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PRONIOSOMAL GEL: AN EMERGING APPROACH FOR CONTROLLED AND ENHANCED TRANSDERMAL DRUG DELIVERY

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Abstract

Proniosomes are advanced vesicular drug delivery systems that have gained considerable attention due to their improved stability, controlled drug release, and enhanced drug permeation characteristics. They are dry or semisolid formulations composed mainly of non-ionic surfactants, cholesterol, lecithin, and suitable solvents, which upon hydration form niosomal vesicles. Proniosomal gels provide several advantages over conventional vesicular systems such as improved physical stability, reduced leakage, ease of transportation, storage, and handling. These carrier systems are widely investigated for oral, transdermal, ocular, intranasal, and targeted drug delivery applications. Proniosomes enhance the bioavailability of poorly soluble drugs and improve therapeutic efficacy by sustaining drug release and increasing drug penetration through biological membranes. Various nonionic surfactants including Spans, Tweens, Brij, Poloxamers, and sugar esters are employed in formulation development depending upon the desired entrapment efficiency and vesicle characteristics. Proniosomal gels are commonly prepared by coacervation phase separation, slurry method, and slow spray coating technique. Evaluation parameters such as vesicle size, zeta potential, entrapment efficiency, in vitro drug release, optical microscopy, and stability studies are important in determining the quality and performance of proniosomal formulations. Due to their non-toxic nature, versatility, and potential for controlled and targeted drug delivery, proniosomes represent a promising approach for future pharmaceutical applications and novel therapeutic systems.

Keywords: Proniosomes, Proniosomal Gel, Vesicular Drug Delivery System, Nonionic Surfactants, Niosomes, Transdermal Drug Delivery, Novel Drug Delivery System.

Introduction

In recent times, no single drug delivery system fulfills all the criteria, but attempts have been made through novel approaches. Many novel approaches emerged covering various routes of administration, to achieve either 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.

Vesicular drug delivery is one of the approaches, which encapsulate the drug e.g.: Liposomes, niosomes, transferosomes, pharmacosomes, and provesicles such as proniosomes and proliposomes. Advantages of liposomes and niosomes over other conventional dosage forms are their particulate nature, which act as a drug reservoir. Few modifications can also be carried out in order to adjust the pattern and the drug release. It was also found out that modified vesicles had properties that successfully delivered drugs into deeper layers of the skin (Kakr *et al*., 2010).

From early 1980s, proniosomes have gained wide attention by researchers for their use as drug targeting agents and drug carriers to have a variety of merits while avoiding demerits associated with the conventional form of drugs. Niosomes are water soluble carrier particles, and these are dried to form a niosomal dispersion on brief agitation in hot aqueous media. This dehydrated product is called proniosomes. The resulting niosomes are very correlative to conventional niosomes and of higher size uniformity. The proniosomal approach reduces the problems associated with dry, free-flowing product, which is more stable during the storage and sterilization. The proniosomes are a versatile delivery system because of the ease of distribution, measuring, transfer, and storage (Walve *et al*., 2011).

Proniosomes were studied as alternatives to liposomes and other carrier systems for entrapping both polar and nonpolar or hydrophobic and hydrophilic drugs. The additional merits with proniosomes are low toxicity owing to non-ionicnature, no requirement of special precautions and conditions for formulation and preparations. In addition, it is the simple method for the routine and large scale production of proniosomes without the use of undesirable solvents. However, stability is a main concern in the advancement of any formulation and even proniosomes have advantages as drug carriers, such as cost productivity, chemically stability in comparision to

liposomes. They also minimize problems of physical stability such as fusion, leakage, sedimentation, and aggregation on storage.

Proniosomal gel:

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 (Mishra *et al*., 2011). 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 (Radha *et al*., 2013).

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.

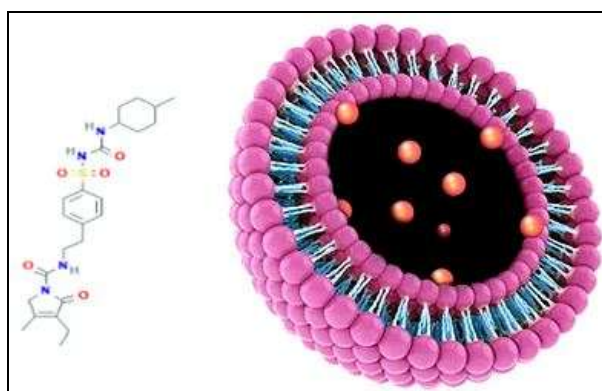

Figure 1: Structure of Proniosome

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.

Composition of proniosomes

The essential and common components of the proniosomal drug delivery system are as follows:

Nonionic Surfactant

Nonionic surfactants are the important structural component in the preparation of proniosomes. These molecules are more stable, compatible and less toxic compared to cationic and anionic surfactant types (Witika *et al*., 2022). Apart from vesicle formation, nonionic surfactants help in controlled drug release, play a part as penetration enhancers in transdermal medication and can be used to improve the bioavailability of poorly water-soluble drugs in oral proniosomal formulation (Yadav *et al*., 2010). Vesicle formation and entrapment efficiency depend on various parameters like Hydrophilic Lipophilic Balance (HLB) value, chemical nature, phase transition temperature, chain length and the size of the hydrophilic group of the surfactant. Surfactants with longer alkyl chains and lower HLB values (between 4-8) were found to have high encapsulation efficiency whereas surfactants with high HLB values having large polar head groups cannot form vesicles. Phase Transition temperature (Tc) increases as the length of the alkyl chain increases providing the highest entrapment for the drug (Rahimpour *et al*., 2015; Biswal *et al*., 2008).

Sorbitan fatty acid esters

Sorbitan fatty acid esters are usually referred to as Spans. The polar head groups are similar in all Spans, while the alkyl hydrocarbon chains are varied. Spans surfactants with different fatty acid chain lengths like Span 20, Span 40, Span 60, Span 80 have been used alone or in combination in preparation of proniosomes. Spans with lower HLB values and increased alkyl chain length exhibit high entrapment efficiency (Abdelbary *et al*., 2017). Span 60 showed higher entrapment efficiency than the other spans (Mokhtar *et al*., 2008).

Polyoxyethylene fatty acid esters:

Tweens, commonly referred to as polysorbates, are polyoxyethylene sorbitan esters. Tween 20 and Tween 60, Tween 80 have been used in proniosomal formulation. However, Tween 80 being a hydrophilic surfactant with a high HLB value elucidates the lower entrapment efficiency in proniosomal formulations (Sandeep and Devireddy, 2014). However, a few articles reported that the drug entrapment efficiency of Tween is superior compared to different Spans containing proniosomes (Ammar *et al*., 2011; Mahrous, 2010).

Sugar esters:

These are non-ionic surfactants with sucrose as the polar head group and fatty acids as non-polar groups. Different grades of sugar esters, such as sucrose stearate S-1670, S-970, S-370, sucrose palmitate P-1670, sucrose myristate, M-1695, and sucrose laurate L-1695 have been used as permeation and absorption enhancers. These have excellent safety profiles and are non-irritants (Laithy *et al*., 2011).

Cremophor:

Cremophor is hydrogenated castor oil. Cremophor has been successfully used in proniosomal gel formulation as a permeation enhancer. The use of cremophor provided proniosomes with favourable physicochemical characteristics and a sustained release pattern suitable for ocular delivery (Soliman *et al*., 2016; Aboali *et al*., 2020).

Poloxamer:

Poloxamer is a polyethylene-propylene glycol copolymer nonionic surfactant that acts as a penetration enhancer by removing the mucus layer and breaking junctional complexes and thus improving the solubility of drug (Li *et al*., 2014; Yapar *et al*., 2014).

Polyoxyethylene alkyl ether

Polyoxyethylene alkyl ethers, such as Brij-35, Brij 72, Brij 78 Brij 92, are nonionic surfactants used as good vesicle forming nonionic surfactants in the proniosomes formulation. Proniosomal gel prepared using Brij 35 showed better entrapment and the highest in vitro drug release with an equimolar ratio (1:1) of Brij 35 and cholesterol (Kumar *et al*., 2016). Proniosomal gel containing Brij 72, Brij 92 having long alkyl chain and lower HLB values showed better vesicle forming ability and higher entrapment efficiency (EE) of the drug within the hydrophobic core (Aboelwafa *et al*., 2010).

Cholesterol

Although, non-ionic surfactants represent the essential component of proniosomal vesicles, the incorporation of cholesterol influences stability and permeability in the vesicle. Cholesterol makes the membrane more ordered by interaction with surfactants through hydrogen bonding and hence able to effectively prevent leakage of drugs from bilayer vesicles. Cholesterol provides rigidity to the bilayer and enhances the entrapment efficiency of proniosomes. The increased drug entrapment is most likely due to increased vesicle size and increased width of lipid bilayer which increase the vesicle volume and entrapment efficiency (Mokhtar *et al*., 2008; Hu and Rhodes, 1999).

The concentration of cholesterol in the formulation depends on the HLB value of the surfactants. Surfactants with high HLB values such as Brij 35, Brij 92, Tween 80 and Pluronic F68 will need higher concentration of cholesterol to form vesicles. On the other hand, proniosomes can be produced even at low cholesterol concentration in case of surfactants with low HLB value such as Brij 72, Span 65 (Manosroi *et al*., 2003).

Lecithin

Lecithin is a phospholipid that acts as a membrane stabilizer and penetration enhancer in proniosomes formulations. It forms a tightly packed bilayer, decreases membrane permeability and prevents drug leakage, thus improving the drug entrapment of the vesicles. Soya lecithin is derived from soybean, while egg lecithin obtained from egg yolk, is most commonly utilized in proniosomal formulations. Soya lecithin is a good penetration enhancer compared to egg lecithin, due to the presence of unsaturated fatty acids in soya lecithin, whereas egg lecithin contains saturated fatty acids (Abdelbary *et al*., 2017; Emad *et al*., 2019; Rawat *et al*., 2011).

Solvent

Solvents like ethanol, isopropyl alcohol, butanol, propanol have been employed in the preparation of proniosomes. Alcohol acts as penetration enhancer. The rate of drug penetration and vesicle size are affected by the different alcohols. The rate of permeation increases with the longer chain length of the alcohol. Maximum drug permeation was observed with isopropanol, possibly due to branched chain structure. Vesicles formed from different alcohols differ in size. Vesicles with ethanol result in the highest size while isopropanol results in vesicles of the smallest size, which may be due to branched chains present in it (Vora *et al*., 1998; Varsha and Savitha, 2019; Mittal *et al*., 2020).

Carrier

Dry Granular Proniosomes are prepared using carriers that are coated with suitable noisome-forming surfactants. The carrier should be non-toxic, water soluble but poorly soluble in the solvent used in the formulation. Commonly used carriers include maltodextrin, sorbitol and mannitol and to a lesser extent magnesium aluminium silicate, spray dried lactose and sucrose stearates are used (Alshora *et al*., 2023; Akhilesh *et al*., 2012).

Hydration medium

Formation of niosomes from proniosomes is carried out by the addition of a suitable hydration medium such as water, phosphate buffer saline. Hydration media affect the vesicle size and entrapment efficiency of the proniosomes (Sankar *et al*., 2010; Mokhtar *et al*., 2008).

Charge inducer

The addition of charge inducers affects the drug encapsulation efficiency and vesicle size. Stearyl amine and dicetyl phosphate are commonly employed as positive and negative charge inducers in the membrane bilayers of proniosomal vesicles (Hu and Rhodes, 1999; Aburahma and Abdelbary, 2012).

Pharmaceutical application of proniosome

Proniosome technology is the effective delivery of a wide range of therapeutic agents through different routes, such as oral, parenteral, dermal, transdermal, ocular, pulmonary, vaginal, and mucosal routes.

- **Oral route:** Administration of the poorly soluble drug through the oral route in the proniosomal form showed increased solubility and bioavailability (Song *et al*., 2015).
- **Transdermal route:** Transdermal drug delivery is a promising alternative to the oral and parenteral route. Proniosomes offer a versatile vesicle delivery concept with the potential for drug delivery via the transdermal route (Ammar *et al*., 2011).
- **Ophthalmic delivery:** Proniosomes offer a promising solution for ocular drug delivery. It improves bioavailability by increasing ocular residence time of drug (Emam *et al*., 2020; Fouda *et al*., 2018).
- **Intranasal delivery:** Proniosomal gel through the nasal route shows a potential platform for the delivery of drugs to the brain (Khatoon *et al*., 2019; Uddin *et al*., 2024).

Classification of proniosomes:

In general, proniosomes were divided into the following types.

- Semi-solid liquid crystal gel.
- Dry granular powder.

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, widemouth 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.

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

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

- Release of drug molecules by niosomes.
- Niosomes adsorption and fusion with stratum corneum.
- Penetration of niosomes through intact sc.
- Components of niosomes act as penetration enhancer and increase absorption of drug.
- 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 (Yadav *et al*., 2010).
- No special conditions required for storage and handling.
- Sedimentation, aggregation or leakage is not seen (Vora *et al*., 1998).
- Uses acceptable solvents in minimum quantity in the preparation (Rajesh *et al*., 2019).
- It shows controlled targeted and sustained release of drugs due to depot formation.

Applications of proniosome

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 (Walve *et al*., 2011).
- **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 (Ali *et al*., 2013).

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 (Sentjurc *et al*., 1999).
- **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 noted9 .The readings were taken for an average of three times (Rao *et al.*, 2018).

- **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 (Sandeep *et al.*, 2014). 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 (Moustafa *et al.*, 2018).

- **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 (0.3 indicate high heterogeneity (Sentjurc *et al*., 1999).

- **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 (Madan *et al*., 2016).
- **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 (ElMeshad and Mohsen, 2016).
- **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 (Gupta *et al*., 2013). 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. 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 (Wagh and Deshmukh, 2012). 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. 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 (Patel *et al*., 2018). 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 (Sudhamani *et al*., 2010).

- **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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