatility as a drug carrier. Proniosomes are propitious drug carriers for the future with greater physical, chemical stability and potentially expandable for commercial feasibility. Proniosomal delivery system holds effective delivery for amphiphilic drugs. Due to the advantages of nontoxicity & penetration enhancing the effect of surfactants & effective modification of drug release, proniosomes have attracted a greater deal of attention for delivering drugs through the transdermal route. Proniosomes in dry form make the possibility of suitable unit dosing as they are further converted into beads, tablets, capsules. The findings of the studies on proniosomes opens the door for the future, use of different carrier's materials with biocompatibility and suitability for the preparation of proniosomes. The future experiments would explore the suitability of proniosomes with more drugs having defined drawbacks for improved & effective intended therapy.

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