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Review Article

Proniosomal gel- An effective approach for topical and transdermal drug delivery

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ABSTRACT

Proniosomes are one of the novel provesicular drug delivery systems which are dry formulations coated with carrier such as non ionic surfactants. Proniosomes are formulated in such a manner that they can overcome the drawbacks of niosomes such as physical instabilities, fusion and aggregation. Proniosomes can be administered by various routes like oral, Intravenous, buccal, topical, transdermal etc in which proniosomes are formulated as gels for topical drug delivery. Proniosomal gels are translucent gels and liquid lamellar crystals of vesicular bilayers which can be formed by the addition of small quantity of gelling agent or water to the dry proniosomes (mixture of non-ionic surfactant, lecithin and cholesterol). Proniosomal gels offer better resistance towards stress caused by skin flexion, mucociliary movement and better percutaneous absorption due to the non-ionic surfactants used. Because of their high stability, ease of application and better percutaneous absorption they are widely used for various category of drugs such as Antifungals, NSAIDS, Anti psychotics, Antihypertensives etc. As proniosomal gels offer good attention towards the topical drug delivery, present review focuses on its preparation methods, applications and recent developments.

Keywords: Coacervation phase separation; Non-ionic surfactants; proniosomal gel; Topical drug delivery.

INTRODUCTION

Proniosomes are the provesicular drug delivery systems which are defined as the dry formulations coated with carriers such as non-ionic surfactants. Proniosomes can be converted into niosomes upon hydrating with hot water right before the use. As niosomes are associated with various drawbacks such as physical instabilities like fusion, aggregation of particles and leakage of the drug these are formulated into proniosomes. Proniosomes can deliver both the hydrophilic and hydrophobic drugs. The principle advantage of proniosomes is that the amount of carrier required for maintaining the surfactant ratio can be easily adjusted. Proniosomal gels are the very recent provesicular drug delivery systems which offer the drug delivery through topical or transdermal route in a versatile manner. Proniosomal gels are a mixture of non-ionic surfactant, lecithin and cholesterol. On addition of a small quantity of water or gelling agent to dry proniosomes they appear as translucent gels. These proniosomal gels are the liquid lamellar crystals of vesicular bilayers, in which the lamellas are stacked together are termed as compact niosomes and can be used for topical/transdermal drug delivery. Proniosomal gels are becoming more popular because of a wide range of applications and better percutaneous absorption compared to other semi solid preparations (Abbas pardakhty et al., 2013).

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Advantages of proniosomes (Singh pankaj kumar et al., 2012)

- Proniosomes do not require any special conditions of storage as in case of niosomes and liposomes.
- They are physically stable compared to niosomes.
- Proniosomes are easy to handle, store and transport.
- They are easy to use as they can be hydrated just before use.
- Proniosomes are uniform in size.
- Hydration of proniosomes is easy than liposomes and niosomes.

Mechanism of permeation of vesicles through skin

The possible mechanisms of permeation of vesicles through skin are (Ashwani singh rawat et al., 2011)

- On absorption and fusion of vesicles onto the skin due to thermodynamic activity at the interface it acts as a driving force for the permeation of drug through stratum corneum.
- By altering the structure of the stratum corneum this leads to ultra-structural changes in the intercellular lipid layer.

- The Niosomal bilayer acts as a rate limiting barrier for the drugs.

Due to the permeation enhancers present in the proniosomes like cholesterol, phospholipids they increases the permeability of the drugs.

Classification of proniosomes: Proniosomes are divided into two types. They are;

Dry granular proniosomes: Based on the type of the carrier used and the method of preparation dry granular proniosomes are of two types (Wlave J.R et al., 2011).

a) **Sorbitol based proniosomes:** Sorbitol based proniosomes are the dry formulations where sorbitol is used as a carrier, which is then coated with a non ionic surfactant. Such proniosomes are prepared by simply spraying surfactant mixture in an organic solvent on to the s orbital powder.

b) **Malto dextrin based proniosomes:** Where as malto dextrin based proniosomes are prepared by fast slurry method. The time required for the formation of proniosomes is independent of the ratio of surfctant concentration so, the proniosomes of high surfactant to carrier ratio can be prepared. The preparation of proniosomes with sorbitol results in the formation of solid, surfactant cake, where as the maltodextrin based proniosomes have high surface area resulting in thin surface coating so that the rehydration process is easy.

Liquid crystalline proniosomes: In the presence of alcohol the ternary lecithin and non-ionic surfactant as monoglyceride forms the lamellar liquid crystals at kraft temperature point. The lamellar liquid crystals are converted to niosomes by dispersing them in water. This organization of lipid/water/ethanol into lemellar liquid crystals are used in transdermal drug delivery. The liquid crystalline proniosomes and proniosomal gels are most widely used for transdermal drug delivery.

Formulation of proniosomal gels: The essential components of proniosomal gels are as follows (Ramandeep kaur et al., 2014):

Non ionic surfactants: The non ionic surfactants used in the formulation of proniosomal gels are selected based on the HLB value of the surfactant as the entrapment efficiency of drug is effected by:

- The HLB value: The HLB value between 4-8 will usually give the vesicles with high compatibility.

Phase transition temperature: Spans 40 & 60 produce the vesicles with high entrapment efficiency and the leakage of drug from the vesicles is also reduced due to high transition temperature. The geometry of the vesicles can be predicted by the critical packing parameter of the surfcatant which must be between 0.5-1 for spherical vesicles.

Lecithin: In the formulation of proniosomal gels lecithin acts as a permeation enhancer and it enhances the % entrapement of the drug due to high phase transition temperature. Based on the penetration capability soya lecithin acts as a good permeation enhancer.

Cholesterol: Cholesterol is one of the important component in the formulation of proniosomes which impart stability and permeability to the vesicles. The entrapement efficiency of the drug depends on the concentration of the cholesterol used. On further increasing the concentration of cholesterol the disruption of the bilayer takes place and the entraped drug leaks out.

Aqueous phase: The most widely used aqueous phases in the formulation of proniosomes include hot water, 0.1% glycerol and phosphate buffer of pH7 etc. The pH of the aqueous phase plays an important role in the entrapment of drug.

Solvent: The selection of suitable solvent plays an important role in formulating the proniosomes as they affect the vesicle size and drug permeation rate of the drug. The size of the vesicles depends on the type of the solvent used and the order is as follows:

Drug selection criteria: The drugs with following criteria are suitable for the formulation of proniosomal gels (Waghmode maya et al., 2012).

Low aqueous solubility, High dosage frequency, Low therapeutic index and Drugs with more adverse effects

Methods of preparation of proniosomal gels: There are 3 methods of preparation which include:

A. Coacervation phase separation method.

B. Slow spray coating method.

C. Slurry method.

A. Coacervation phase separation method: This is the most widely used method for the preparation of proniosomal gel. In this method required quantities of drug along with the surfactant, cholesterol and lecithin were weighed accurately and transfer them into a dry wide mouthed glass vial. Then add required quantities of solvent and heat it over a water bath at about 60-70^{o}C by closing the open end of the glass tube to prevent the solvent loss. The heating is continued until the surfactant has dissolved properly then cool down the mixture to room temperature till the dispersion forms proniosomal gel (D. Nagasamy venkatesh et al., 2014).

B. Slow spray coating method: Take required quantities of carrier to the round bottomed flask and attach it to the rotary evapourator.Then add required quantities of surfactant and cholesterol mixture by spraying the aliquots on to the carrier and evacuate the evaporator and place the rotating flask on a water bath under vaccum at 65-70^{0}C for about 15-20min. Repeat the process till all the surfactant has

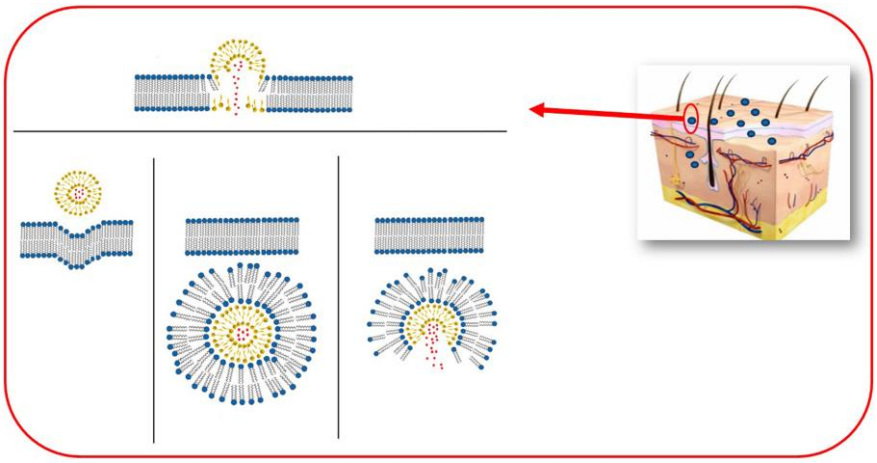

Figure 1: Mechanism of action of niosomes as skin Drug Delivery System

Table 1: Clinical applications of proniosmal gels

Drug	Uses	Drug	Uses
Griseofulvin (Guptasandeep et al., 2009)	Enhancing the permeability of drug into skin.	Metoprolol tartrate (Hayder K. Abbas et al., 2013)	Controlled drug delivery and decreasing the dosing frequency.
Hydrocortisone (Sankar. V et al., 2009)	Controlled drug release.	Dithrano (PatsariyaSurendra Kumar et al., 2014)	Overcoming the GI side effects of the drug.
Terbutaline (Alaa A et al., 2010)	Increasing the biavailability and decreasing the GI side effects of the drug.	Lornoxicam GhadaAhmed (Abdelbary et al., 2013)	Decreasing the Gastro intestinal side effects.
Celecoxib (M. Intakhab Alam et al., 2010)	Overcoming low bioavailability.	Acyclovir (Rajesh Asija et al., 2014)	Overcoming short half life and low bioavailability.
Gugulipid (Chetna Goyal et al., 2011)	Acts as an herbal formulation with low side effects.	Propranolol Hcl (Jeevana Jyothi. B et al., 2014)	For sustained drug delivery.
Lisinopril dihydrate (Shamsheer Ahmad S et al., 2011)	Decreasing the intestinal side effects.	Oxybutynin chloride (Rajan Rajabalaya et al., 2015)	To overcome the GI side effects.
Neem seed oil (Chandel et al., 2012)	Herbal antifungal with less sideeffects.	Ketoconazole (Gagandeep Benipal et al., 2015)	Increases the bioavailability of the drug and overcomes the Hepatic first pass metabolism.
Carvedilol (Hemant N. Patil et al., 2012)	To prolong and control the drug release with high permeability.	Clotrimazole (Litha Thomas et al., 2012)	Increasing the bioavailability and half life.
Naproxen (Varsha Gadekar et al., 2013)	To decrease the serious systemic side effects.	Ibuprofen (Thulasi Chowdary G et al., 2013)	To overcome the GI side effects.

been added and evaporation is continued to obtain a dry free flowing powder of proniosomes.

C. **Slurry method:** Weigh required quantities of surfactant and cholesterol to the solvent and transfer this mixture into the drug containing round bottomed flask. Then add chloroform if the surfactant loading was improper and evaporate the solvent at 50-60^{o}C, 600mm Hg pressure. After evaporation of the solvent collect the dry free flowing proniosomes formed and add 1% gelling agent to obtain the proniosomal gel.

Evaluation of Proniosomal gels

Thermal analysis: It was carried out by using Differential Scanning Calorimetriy. It must be carried out for both the proniosomal vesicles loaded with drug and without drug at a temperature of 50-250^{0}C by maintaining the heating rate of 10^{0}C per minute.

Morphological evaluation

Physical appearance: Proniosomal gels has to be viewed by naked eye for characterizing the colour and physical state and then viewed under optical micro-

scope at 40x magnification to determine the crystal characteristics of the drug.

Shape and surface characteristics of the vesicles: The proniosomal gels was hydrated with a hydrating medium and place the Niosomal suspension thus obtained on a slide then observe under the microscope (Neeraj bhandari et al., 2012). To determine the surface characteristics of the vesicles Transmission Electron Microscopy is performed by coating the Niosomal suspension on a carbon grid for staining. After drying, it was viewed under Transmission Electron Microscope.

Vesicular size distribution: The size of the vesicles of Niosomal suspension formed after the hydration of proniosomal gel was determined by observing the dispersion under the optical microscope at 100 x magnification. At least 200 vesicles are to be measured using stage and optical microscope. The analysis of vesicle size is also determined by Differential Light Scattering method in which the proniosomal gel was hydrated with phosphate buffer with agitation.

Rate of spontaneity: The number of niosomes formed on hydration of proniosomes for 20min are noted by taking approximately 20mg of proniosomal gel spread uniformly on the walls of the glass bottle. Then add few ml of phosphate buffer along the sides of the walls and collect the sample after 20min then place under the neubauers chamber and count the number of vesicles.

Drug entrapment efficiency

Centrifugation: The Niosomal suspension prepared by dispersing the proniosomal gel in phosphate buffer was centrifuged at 18000rpm in a cooling centrifuge at a temperature of 200^0C for 30min to separate the drug entrapped in niosomes. The sediment vesicles were collected and resuspended in 1ml of 30% PEG-400, 1ml of 0.1%Triton x-100 solution. The resulting solution was filtered and diluted with phosphate buffer saline and analysed.

$$\%\ Entrapment\ efficiency = \frac{Amount\ of\ entrapped\ drug}{Amount\ of\ total\ drug} \times 100$$

Dialysis:

The prepared Niosomal suspension was dialysed in a dialysis tube using suitable dissolution medium and the samples were collected at suitable time intervals, centrifuged and analysed for the drug content in UV spectroscopy.

Gel filtration

The unentrapped drug is removed from the Niosomal suspension by using Sephadex-G-50 column by eluting with suitable mobile phase and analyzed with suitable analytical techniques.

In vitro drug release studies: It can be performed by using Franz Diffusion Cell. The dialysis cellophane Membrane was mounted between the donor and receptor compartments and the capacity of the receptor compartment was 30ml. The area of the donor compartment was 2.54cm^2. The weighed quantity of proniosomal gel was placed on one side of the dialysis membrane and phosphate saline of pH 7.4 is used as a receptor medium (Yasam venkata ramesh et al., 2014). The receptor compartment was surrounded by water jacket to maintain the temperature of 37 ± 0.5^0C. The heat was maintained using thermostatic hot plate with a magnetic stirrer. The receptor fluid was stirred by using a Teflon coated magnetic bead fitted to the magnetic stirrer. At every sampling interval the withdrawn samples were replaced with equal amounts of fresh receptor liquid. The samples thus withdrawn were analyzed spectrophotometrically. The maintenance of sink conditions is essential.

Stability studies: Stability studies were performed to determine the ability of vesicles to retain the drug by placing the proniosomal gel at three different temperature conditions like Room temperature (25 ± 2^0C), Refrigeration temperature (4-8^0C) and in oven (45 ± 2^0C). During the stability studies the samples of proniosomal gels are to be placed in aluminium foil sealed glass vials. The samples were withdrawn at regular time intervals for a period of 6weeks and observed microscopically for the change in consistency, solid drug crystals and liquid crystalline structure. The samples were also analysed for particle size and percentage drug entrapment.

CONCLUSION

Proniosomes provide a promising drug delivery with great potential towards physical and chemical stability, ease of preparation, and economical viability. They had attained a great attention for the delivery of drugs through topical and transdermal routes because of their nontoxicity, penetration enhancement due to surfactants. As proniosomes are in the form of vesicles and the components like non ionic surfactants used in the formulation of proniosomes itself acts as permeation enhancers and penetrate readily into the skin. Proniosomes in the dry form makes the possibility of unit dosing by converting them into beads, tablets capsules and gels. Thus they provide an open platform to explore their suitability for drugs with various drawbacks to provide an effective and intended therapy.

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