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Proniosomes an Effective Carrier for Drug Delivery: A Review

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ABSTRACT

To achieve the targeted and controlled drug distribution, new drug delivery systems have arisen that incorporate diverse routes of administration. One such route is the vesicular route of drug delivery. Many vesicles have been used as a carrier to have a better result. But all of them have shown some instabilities. To overcome that one of the carriers used is Proniosomes. Proniosomes are a new formulation that is used in the provesicular system of type of delivery. They are formulated as dry particles which are soluble in water coated with a surfactant and are further dehydrated to create noisome dispersion by using the media which is hot and it is easily converted to its niosomes. The formed niosomes are considered to be same as that of the original noisome, except they are smaller and more homogeneous. This review article shows the types, components, advantages, mechanism of action, methods, applications, and examples of drugs that can be used through various routes.

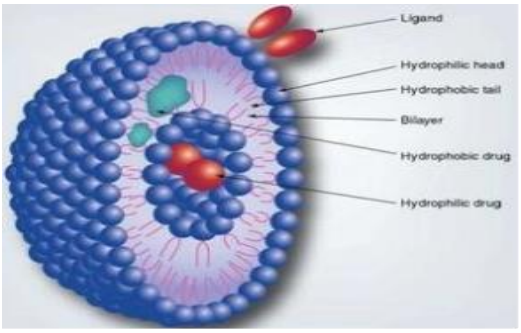
INTRODUCTION:

To achieve targeted and regulated drug distribution, new drug delivery systems have arisen that incorporate diverse routes of administration. One such route of administration is by formation of vesicles. In vesicular route, drug encapsulated vesicles are the main important part of the system that aids in the prolongation of drug action in the systemic circulation.[1]By selective absorption, it reduces toxicity and circulates the amount of medication required by the body. As a result, many of the vesicles have been developed which includes liposomes, Niosomes, Proniosomes.[2]

Among them, liposomes made up of spheroid structures. These structures are made up of a composition of lipids called as phospholipids. For application in pharmaceutics liposomes have been intensively used, a vesicle with a controlled release mechanism or a substance with improved solubility. However, it has shown certain issues using medication administration in general and also some of the challenges faced such as the degradation, hydrolysis, and sedimentation etc.[3]In general dispersions of liposomes causes significant drawbacks, such as different purity, high price of natural phospholipids, chemical instability.[4]

To give more stability to medication niosomes have been developed. The drugs that are considered to be the both lipid dissolving, water dissolving are encapsulated in the vesicles of niosomes. By modifying its distribution related to organ system by increasing its stability niosomes works similar to that of the liposomes. The niosomes are having several advantages over the liposomes but it is also having some of instabilities. To resolve these insecurities a vesicle called Proniosomes has been developed.[5] Proniosomes have unique encapsulation efficiency and diffusion mechanism which helps in enhancing the bio availability of drug which has been explained with an example. Isradipine is incorporated into the albino wistar rats to check the oral bio availability of Proniosomes. Different amount of non- ionic surfactants , stabalizing agents were added to the optimized Proniosomal formulation along with control oral suspension. The pharmacokinetic parameters were checked and evaluated, which showed that optimized Proniosomal formulation shown significant enhancement in biovailability.[6]

Proniosomes are considered to be an unique vesicular delivery.[7] They can be prepared or made as an dry free flowing powder or as an gel (e.g. sorbitol, mannitol, maltodextrin, sucrose stearate etc). By using water as a hot aqueous media, Proniosome formulations can be easily converted to niosomes before application**.** [8]



(Fig 1) Structure of Proniosomes

ADVANTAGES OF PRONIOSOMES [9,10]

The stability issues related to the physical and chemical can be avoided.

Storage and handling convenience.

Sterilization, transportation, distribution, dose homogeneity on storage, and scale-up are not

Difficult.

Improved bioavailability and minimal negative effects are achieved by drug administration.

TYPES OF PRONIOSOMES[11,12]

Proniosomes are classified mainly as:

- Dry Granular Proniosomes
- Liquid Crystalline Proniosomes

Proniosomes made up of Dry Granules:

Dry Granular Proniosomes are formed by using two main carriers such as the sorbitol and maltodextrin.

These are further divided into two categories.

Proniosomes made up of Sorbitol:

These are the formulations made up of dry particles called as the sorbitol which is used as the main carrier, which is coated with the surfactant which are non- ionic. This method involves the spraying the powder into the solvent and then evaporating it, which results in the

formation of thin layer of surfactant, which after the removal of water forms the vesicles which are multilamellar in nature.

Maltodextrin-Based Proniosomes:

A maltodextrin-based Proniosome formulation has recently been created that can be used to deliver hydrophobic or amphiphilic medicines. The advantage of these formulations is that they use the hollow particles with a large surface area along with the amount of carrier required to sustain the surfactant that could be easily altered and to create the Proniosomes with a high surfactant-to-carrier mass ratio.

Proniosomes composed of liquid Crystalline:

The surfactant which are made up of chains which are lipid in nature are transformed into a state in which the water is generally used in a contact phase.

The methods involved are:

- Increasing kraft point (Tc) temperature
- By adding a solvent that dissolves lipids
- Temperature and solvent are both used.

MECHANISM OF PRONIOSOME VESICLE FORMATION [13,14,15]

In the formulation of Proniosomes nonionic surfactant plays a major role, which are determined by the following three factors:

Values of the surfactant, Structures of components, the most important Critical Packing Parameter (CPP). By using this, Proniosomes have the ability in forming the niosomes that look like the niosomes themselves.

$$CPP = \frac{V}{Lc \times a}$$

Here V, Lc, and a are the volume, critical length, area of lipophilic and hydrophilic group respectively.

Between 0.5 – 1 the Critical Packing Parameter shows the vesicles are nearly formed by the surfactants. The Critical Packing Parameter which is less than 0.5 micelles called Spherical

micelles are said to be produced. When Critical Packing Parameter is greater than 1 inverted micelles are believed to be produced.

COMPONENTS RELATED TO PRONIOSOMES [16, 17]

The proniosomes containing components are listed as mainly Surfactants, Stabilizers, Solvents.

Surface Active Agent

These are composed of amphiphilic compounds. As a result, a surfactant molecule has a component that is water soluble as well as water insoluble in nature. Most importantly they used as the permeation enhancers, solubilizing agent and along with other types of agents.

Materials used as carrier

The carrier used provides the stability and also helps the Proniosomes to reach their target site. The used carriers should not cause any harm to the body. Sorbitol, Mannitol, Glucose, Lactose, and Sucrose are some of the most commonly utilized carriers.

Stabilizers for Membranes

Membrane stabilizers such as cholesterol and lecithin are commonly employed. One of the major material used for the membrane formation is cholesterol. The cholesterol used helps in preventing aggregation and also stabilizes the membrane. Lecithin contains a lot of phosphatidylcholines. Egg lecithin, Soya lecithin are two different types of lecithin. It works as both a stabilizer and a penetration booster.

Phases of Solvent and Aqueous Phase

Alcohol as a solvent for proniosomes has a significant impact on vesicle size and drug permeation rate. The vesicles formed are of different sizes and it follows certain order : Ethanol is followed by propanol, butanol, and isopropanol. Because ethanol has a higher solubility in water, it creates the largest vesicles, whereas isopropanol generates the smallest vesicles due to the presence of a branched chain.

PREPARATION METHOD FOR PRONIOSOMES [18,19]

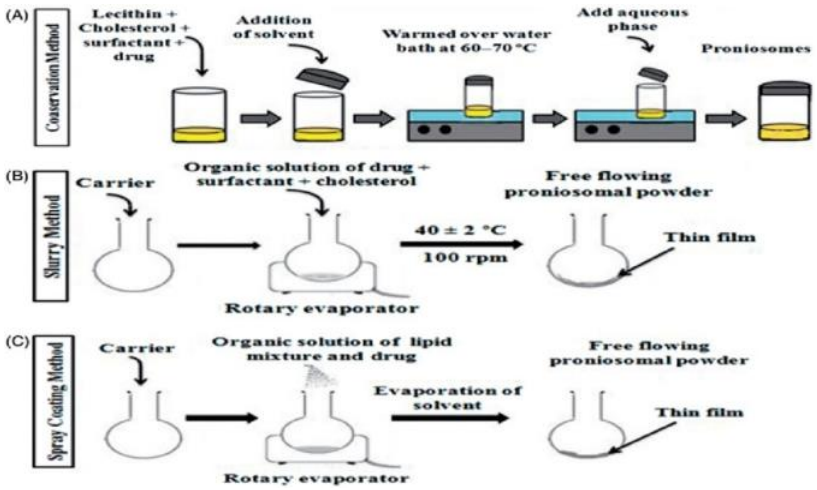


Fig (2) Methods for Preparation of Proniosomes

Mainly three methods are used for preparing the proniosomes.

They are 1. Coacervation Phase Separation Method

2. Slurry Method

3. Spray Coating Method

"Coacervation - Phase Separation Approach" for Proniosomal Gel Preparation:

Surface active agents were accurately weighed and blended with the proper amount of cholesterol in glass vials. Then ethanol was added to the surfactant or surfactant/cholesterol mixtures, by tightly sealing the vial and warmed in a water bath until the lipids were completely dissolved. A small amount of distilled water added to each of the generated lipid solutions while warming in the water bath for 3–5 minutes until a clear solution was produced. Then cooling it to the certain temperature, there will be a formation of Proniosome gel.

Incorporation of drugs into Proniosomal Gel Formulations:

If the medicine is lipid-soluble, it can be added to the mixture containing either cholesterol or non ionic surfactant and dissolved with ethanol. However, depending on the drug's physicochemical qualities, the alchohol is used as a first solvent to dissolve then it is added to the lipid solution to form the gel .

Preparation of a free-flowing Proniosomal dry powder by Slurry Method:

In this procedure, the slurry is prepared in a flask along with its carrier or the solution containing surfactant mixture which is fitted to a rotary evaporator where vacuum is applied to generate a dry and free-flowing powder which is then stored at a required temperature.

Spray-Coating as a Technique:

Proniosomes are made by evaporating the solvent by spraying it onto the carrier as well as using a surfactant. Method must be repeated to form a thin layer of coating material which finally results in the formation of vesicles.

CHARACTERIZATION OF PRONIOSOMES [20, 21, 22]

Characterization is a very important phenomenon to obtain results.

Morphology related to shape and surface: The microscopy called Scanning Electron Microscopy shows the morphology of vesicles formed. With a sputter coater attached to the device, the created proniosomes are placed on metal stubs and coated with conductive gold. After that, pictures are taken to check the shape and morphology of the surface.

Particle size: Optical microscopy at 100X magnification is used to determine vesicular size. Niosomal dispersion is made by mixing the saline solution with proniosomes in a tiny glass vial for 10 minutes with intermittent stirring. Under a microscope, the dispersion is examined, and the size of vesicles is determined using a stage micrometer.

Vesicle size: A particle size analyzer is used to determine vesicular size. Using the same solvent that was used to prepare the niosomes, the niosomes are diluted to 100 times their original volume. A small volume sample holding cell and a He-Ne laser beam focused with a minimum power through a Fourier lens to the center point of a multi-element detector device and vesicle size is determined.

Drug Content Determination: The drug content is determined by lysing equivalent weight of proniosomes in methanol. Using methanol, the solutions are diluted. Then from that required mili liter of this solution are diluted with phosphate buffer. Samples are taken out, and the amount of drug present is measured against its specific wavelength.

***In-vitro* Diffusion Studies**: A separate diffusion cell device is used for studying the *invitro* studies, followed by studying the diffusion mechanisms. The required amount of proniosomal

formulation placed on dialysis membrane .The receptor compartment was filled with required buffer solution, stirred magnetically at required rpm. Then the drug content determined by collecting required amount of receptor fluid every hour. The volume withdrawn it should be replaced with required volume of buffer, then sample is analysed spectrophotometrically at required nanometer.

Stability Studies: According to ICH recommendations, dried Proniosome powder stability is determined by accelerated stability in the range of 40 degree Celsius/75 degree Fahrenheit relative humidity for international climatic zones and conditions. For countries in zones I and II, long-term stability studies are conducted at 25 degree Celsius and with a humidity range of 60%. The temperature in zones III and IV is 30 degrees Celsius with a relative humidity of 65%.

PRONIOSOMES ITS APPLICATION IN VARIOUS ROUTES OF DRUG DELIVERY[23, 24, 25, 26, 27,28 ,29]

Proniosomes show various applications by different delivery ways. Such as Parenteral, Oral, Ocular, Dermal, Transdermal, and other types of routes for drug delivery.

Oral Route:

Oral administration is the most accepted method of drug delivery. But it has shown some of the insecurities. To overcome this, studies have been conducted to deliver the drug in proniosomes powder which helped to increase the oral acceptability and solubility.

Parenteral Route:

Parenteral administration is a typical method for administering pharmacological substances with low bio availability and a limited therapeutic index. In emergency clinical situations, the parenteral route has numerous advantages, including ease of access, rapid onset of action. But parenteral route causes some patient incompliance and these inconveniences overcome by using certain nanocarriers. One of the carriers used are Proniosomes. A Proniosome that is administered via parenteral route formulation helps to have the constant plasma levels, helps improving or removal of toxic traits, which is a significant barrier to improving patient compliance.

Transdermal and Dermal Route:

The dermal layer works as a selective penetration barrier, by allowing specific molecules from entering through its surface. Drug carriers are utilized to target and deliver a drug to its intended location of the action. The penetration depends upon the type of carrier taken. By conducting the research it was found that, Proniosomes are an easy drug delivery mechanism system that can deliver medications transdermally. Furthermore, topical administration has the potential to improve the release mechanisms.

Ocular Route:

It is the most unusual, difficult routes for experts to deliver the drug. An ocular formulation should bypass the eye's protective barriers to release the medicine without harming the tissues. Because of the certain mechanisms involved in occular delivery, they shown some insecurities and that has been overcome by the proniosome gel which increased the delivery capacity and helped the patient convenience.

Here are some of the examples of drug formulations used in different routes by using Pronisomes as a vesicle.[25, 26, 27, 28, 29]

Proniosomal Oral Tablets for Controlled Delivery by using Maltodextrin as a carrier:

Using the slurry method with maltodextrin as a carrier, Acemetacin powder form of proniosome formed. The direct compression method was used to compress positively charged proniosomes. Weight variability, friability, hardness, drug content homogeneity, and dissolving characteristics were all assessed in the tablets. The acemetacin and its composition by using cholesterol was increased from 10 to 20 percentage and the efflux of the medication was significantly reduced, according to the findings. The packaging of Acemetacin Proniosomal powder into tablets was suggested in this study as a way to manage and extend its pharmacologic effects.

Tenoxicam as a tablet for Transdermal delivery using Proniosome as a carrier:

This drug is widely used to cure the disorders related to Rheumatism. Proniosome gel has been formulated, examined to reveal the structure of vesicles, and its effectiveness related to its entrapment factor studied. By using male rats, the behaviour inside the body investigated and compared with marketed product. When compared with marketed tablets, the examined

Proniosomal formula was revealed to be non-toxic and had much stronger anti-inflammatory and analgesic effects.

Proniosomes containing the Tretinoin for Acne:

It is a popular drug used for treating psoriasis, acne, and cancer etc. However, adverse effects have also shown. As a result, the goal of this research was to construct Proniosomes loaded with Tretinoin to improve the medication behaviour of drug. Evaluation parameters tested and drug released mechanism has been found out. Hence Proniosomes found to be an effective released mechanism for delivery.

Lomefloxacin HCL loaded Proniosome for Ocular Delivery:

The goal of this study is to create and test new Lomefloxacin HCl (LXN) ocular Proniosomal gels. Several surfactants has been used and in combination with Span 60.The evaluation parameters has been tested. It has shown that only Span 60 helped to form the LXN proniosomal gel when employed alone, and remaining surfactants formed gels with Span 60. The amorphous form of Lomefloxacin was confirmed by differential scanning calorimetry. A stability assessment revealed there is no change in entrapment efficiency of drug. Evaluation tests confirmed that Lomefloxacin-Proniosomal gel has superior antibacterial therapeutic efficacy over commercially available Lomefloxacin eye drops.

Acyclovir loaded Proniosmes for buccal administration:

Span 60 and cholesterol were used to formulate Acyclovir Proniosomes. The produced Proniosomes were incorporated with polymeric films made from the required quantity of excipients. Then the evaluation parameters were performed. Then from the result it was found that Proniosomes acts as an important carrier for the delivery of drug through buccal route.

Some of the Industrial Applications[30, 31, 32]

Proniosomes is formulated in industry in gel form with the help of Coacervation -Phase Separation method. For example Gugulipid loaded Proniosome gel used to study the Anti - inflammatory activity, using Carrageenan induced rat hind-paw method. It is prepared as powder with the help of slurry method .To overcome the limitations of conventional dosage form ,Captopril loaded Proniosomes were prepared in dry powder form . They can also be formulated in the form of nebulizers. A nebulisable delivery of cromolyn sodium has been

formulated for controlled release by using the non-ionic biocompatible surfactants of sucrose stearates.

CONCLUSION:

Proniosomes are the new drug delivery technologies used in recent drug delivery formulations. These are the dry formulation powders which are uniformly converted to niosomal dispersion. The proniosomes are further divided into different types on the basis of formulations that is prepared. In order to formulate the Proniosomes basically three methods are used, one gives the Proniosome gel and other two methods gives the Proniosome powder. Proniosomes are composed of different components to give the best result. They are used in different routes having different drug formulations to enhance their activity. Hence by considering the above data, Proniosomes came out as an important drug delivery system to achieve the targeted action.

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