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INSIGHTS OF PRONIOSOMES IN TRANSDERMAL DRUG DELIVERY A POTENTIAL DRUG CARRIER

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Abstract

Proniosomes, a potentially useful drug carrier, have been developed as result of strategies that maintain the niosomal delivery mechanism while retaining their beneficial characteristics. Proniosomes are a dry formulation made with an appropriate carrier coated in nonionic surfactants. It is hydrated right before usage to transform into niosomes. These proniosomes derived niosomes are just as effective as regular niosomes, if not more so. This review aims to highlight many topics including the manufacture, characterization, entrapment efficiency, factors affecting, recent developments, uses, and benefits of proniosomes.

Keywords: Transdermal Drug Delivery, Niosomes, Proniosomes, Characterization, Applications, Drug Carrier.

INTRODUCTION

Although there isn't currently a single medicine delivery system that satisfies every requirement, attempts have been made using creative strategies. To achieve either regulated or targeted delivery, several innovative approaches covering different routes of administration have arisen. Maintaining a steady and effective drug level in the body while reducing adverse effects is the major goal of innovative drug delivery. It also uses drug carriers to target drug delivery, which localizes the drug's activity. [1]

Lipid nanoparticles known as niosomes have an aqueous area surrounded by the closely spaced, concentric bilayers made from hydrated, nonionic surfactants, which may be or may not be include cholesterol and its byproducts. Amphiphilic molecules with two different hydrophilic and hydrophobic areas in their chemical structure are known as non-ionic surfactants. Niosomes, their aggregation structures, resemble phospholipid vesicles and can encapsulate hydrophilic and lipophilic compounds similarly to liposomes. Hydrophilic compounds can be entrapped in the aqueous core of the bilayers to achieve loading, while lipophilic compounds are integrated into the lipophilic domain. It was an alternative to the liposome, but Niosomes dispersions also have issues with physical characteristics, such as fusion of vesicle, sedimentation, drug breach during storage, and the accumulation, despite their benefits over liposomes. Proniosomes, is the dry powder, have been created via straight forward preparation technique to avoid the issues mentioned above during maintaining the characteristics and makeup of niosomes. [2]

Transdermal drug delivery as an alternative to overcome the barrier of the other drug delivery system. For transdermal drug delivery, the barrier, which is stratum corneum, making it difficult for most drugs to penetrate skin by this method. Using vesicular carriers is one strategy among many that could be used to boost the quantity of drugs transported across the stratum corneum. By enhancing drug solubilization, drug partitioning into the skin, and skin lipid fluidization, these methods can improve skin transportation. [3]

When compared to niosomal dispersion, their semisolid/liquid crystalline compact nature is what is making them more and more attractive. Proniosomal gels typically have a semisolid gel texture that is transparent, translucent, or white. This texture helps to keep the gels physically stable while being stored and transported. Instead of the micellar solution, lyotropic liquid crystals are formed when the majority of surfactants dissolve in water. Bilayer surfactant sheets are stacked in the lamellar phase, in contrast, the hexagon-shaped arrangement of the cylindrical units. A three-dimensional, curved, bio continuous lipid bilayer that divides two parallel networks of water channels makes up the cubic phase. Because of their great viscosity and clarity, liquid crystals are visually appealing. [4] Proniosomes in the transdermal drug delivery is consider as one of the most promising and flexible delivery system. [5]

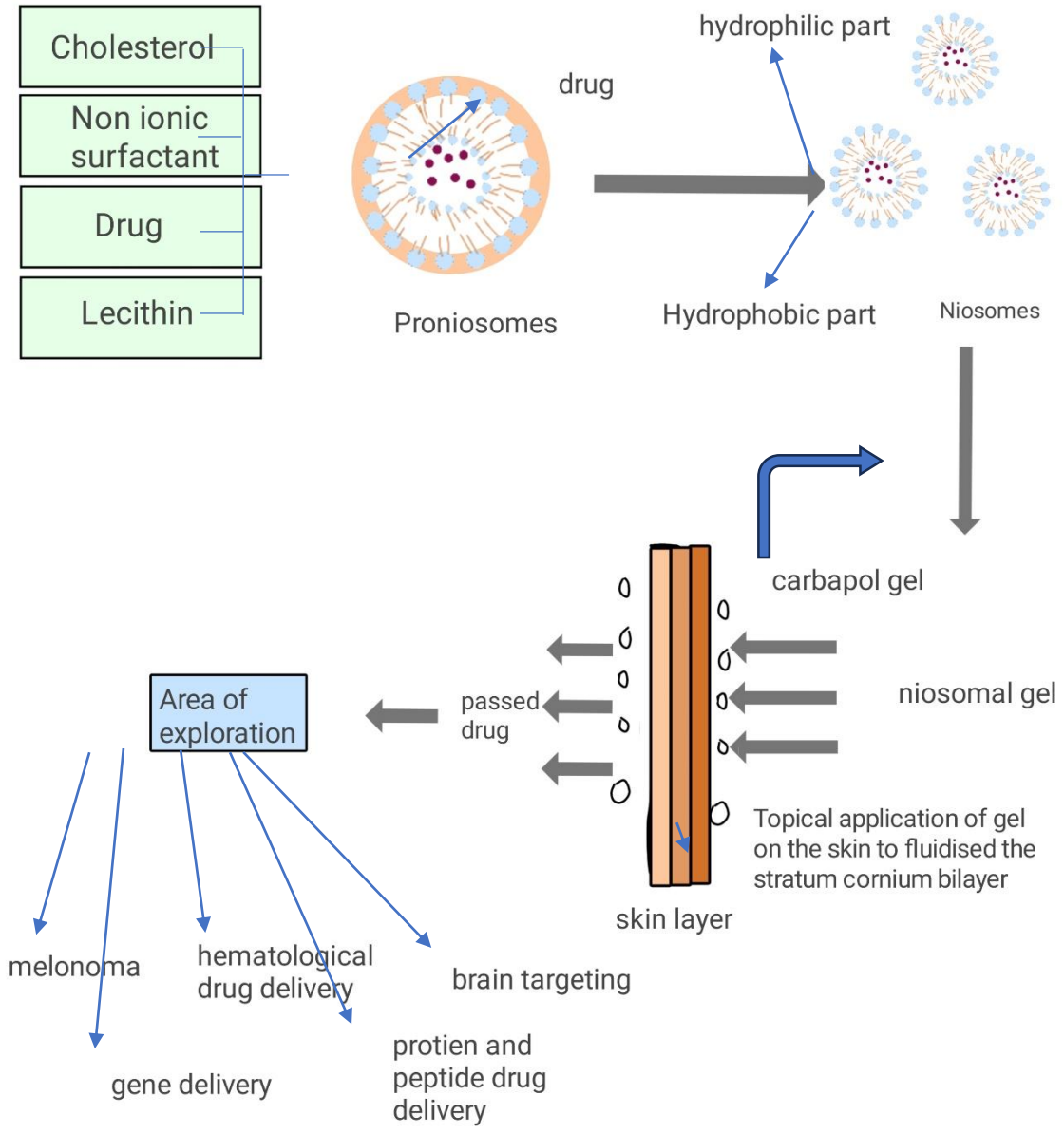

Figure 1: Novel approach to proniosomal transdermal drug delivery

PREPARATION OF PRONIOSOMES

Slurry method

Slurry technique was used to manufacture proniosomal formulations. In 20 milliliters of chloroform, a predetermined quantity of cholesterol, surfactant, and 5 mg of drug were get dissolved. The mixture was transferred into a flask with a circular bottom that held sucrose as a carrier. A rotary evaporator spinning at 60 rpm was used to evaporate the solvent at 40 C. The powder residue was left overnight after it had completely evaporated. In anticipation of additional analysis, the residue was scraped, put through a 0.45 mm screen, and kept in the desiccator. [7]

Coacervation phase separation

Properly weighed proniosomal surfactants, lipids, and drug can be prepared in a clean, using this method 5.0 mL wide mouth glass vial, and alcohol is added. To prevent solvent loss, a glass rod was used to thoroughly mix all the materials after heating, and the open end was covered with duct tape to prevent spillage... The surfactant mixture was completely dissolved in a bath of 60-70C over ice for approximately 5 minutes. Upon cooling, the aqueous phase is converted back into proniosome form by adding water and heating it in typically bathed in warm water until forming an opaque solution.[8]

Preparation of niosomes

Following a brief agitation period of 80ºC, 10 mg of proniosomes were get dissolved in 0.5 L of MilliQ water. Then further resulting solution was then homogenized for 10 min to produce niosomes, which were then analyzed for polydispersity index, hydrodynamic diameter, and zeta potential. The Span 60 surfactant has strong interfacial activity and polar and non-polar segments, which is why the proniosomes dissolve in water. Cholesterol that alters the bilayer membrane fluidity and increases entrapment effectiveness and stability over time. Based on both hydrophilic and lipophilic balance of the surfactant and the constituent's structures of chemical, proniosomes can develop into bilayer vesicles, or niosomes. These factors led to the selection of Span 60 and cholesterol in this. Depending upon their chemical structure of the constituents and the surfactant's hydrophilic lipophilic balance, proniosomes can develop into bilayer vesicles, or niosomes. These factors led to the selection of cholesterol and Span 60, respectively, to the membrane stabilizer and nonionic surfactant in this work. To test the antioxidant, trapping, and release capabilities, 0.5 g of proniosomes get dissolved in 0.1 L of MilliQ water at 80ºC. [9]

CHARACTERIZATION OF PRONIOSOMES

Fourier Transform Infrared Evaluation

For analysis of interplay among various components utilized to preparation of proniosomes, two FT-IR spectrophotometers and a PerkinElmer UTAR were utilized. To verify that there were no interactions that could alter the drug molecule, the spectra were examined, and the peaks were examined for compatibility with the contents. After this process, analyses were conducted on the pure form of drug, each carrier, the mixing of all constituents, and other formulae. To obtain the most precise findings, in zinc selenide crystal surface samples were placed and pressure arm were used to deliver a 80 and 90 forced gauge. Ultimately, samples were meticulously scanned using PerkinElmer Spectrum software. [10]

Micromeritic properties of proniosomes

The flow rate is critical when managing and analyzing powder. The property of flow were investigated using the Angle of repose, Hausner's proportion, and Carr's compression index. To determine the angle of repose, using standard fixed funnel approach. The bulk and tapped densities of proniosome particles were utilized to calculate the Hausner's proportion and Carr's compression index. [11]

Determination of Angle of repose

Dry proniosome powder was subjected to the cylinder and funnel method for measuring its angle of repose. The powder was poured into the hoppers after placement so that the outlet was approximately 10 cm above the outermost layer. This was achieved by allowing the powder to form a cone when it left the hopper, allowing the value to be determined. The proniosome powder was placed in a cylinder that was tightly sealed. When the powder falls, it forms a cone on the surface of the cylinder. Value can be determined by measuring their height and diameter.

Formula is used to determine the angle of repose. $Tan(\Theta) = h/r$

Where, h & r = height & radius of the pile of powder, Θ = Angle of repose respectively. [12]

***In vivo* studies**

In these studies, the drug released from the proniosomal formulation can determined by various method, including the Franz diffusion cell, Cellophane dialyzing membrane, United States Pharmacopeia (USP), Keshary-Chien diffusion cell, which dissolution equipment Type-1, and spectra Por molecular permeable membrane tubes. To release the drug from proniosomes-derived niosomes vesicles, one or more of the following methods may be used: drug diffusion from a phospholipid membrane, desorption from the vesicle surface, or a both diffusion techniques and desorption. [1]

Optical microscopy

The niosomes were examined using a microscope after being put on glass slides. After enough dilution, the microscope's 1200 magnification is utilized for morphological inspection. The preparation's photomicrograph was captured with a digital single-lens reflex camera straight from the microscope. [13]

Entrapment efficacy

Centrifugation and dialysis were employed to extract the free drug from within the niosome suspension. After transferring the lysosomal suspension to a dialysis glass with a permeable cellulose membrane firmly attached to one side, the dialysis tube was suspended in 0.1 L of pH-controlled saline and stirred by magnetic stirring. Free drug and niosome suspension were separated in the medium through a permeable cellulose membrane. Following six hours of intensive dialysis, optical density readings were recorded, and using UV spectrophotometric technique amount of drug that entrapped can calculated. The formula which used to calculate Entrapment Efficiency. [14]

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

Characterization of Proniosomes gel

To measure the size and distribution of the niosomes Zetasizer Nano-ZS90 was used that were generated following the hydration of proniosomal formulation. For the analysis, one milliliter of the diluted sample was used, and disposable sizing cuvettes were used to make size measurements in triplicate at 25C. Proniosomes were also assessed using optical microscopy to verify that hydration is the mechanism of niosomes production. Prepared proniosomal gel was applied to the microscopic slide and examined at 100x magnification using a standard light microscope. [15]

Factor affecting the formulation of proniosomes.

Proniosomes formulation is influenced by a few processing variables, including chain length of surfactant, cholesterol content, pH medium, total lipid concentration, and lipid charge (Figure). [16]

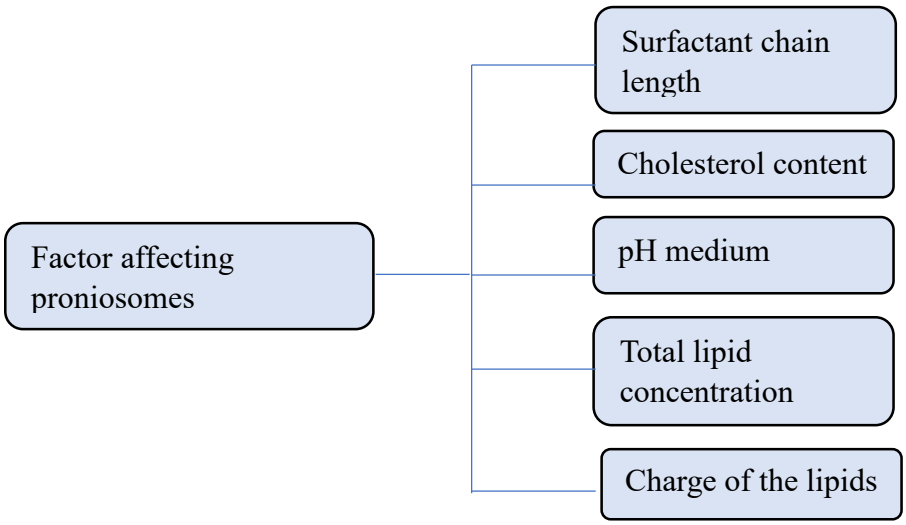

Figure 2: Factors affecting the proniosomal formulation

Studies related to application of proniosomes.

Different drug molecules of proniosomes have been shown in Table 1.

Table 1: Applications of proniosomes from various study

S. No.	Drug	Therapeutical Category	Result	Ref.
1.	Aceclofenac	NSAIDs	From niosomes characterization it shows non-significant differences in, vesicle size, content uniformity and entrapment efficiency.	17
2.	α-Mangostin	Anti-melanogenic	By enhancing α-mangostin conc. in viable epidermis layer might be attributed to the proniosomes permeation enhancement.	18
3.	Mefenamic acid	NSAIDs	Proniosomes are assuring nano-vesicular carriers and a secure substitute to improve the Mefenamic acid topical delivery.	19
4.	Letrozole	Anticancer	A PEGylated formulation of niosomes Letrozole, and reported that the formulation of niosomal was toxic to *in vitro* Michigan Cancer Foundation-7 cancerous cells	20
5.	Tenoxicam	NSAIDs	When compared to the oral tenoxicam pill, the studied tenoxicam-loaded proniosomal formula demonstrated notably greater anti-inflammatory and analgesic effects while remaining non-irritating.	5
6.	Carvedilol	Antihypertensive	Proniosomal gel was studied with different surfactants to optimize transdermal distribution.	21
7.	Levonorgestrel	Antifertility	The system's high degree of stability further supports proniosomes potential for systemic therapeutic administration.	22

8.	Estradiol	Hormonal insufficient	The encapsulation nonionic surfactant in Proniosomal formulation enhance the skin permeation of drug.	23
9.	Frusemide	Diuretic	This is applied in transdermal to reduces the glucose levels in blood.	24
10.	Flurbiprofen	NSAIDs	Cholesterol free proniosomes with increased drug release rate was identified.	25
11.	Indomethacin	NSAIDs	Increased entrapment efficiency with increase in cholesterol.	26

APPLICATIONS OF PRONIOSOMES

1) **Transdermal drug delivery:** Proniosomes show significantly improved drug absorption through the skin. In cosmetic application niosomes was one of the major applications that has utilized by the proniosomes in transdermal drug delivery. Antibiotics left in proniosomes are used topically to treat acne. Compared to non-locking drugs, the penetration of the drug through the skin increases considerably. The proniosome can be used for tetanus toxoid topical immunization. However, existing technology in proniosomes permits only a mild immune response, necessitating greater research in this area. [27]

2) **In Anti-neoplastic Treatment:** Serious side effects of antineoplastic drugs are many. Niosomes have the ability to modify drug metabolism, extend its half-life, enhance circulation, and mitigate adverse effects. In two distinct experiments, methotrexate and doxycycline were entrapped in niosomes and showed favorable effects on plasma levels and tumor proliferation in addition to a delayed clearance of the entrapped drugs. The researchers are developing dipalmitoyl phosphatidyl choline proniosomes (PPT-DPPC-PL) to increase PPT-DPPC stability. [12]

3) **Cosmetics and cosmeceuticals:** Most of the time, biological differences in normal skin are the focus of cosmetics. The skin is an intricate organ that only permits certain substances to enter. Therefore, transporting the active ingredient to the site of action is crucial when it comes to the composition of cosmetics and/or skincare products. A cosmetic or skincare product's activity may alter depending on how it is applied. For instance, longer application times typically result in more activity. Because of their special qualities, proniosomes gel is employed as efficient delivery systems for cosmeceuticals and cosmetics. [28]

4) **Vaccine and antigen:** Many non-ionic surfactants have employed as adjuvants for vaccines because of their immunostimulatory qualities. A niosome adjuvant made of 1-monopalmitoylglycerol, cholesterol, and diacetyl phosphate in a 5:4:1 ratio was tested using mice injected subcutaneously with ovalbumin or a synthetic peptide with a known T-cell epitope along with bovine serum albumin. It was also shown that the same niosome formulation administered intraperitoneally can act as a vaccination adjuvant in immunologically reconstituted human SCID mice. [29]

CONCLUSION

Proniosomes are a promising and effective drug delivery method. Buffer solution in their interior often at the proper pH medium. Their vesicular membrane is primarily made up of cholesterol and nonionic surfactants. There are several ways to create proniosomes, and these techniques impact not only the drug's characteristics but also the amount, type, and structure of surfactant as well as the cholesterol content and lipid content. During delivery, they increase the entrapped drug's stability. Special handling, storage, or industrial manufacturing conditions are not needed for them. Furthermore, they can be made using various structural properties and tailored for certain delivery methods. In general, proniosomes are a very useful tool for delivering drugs and focusing on a variety of therapeutically active moieties. Compared to traditional drug delivery methods, they may be able to offer better care.

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