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REVIEW ON FORMULATION AND EVALUATION OF PRONIOSOMAL GEL

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ABSRACT

Proniosomes, prepared in dry form and hydrated by agitation in hot water to form niosomes provide an alternative with prospective for drug delivery via the transdermal route. The transdermal route of drug delivery has many advantages for administration of drugs in local and systemic therapy. But skin is widely recognized for its effective barrier properties compared with other biological membranes. The low permeability of the skin makes it a dermal delivery is an alternative route, but dermal delivery is an alternative route. Newer drugs of lipophilic nature emerge poor bioavailability, irregular absorption, and pharmacokinetic changes. Therefore, this novel drug delivery system has been proved advantageous over other oral and topical delivery of drug candidates to bypass such disruption. This Proniosomal gel basically is a compact semi-solid liquid crystalline (gel) composed of non-ionic surfactants easily formed on dissolving the surfactant in a minimal amount of acceptable solvent and the least amount of aqueous phase and phosphate buffer. Topical application of gel under occlusive condition during which they are converted into nisomes due to hydration by water in the skin present itself. Proniosomal gels are typically present in transparent, translucent, or white semisolid gel texture, which makes them physically stable throughout storage and transport. This review provides an important overview of the preparation, formulation, evaluation, and application of Proniosomal gel as a drug delivery carrier.

KEYWORDS: Coacervation phase separation, Topical drug delivery, Vesicular drug delivery, Proniosomal gel, Non-ionic surfactants.

INTRODUCTION

Delivering drug with a controlled rate and targeted delivery received much attention in recent years. The application of nanotechnology to medicine has provided the development of multifunctional nanoparticles that, acting as drug carriers, can be loaded with different drugs. A nanocarrier present a great approach in drug delivery with promising features such as protection of drug from degradation and cleavage, controlle drelease, and in case of targeted delivery approaches the delivery of drug molecules to the target sites.

Drug delivery systems using colloidal particulate carriers such as liposomes or niosomes have proved to possess distinct advantages over conventional dosage forms because the particles can act as drug reservoirs, can carry both hydrophilic drugs by encapsulation or hydrophobic drugs by partitioning of these drugs into hydrophobic domains and modification of the particle composition or surface can adjust the drug release rate and/or the affinity for the target site.

The vesicles in a dispersed aqueous system may suffer from some chemical problems associated with degradation by hydrolysis or oxidation as well as physical problems as sedimentation, aggregation, or fusion of liposomes during storage. To overcome the limitations (especially chemical and physical stability) of vesicular drug delivery systems like liposomes, niosomes, transferosomes, and pharmacosomes, the pro-vesicular approach was introduced

This includes

A. Proliposomes

B. Pro-niosomes

C. Dry granular liposomes

D. Mixed micellar proliposomes

E. Pro-transferosomes.[5,6,9]

NIOSOMES

Niosomes are non-ionic surfactant vesicles that are capable to entrap hydrophilic as well as lipophilic drug candidates because they have an infrastructure consisting of both hydrophilic and hydrophobic moieties together. Niosomes are also osmotically active, stable, providing the stability of entrapped drug. They are advantageous than other vesicles as being cheap and chemical stability. The size of niosomes is microscopic and lies in nanometric scale. The

particle size ranges from 10-100 nm. Transdermal therapeutic systems have generated an interest as these systems provide the considerable advantage of non-invasive parental routes for drug therapy, avoidance of first-pass gut and hepatic metabolisms, decreased side effects and relative ease of drug input termination in problematic cases.[14,21]

PRONIOSOMES

Proniosomes are a type of drug delivery system that can be used to encapsulate and deliver therapeutic agents. They are a precursor to niosomes, which are vesicular systems composed of non-ionic surfactants and cholesterol. Proniosomes, on the other hand, are dry formulations that can be easily rehydrated to form niosomes.

The term "proniosome" is derived from "pro" (meaning precursor) and "niosome." Proniosomes are essentially free-flowing powder blends of non-ionic surfactants and a carrier material, such as a sugar or a porous inert carrier. When these proniosomes come into contact with water, they spontaneously form niosomes.

Niosomes, including those derived from proniosomes, have gained attention as drug delivery vehicles due to their ability to encapsulate both hydrophilic and hydrophobic drugs, improve drug stability, and provide controlled release. They can be utilized in various pharmaceutical, cosmetic, and biomedical applications.

Advantages of Proniosomal Gel

1. **Enhanced Drug Delivery**: Proniosomal gels can improve the delivery of drugs through the skin. The niosomal vesicles in the gel can encapsulate both hydrophilic and lipophilic drugs, facilitating their transport across the skin barrier.
2. **Increased Drug Stability**: Proniosomal formulations can protect drugs from degradation, offering improved stability. This is particularly important for drugs that are sensitive to light, heat, or oxidation.
3. **Sustained Release:** Proniosomal gels can provide sustained release of the encapsulated drug over an extended period. This can lead to prolonged therapeutic effects, reducing the frequency of application and improving patient compliance.
4. **Improved skin permeation:** The vesicles in proniosomal gels can enhance the permeability of the skin, allowing for better penetration of the drug. This is beneficial for drugs that have poor skin penetration on their own.

5. **Reduced side effects:** By facilitating controlled release and targeted delivery, proniosomal gels may minimize systemic absorption and reduce potential side effects associated with high drug concentrations in the bloodstream.
6. **Ease of Application:** The gel formulation provides a convenient and easy-to-apply topical system, enhancing patient compliance. It also allows for localized treatment at the site of application.
7. **Versatility:** Proniosomal gels are versatile and can be adapted for various types of drugs, making them suitable for a wide range of therapeutic applications, including dermatology, cosmetology, and pain management.
8. **Enhanced Bio-availability**: The encapsulation of drugs in proniosomal vesicles can improve their bioavailability by protecting them from enzymatic degradation and facilitating absorption.

Classification of Proniosome

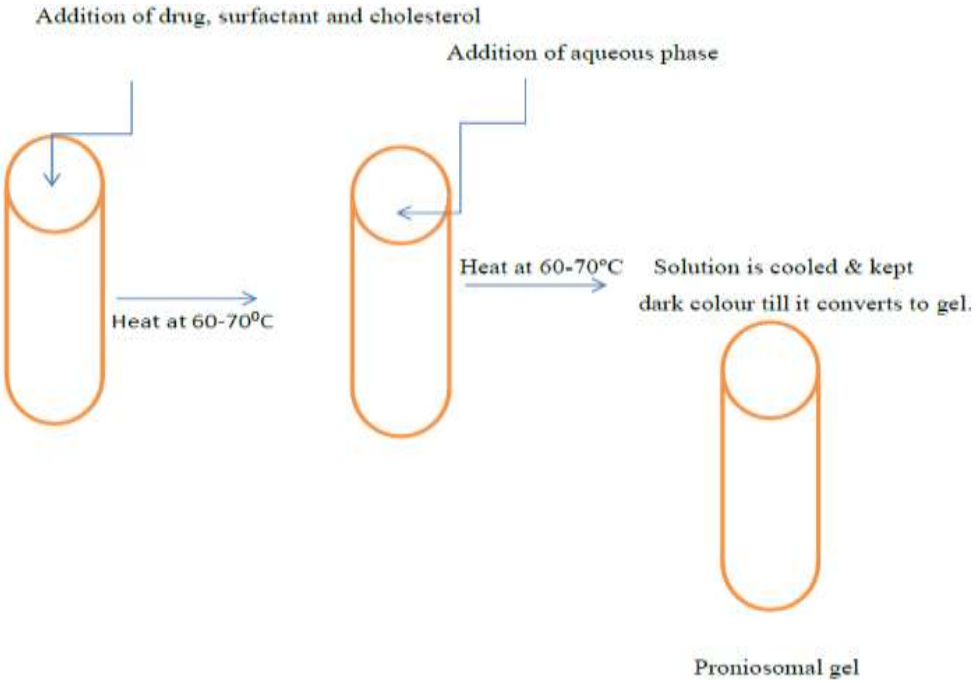
1. Semi-solid liquid crystal gel
2. Dry granular powder

Methods of Preparation of Proniosomes

1. Coaservation phase seperation
2. Slow spray coationg method
3. Slurry method

Coaservation Phase Seperation

Coacervation is usually defined as the spontaneous formation of a dense liquid phase from a macromolecular solution of poor solvent affinity. In coacervation the loss of salvation arises from the interaction of complementary macromolecular species. Coacervation is a phenomenon in which a macromolecular aqueous solution separates into two immiscible liquid phases. The denser phase, which is relatively concentrated in macromolecules is called coacervate and is in equilibrium with the relatively dilute macromolecular liquid phase. Liquid-solid separation is known as precipitation also it means coacervation.



COASERVATION PHASE SEPERATION

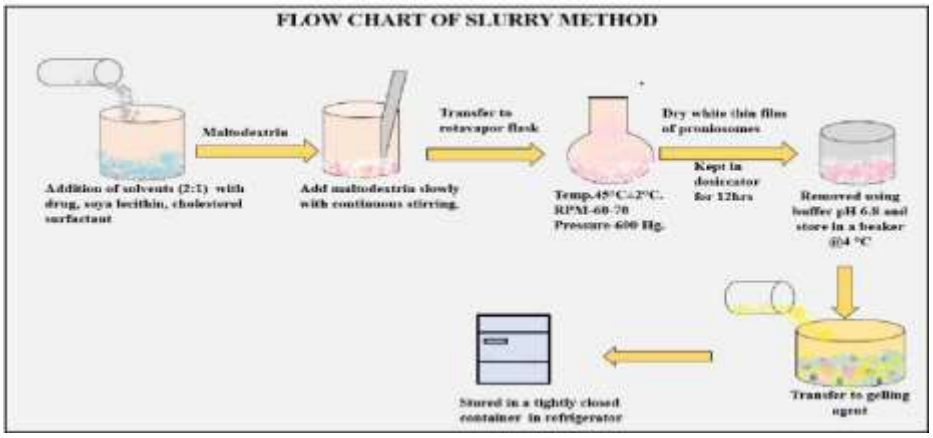
SLOW SPRAY COATING METHOD

This method involves preparation of proniosomes by spraying surfactant in organic solvent onto sorbitol powder and then evaporation of the solvent. Because the sorbitol carrier is soluble in organic solvent, it is necessary to repeat the process until the desired surfactant loading has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows multi lamellar vesicles form as the carrier dissolves. The resulting niosomes are very similar to those produced by conventional methods and the size distribution is more uniform. It is suggested that this formulating hydrophobic drug in a lipid suspension without concerns over instability of the suspension or suspectibility of the active ingredients hydrolysis**.**

SLURRY METHOD

Maltodextrin as a carrier is added into 250ml round bottom flask and the entire volume of surfactant solution was added directly to the flask to form slurry. If the surfactant solution is less, then additional amount of organic solvent can be added to get slurry. The flask was attached to the rotary evaporator and vaccum was applied until the powder appeared to be dry and free flowing. The flask was removed from the evaporator and kept under vaccum overnight. Proniosomal powder was stored in sealed container at 4ºC. The time required to

produced proniosomes is independent of the ratio of surfactant solution to the carrier material and appears to be scalable.



FORMULATION ASPECT OF PRONIOSOMES GEL

Proniosomes gel is comprised of ingredients like lecithin, cholesterol, non-ionic surfactants carbopol gel, alcohol and aqueous phase.

(a) Lecithin: It acts as penetration enhancer.

(b) Cholesterol: In proniosomal gel, cholestrol plays roles likes prevents leakage of the drug from vesicles.

(c) Surfactants: Using non ionic surfactants, hence large size vesicles are formed. In proniosomal gel, surfactants plays roles likes increase drug flux rate approach the skin.

(d) Solvent: Alcohol has great influences on vesicles size. For providing the softness of vesicles membrane.

(e) Mannitol: It is used in proniosome formation.

PREPARATION OF GEL BASE

Carbopol 934 (1%w/v) was accurately weighed and dispersed into double distilled water (90ml) in a beaker. This solution was stirred continuously at 800 rpm for 1 hour and then 10ml of propylene glycol was added to this solution. Volume of gel was adjusted to 100ml and then sonicated for 10 min on bath sonicator to remove air bubbles. Final pH of the gel base was adjusted to 6.8. Proniosome suspension was incorporated into the gel base.

DRUG CRITERIA

The drug selection criteria could be based on the following assumptions.

1. Low aqueous solubility of drugs.
2. High dosage frequency of drugs.

3. Short half life.
4. Controlled drug delivery suitable drugs.
5. Higher adverse drug reaction drugs.

EVALUATION OF PRONIOSOMAL GEL

1. Determination of pH

The pH of the proniosomal gel formulation was measured utilizing the digital pH meter. A small quantity of formulation was moved to a beaker comprising a specific volume of purified water. The electrode was dipped into the formulation and the pH of proniosomal gel was noted.

2. Homogeneity

The homogeneity was determined with the visual inspection of the proniosomal gel formulation. They were tested for their appearance and the existence of any aggregates.

3. Spreadability

This parameter of proniosomal gel was determined by utilizing two slides (5 cm^2). The 0.5g of the formulation was put in the middle of two slides and held aside for 1 min. The diameter of the spread circle of proniosomal gel was measured and compared.

4. Appearance

The proniosomal gel bases were inspected visually for clarity, color, and appearance of any particles.

5. Drug content

The drug content present in the formulation was calculated using scanning through UV Spectrophotometer and High-performance liquid chromatography.

6. Determination of entrapment efficiency

Ultracentrifugation technique is used to determine the entrapment efficiency of proniosomes. Ultracentrifugation is performed at 1500rpm for 60 min at 4°C. Sediment and supernatant liquid is separated and the amount of sediment was determined and drug entrapment efficiency was calculated using the equation

% Entrapment efficiency = Amount entrapped API x 100

7.Infra-red spectroscopy

The IR spectrum of proniosomal gel was obtained by using an FT-IR spectrophotometer, in the (IR range of 4000-400 cm^{1}).

8.Viscosity

The Brookfield Rheometer with spindle no 64 at 10 rpm was used to determine the viscosity of the proniosomal gel formulation. The assembly was connected to a thermostatically controlled circulating water bath maintained at 25℃. The viscosity was determined and added up to the beaker encased with a thermostatic jacket. The spindle was allowed to move into proniosomal gel and the values were noted.

9.*In-vitro* drug release study

The Franz diffusion cell apparatus was utilized to study the in-vitro drug release of the formulation. The formulation was spread on a dialysis membrane which was positioned in the middle of the donor-receptor chamber of the Franz diffusion cell. The temperature was maintained at 30℃. This assembly was subjected to magnetic stirring and stirred continuously using a magnetic field. The % drug liberated from proniosomal gel formulation was calculated.

10.Stability study

Accelerated stability of proniosomal gel was carried out according to ICH guidelines. The stability study was performed at 25 ±2°C and 60 ±5% RH in an environmental stability chamber over three months to assess the stability of topical nanogel. The formulation was transferred to amber-colored glass vials plugged and kept in the stability chamber. The consistency, drug content and in-vitro drug release were measured after three months.

APPLICATIONS OF PRONIOSOME DERIVED NIOSOMES

1. Targeting of bioactive agents

One of the most useful aspects of proniosomes is their ability to target drugs to particular area. Proniosomes can be used to target drugs to the reticulo-endothelial system. The reticulo-endothelium system (RES) preferentially takes up proniosomes vesicles.[10] The uptake of proniosomes is controlled by circulating serum factors called opsonins. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of the drugs can also be used for treating parasitic infections of the liver. Proniosomes can also be utilized for targeting drugs to organs other than the RES. A carrier

system (such as antibodies) can be attached to proniosomes (as immunoglobin bind readily to the lipid surface of the noisome) to target them to specific organ.

2. Anti-neoplatic treatment

Most of the antineoplastic drugs cause severe side effects. Proniosomes can alter the metabolism; prolong circulation and half life of the drug, thus decreasing the side effects of the drugs. Proniosomal entrapment of doxorubicin and methotrexate showed beneficial effects over the unentrapped drugs, such as decreased rate of proliferation of the tumor 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 the side effects and thus allowed greater efficacy in treatment.[1,11]

4. Transdermal drug delivery delivery

The major drawback of transdermal route of delivery is slow penetration of drug through skin, and increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes.

5. Cosmetic delivery

The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L‟Oreal. Niosomes were developed and patented by L‟Oréal in the 1970s and 80s. The first product Niosome‟ was introduced in 1987 by Lancôme. The advantages of using niosomes in cosmetic and skin care applications include their ability to increase the stability of entrapped drugs, improved bioavailability of poorly absorbed ingredients and enhanced skin penetration.[10]

6. Hormone delivery

The in-vitro permeation of estradiol from vesicular formulations through human stratum corneum was studied. The vesicles were composed of non-ionic n-alkyl polyoxyethylene ether surfactants (CnEOm). Two mechanisms are proposed to play an important role in

vesicle–skin interactions, i.e., the penetration enhancing effect of surfactant molecules and the effect of the vesicular structures caused by their adsorption at the stratum corneum suspension interface.

7. Uses in studying immune response

Proniosomes are used in studying immune response due to their immunological selectivity, low toxicity and greater stability. Proniosomes are being used to study the nature of the immune response provoked by antigens.

8. Proniosomes as carriers for haemoglobin

Moser et al., (1989) conducted the study with taking niosome as a carrier for haemoglobin within the blood and suggested that the pronoisome vesicles can be used as carrier for haemoglobin in aneamic patients as pronoisome is permeable to oxygen.

9. Other Applications

a. 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.

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 indose and toxicity. The evolution of niosomal drug delivery technology is still at an infancy stage, but thistype of drug delivery system has shown promise in cancer chemotherapy and anti- leishmanial therapy

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