INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

PRONIOSOMAL GEL A NOVEL APPROACH FOR DRUG DELIVERY: A REVIEW

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ARTICLE INFO

Article history
Received 13/03/2017
Available online
31/03/2017

Keywords
Vesicular Drug Delivery,
Proniosomes,
Nonionic Surfactant,
Niosome.

ABSTRACT

One of the most important ways for non-invasive delivery of drugs is human skin. But some high molecular weight (> 500 Dalton) compounds can't cross the skin. Such type of compounds require some novel techniques. Vesicular systems like liposomes, niosomes, proniosomes are mainly used for this purpose, they have the ability to transfer the high molecular weight compounds across the skin. This article mainly describes the significance of Proniosomes. Proniosomes are the water-soluble carrier particles covered with a nonionic surfactant. It has the potential advantages over liposomes and niosomes. The Proniosomal gel is one of the new vesicular system used for transdermal drug delivery. Proniosomal gel is a semisolid crystalline product of nonionic surfactant. This review provides an overview of preparation, formulation, evaluation of proniosomes and which are the herbal drugs formulated as a proniosomal gel.

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*Please cite this article in press as **Lakshmi Radhika K** et al. Proniosomal Gel A Novel Approach for Drug Delivery: A Review. Indo American Journal of Pharmaceutical Research.2017:7(03).*

INTRODUCTION

Nanotechnology has brought new changes in the field of science, which leads to the development of novel dosage forms such as liposomes, niosomes and proniosomes. Proniosomes are defined as the dry formulation of water-soluble carrier particles covered with nonionic surfactants upon hydration, they form niosomes. Proniosomes are formulated in such a way that, they can overcome the limitations of niosomes such as physical instabilities, aggregation, fusion etc. Various routes can be used for the administration of pronisomes like oral, buccal, intravenous, topical and transdermal etc. Proniosomal gels are one of the recent vesicular drug delivery systems for transdermal drug delivery. It is a mixture of nonionic surfactant, cholesterol and lecithin. The non-ionic surfactants are preferred in the proniosomal preparation is mainly due to they have the ability to enhance solubility and bioavailability of poorly water soluble drugs[1].

The proniosomal gel (Translucent in nature) is formed by the Addition of small quantities of gelling agent to the dry proniosomes. Proniosomal gel provides many advantages like greater physical and chemical stability, high reflux through the skin, better percutaneous absorption. Due to these properties, various types of drugs are formulated as proniosomal gel[2].

Structure of proniosomes

Proniosomes are microscopic lamellar vesicles, combine with non-ionic surfactants (Span, Tween etc) and cholesterol followed by the addition of an aqueous media. The arrangement of the nonionic surfactants are in such a way that the hydrophilic portion phase outward and the hydrophobic ends are in opposite direction to form a bilayer[3].

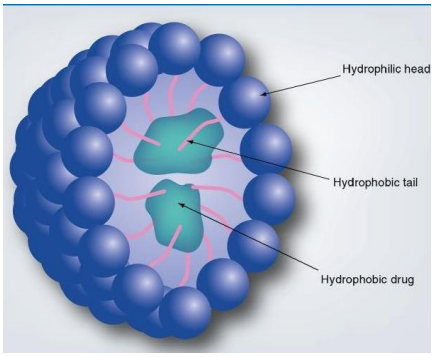

Figure 1[4]: structure of proniosome.

Advantages of proniosomes

- Avoid stability problems like fusion, aggregation, sedimentation and leakage on storage.
- Requires no special condition for storage.
- Sterilization, transportation & distribution is easy.
- Improve bioavailability of poorly water soluble drugs.
- Hydrophilic and lipophilic drugs can be formulated as proniosomes.
- Due to depot formation, controlled and sustained release of drugs takes place.
- Biodegradable, biocompatible to the body.
- Prevent the hydrolysis of encapsulated drugs which reduce shelf life of the product [5].

Formulation of proniosomal Gel

The main components are:-

- Surfactants
- Cholesterol
- Drug
- Aqueous Phase
- Solvent
- Phosphatidyl Choline[6]

Surfactants

Non-ionic surfactants are mainly used for the preparation of proniosomes, due to:-

- It increases solubility and bioavailability of poorly water soluble drugs
- Less toxic, Less irritating to skin
- Maintain near physiological pH.

The selection of the surface active agents mainly depends upon-

HLB (Hydrophilic Lipophilic Balance)

The surfactant which has HLB value between 4 to 8 is used for the preparation of proniosomal formulations. Tween and span are most commonly used non-ionic surface active agents, the encapsulation efficiency of the span is high compared to tween. These surface active agents are amphiphilic in nature(consist of hydrophilic and hydrophobic groups). Because of their amphiphilicity, they are used as solubilizers, wetting agents, emulsifiers and permeability enhancers[7].

Chemical structure

Chemical structure of surfactants influences drug entrapment efficiency. The drug encapsulation efficiency increases with increasing the alkyl chain length.

Phase transition temperature(Tc)

Phase transition temperature is the another factor which influences the entrapment efficiency. Many studies reported that tween having less phase transition temperature compared to span. So that span
provides the high encapsulation for the drug compared to tween[8].
Example for non-ionic surfactants: Fatty alcohol, Cetyl alcohol, Stearyl alcohol, Alkyl ethers, Alkyl esters or alkyl amides[9].

Cholesterol

Cholesterol is another component used for the proniosome preparation. It influences the solubility, permeability of the vesicle and prevents leakage of the drug from the membrane. It is mainly due to the interaction between the cholesterol and non-ionic surfactants. The entrapment efficiency increasing with increasing the cholesterol level to a particular limit, after this level the entrapment efficiency lowers. This is mainly because the added cholesterol molecule fits into the bilayers, that formed by combining the surfactant monomer units. This results increased rigidity and decreased the permeability of the niosomal membrane as compared to cholesterol without preparation. If further increases the cholesterol level it will compete with the drug for the accommodation in bilayers. That will change the regular structure of the vesicular membrane [10].

Lecithin

Lecithin acts as a stabilizer in the proniosomal preparation. They are generally named according to their source of origin. If it is obtained from soya beans and egg yolk is known as soya lecithin, egg lecithin respectively. One of the most important constituents of lecithin is phosphatidylcholine. Lecithin plays as a permeation enhancer. They enhance the percentage of drug entrapment due to high phase transition temperature.

Aqueous phase and solvents

Ethanol, Propanol, Isopropanol, Butanol are the alcohols used in the proniosome preparation. Ethanol is the most commonly used in the preparation because it gives the highest vesicle size due to its greater solubility in water. Alcohols which forms vesicles is of different size, they follow-

Ethanol > Propanol > Butanol > Isopropanol.

Phosphate buffer pH 7.4 & 0.1% glycerol is used as the aqueous phase in preparation of proniosomes. pH of the hydrating medium also play an important role in entrapment efficiency[11].

Drug

The selection of the drug in the preparation of proniosomal formulation depends upon following criteria:-
1) Drugs which have low solubility in water
2) Drugs have high dosage frequency.
3) Short half-life drugs.
4) Drugs have high ADR [12].

Carriers

Maltodextrin and sorbitol are the first choices for proniosome preparation. Sorbitol is a hexahydric alcohol related to mannose. Among these two carriers, maltodextrin is most commonly used because it increases encapsulation efficiency. Preparation of proniosomes with maltodextrin as a carrier was found to be found to be safe, non-toxic and easy to prepare. Other examples of carriers are glucose monohydride, magnesium aluminum silicate, sucrose stearates, mannitol, microcrystalline cellulose, spray dried lactose etc[13].

Types of proniosomes

Proniosomes are mainly 2 types-

- Dry Granular Proniosomes
- Liquid Crystalline Proniosomes

Dry granular proniosomes

According to the carrier used and method of preparation, the dry granular proniosomes are again classified into:

Sorbitol-based proniosomes:-

It is a dry formulation, in which sorbitol is used as a carrier, which is covered with nonionic surfactants, upon hydration in hot water they converted into niosomes.

Maltodextrin-based proniosomes:-

The fast slurry method is used for the preparation of maltodextrin based proniosomes. Maltodextrin is a polysaccharide and it has high solubility in water used as a carrier in proniosome preparation. Maltodextrin particles are used to increase the surface area. The higher surface area results in thinner surfactant coating which is suitable for rehydration process[14].

Liquid crystalline proniosomes

Liquid crystalline pronisomes mainly used for the transdermal drug delivery. Aluminium foil(as backing membrane) along with plastic sheet is present in a transdermal patch[15].

Preparation of Proniosomal gel

The different methods and compounds are used for the preparation of proniosomes. Among these methods, Coacervation phase separation is most commonly used technique for proniosomal gel preparation.

SLOW SPRAY COATING METHOD

Accurately weighed the quantity of the carrier material transfer into a round bottom flask and keep it in a rotary evaporator. After that spraying the required quantities of Surfactant and Cholesterol mixture onto the carrier and evacuate. Then keep the round bottom flask in a water bath under 65-70^{0}C for 20 minutes. Repeat the procedure with the remaining quantity of the surfactants, and continue the evaporation to get a free flowing proniosome powder. Then this powder mixed with the suitable gelling agent [1-2%].

SLURRY METHOD

In this method, Prepare the stock solution of surfactant and cholesterol in a suitable solvent. Transfer this mixture into round bottom flask containing the drug. If the surfactant is not loaded properly add chloroform, then evaporate the solvent at 50-60^{0}C|600 mm Hg pressure. After the evaporation, the free flowing proniosome is formed. To this add suitable gelling agent to obtain proniosomal gel[16].

COACERVATION PHASE SEPERATION TECHNIQUE

It is the most commonly used method for the preparation of proniosomal gel. In this method accurately weighed the quantity of drug along with surfactant, cholesterol, lecithin is taken in a wide mouth glass vessel. Then add sufficient quantity of solvent (ethanol) and heat the mixture in a water bath at a temperature of 50-60^{0}C. The open end of the glass vial is covered with a lid to prevent the evaporation of the solvent. To this mixture add aqueous phase phosphate buffer pH 7.4. Warm the mixture over a water bath at 50-60^{0}C until the drug dissolved completely in a surfactant mixture completely. The proniosomal gel is formed by either cool the mixture at room temperature or add a suitable gelling agent to the heated mixture and cool it on ice bath [17, 18].

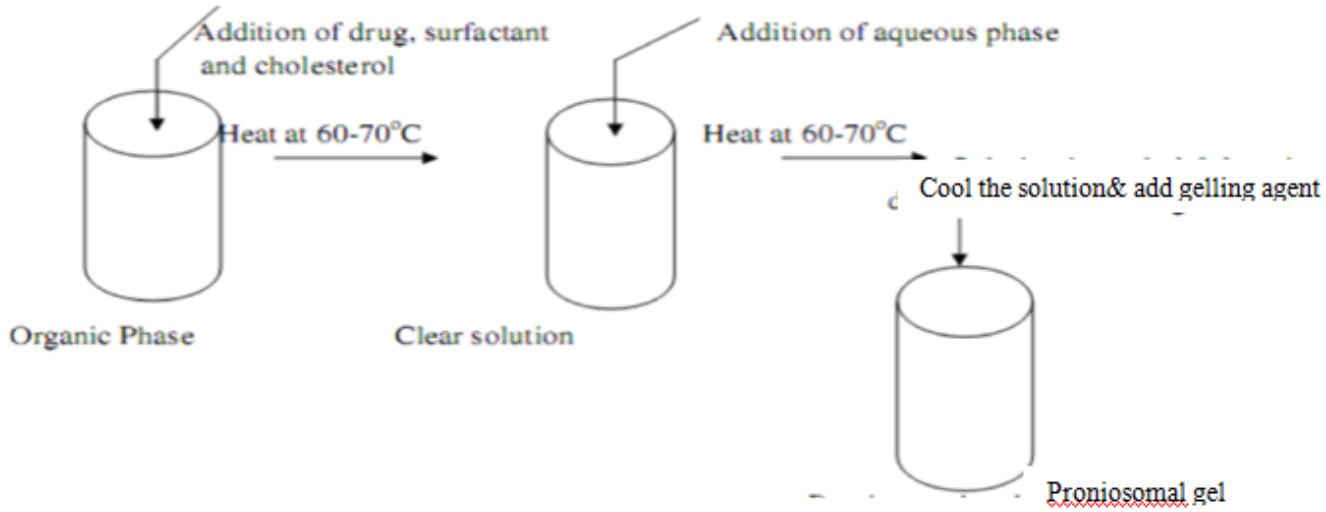

Figure 2: preparation of proniosomal gel by coacervation phase separation method[19].

HERBAL DRUGS FORMULATED AS PRONIOSOMAL GEL

Several technological advances have been made in the drug delivery to overcome problems associated with the permeation of the drug through the skin. The most recent method is to formulate drug as a Proniosomal gel. It has several advantages over other conventional routes. Due to these advantages many synthetic drugs like antimicrobial, antihypertensives, anti-inflammatory, NSAID's formulated as a proniosomal gel. To reduce the side effects of this modern medicine, various natural plant extracts can be used for different activities. Herbal novel drug delivery system which is one of the promising tool for drug delivery, so that many researchers focuses in that field. There are mainly three reasons for using the herbal medicines, they are-

1. Modern medicines failed to treat common health conditions
2. Many natural agents are able to produce better results than drugs or surgery without the side effects.
3. Peoples highly concerned about the safety of drugs[20].

The first plant material formulated as a proniosomal gel is *Withania somnifera* (commonly known as Ashwagandha). It is one of the most commonly used medicine in Ayurveda. Ashwagandha root is used for several health disorders like arthritis, adenopathy, asthma, hypertension. The most important component present in this plant is withanolides, they are responsible for the anti-inflammatory activity. The Coacervation Phase separation method is used for the preparation of the *Withania somnifera* proniosomal gel. As a result of this method, the proniosomal gel gives high entrapment value, prolonged drug release and significant anti-inflammatory property. The anti-inflammatory activity of the Withania somnifera leaf extract proniosomal gel is tested by carrageenan induced rat hind paw method and it is compared with a standard, diclofenac. This study shows that the proniosomal formulation is very stable and effective drug delivery system for *Withania somnifera* leaf extract[21].

Another herbal material that is used for the Preparation of proniosomal gel is Neem seed oil. A research is conducted in 2012 on Preparation and evaluation of proniosomal gel of neem seed oil. This article mainly focuses on the formulation of neem seed oil containing proniosomal gel and evaluate their properties as topical drug delivery system. Here the proniosomal gel was prepared by the slurry method and the antimicrobial studies conducted by agar well diffusion method. Neem seed oil consists of several terpenoids, alkaloids, steroids, flavonoids, glycosides. Apart from that it also consists of nimbidin, nimbinin, nimbin, azadiron, nimbicetin etc are also present. Neem has antibacterial, antifungal, antiviral, antiseptic properties. The proniosomal gel of neem seed oil mainly used in following conditions like pimple, acne, burns, cut etc. The formulated proniosomal gel of Neem seed oil was evaluated and give results like uniform drug distribution, drug entrapment and microbiological data. The anti microbial activity of neem seed oil is evaluated against Gram positive and Gram negative organism. Based on the results obtained from the anti microbial study, shows that neem seed oil proniosomal gel is highly effective and it can be used for various topical treatments[22].

Guggul lipid(*Commiphora wightii* belongs to the family Burseraceae) is the another naturally occurring material used for the preparation of proniosomal gel. The major constituent present in the guggul lipid is guggulsterone. The guggul lipid mainly acts as a hypolipidemic agent. Apart from that it also has antimicrobial, anthelmintic, anti-inflammatory, antiarthritic and antioxidant properties. A research is conducted by Goyal C *et al* on the topic Preparation and evaluation of Guggul lipid-loaded Proniosomal gel for anti-inflammatory activity. Here, the proniosomal is prepared by coacervation phase separation method. And the resulting formulation is evaluated for encapsulation efficiency, drug release, particle size, anti-inflammatory properties. According to the results obtained from the evaluation, shows that the entrapment efficiency of guggul lipid proniosomal gel has faster release initially, followed by a slow sustained release of the drug. Carrageenan-induced rat hind paw edema model is used to check the anti-inflammatory activity, it shows that the proniosomal gel possesses approximately good anti-inflammatory activity but not as good as modern medicine. So that the studies are going on regarding the proniosomal gel formulation with permeation enhancers, that may provide a proniosmal gel with good anti-inflammatory activity than commercial NSAIDs[23].

Curcumin is the another drug formulated as a proniosomal gel**.** A research is conducted on the topic Proniosomal formulation of curcumin, this research mainly focuses on the anti-inflammatory and anti-arthritic activity of curcumin proniosomal gel. Curcuminoids are the oleoresins obtained from the ethanolic extract of Turmeric. Many studies show that curcumin has a wide range of therapeutic applications like anti-microbial, anti-inflammatory, antidiabetic, anti-HIV, anticancer, antispasmodic, antioxidant, antiamoebic etc. Curcumin has many problems like less bioavailability, poor solubility in the acid medium while taking orally. This can be avoided by formulating curcumin as transdermal drug delivery system. Then the formulated proniosomal gel compared with a standard gel. This study shows that the formulated proniosomal gel of curcumin has good anti-inflammatory and anti-arthritic activity[24].

CONCLUSION

Proniosomes are one of the most important delivery system among the vesicular drug delivery systems with greater advantages over the other conventional dosage forms. Proniosomal drug delivery system is found to be very effective for the delivery of drugs through transdermal or topical route because it has the wide range of applications like nontoxicity, effective drug release and greater penetration through the skin. Proniosomes that is obtained as dry form, able to convert into different formulations like the tablet, capsule, gel etc. This review also gives the information about herbal drugs used for proniosomal gel preparation. The researches are going on in the field of the herbal novel drug delivery system. Incorporation of the phytochemicals in modern dosage form helps to improve patient compliance and avoid repeat administration.

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