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PRONIOSOME AS NOVEL DRUG CARREIER - RECENT REVIEW

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ABSTRACT

Improvement in the nanotechnology brings revolutionary changes and helps in preparing a novel formulations. The Preparation of proniosomes is one of the new progression in nanotechnology. The proniosomes minimize the problems over the niosomes in terms of its physical stability such as aggregation, fusion and leaking. The proniosomes derived niosomes are better than conventional niosomes in terms of their morphology, particle size, particle size distribution, and drug release. A slurry method was commonly used to produce proniosomes using (maltodetrin, sorbital, mannital.) as a carreir The time required to produce proniosomes by this simple method is independent of the ratio of surfactant solution to carrier material The encapsulation efficiency of proniosomes is depends upon the amount of carrier used in the process. The present review describes the classification, method of preparation and applications of proniosomes as a potential drug delivery system.

KEYWORDS

Proniosome, Nanotechnology and Vesicular carrier.

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INTRODUCTON

In the past few decades, significant attention has been focused on the development of novel drug delivery system named as Controlled Drug Delivery System. This formulation shows the prolonged action and it gives continues release of their active ingredients at a predetermined rate and predetermined time. Recently, different carrier systems and technologies have been broadly studied with goal of controlling the drug release and improving the usefulness and selectivity of the formulation. Now-a-days, the vesicular systems like niosomes or liposomes are developed and having specific advantages while avoiding demerits

associated with conventional dosage forms. To overcome the disadvantage of vesicular system, Proniosomes are intended. Proniosomes are coated with surfactant and can be hydrated to form niosome dispersion by brief agitation with hot aqueous medium. And also an additional convenience for the conveyance, circulation; storage and scheming[1].

Proniosomes as drug carriers

Proniosomes are promising drug carriers, because of better chemical stability and also many disadvantages associated with liposomes. Proniosomes are dry formulations of surfactant coated carrier vesicles, which can be rehydrated to form niosome, and resulting niosomes are very similar to conventional niosomes of uniform in size. Being dry, free flowing product, proniosomes minimizes stability problems during storage and sterilization. And also exhibit the merits of ease to transportation, distribution, and storage. And it makes proniosomes a pronouncing versatile delivery system[2].

ADVANTAGES OF PRONIOSOMES OVER THE NIOSOMES

1. Proniosomes avoids the problems of physical stability drug.
2. It avoids encapsulation of hydrolysis drugs.
3. Additional convenience in transportation, distribution, storage and dosing.
4. Can carry both hydrophilic drug and hydrophobic drug.
5. Extensively used in various drug delivery system like drug targeting controlled release and permeation enhancement of drug[3].

TYPES OF PRONIOSOMES

Dry granular type of proniosomes

Dry granular proniosomes are involves the coating of water-soluble carrier such as sorbitol and maltodextrin with surfactant. The subsequent coating process is a dry formulation in which each water-soluble particle is covered with thin film of surfactant. It is essential to prepare vesicles at a temperature above the transition temperature. The non-ionic surfactant being used for the formulation. There are further categorized as follows:

Sorbitol based proniosomes

Sorbitol based proniosomes formulation involves sorbitol as the carrier, which is further coated with non-ionic surfactant and is used as niosomes within minutes by addition of hot water followed by agitation[4].

Maltodextrin based proniosomes

A proniosome formulation based on maltodextrin was recently developed. Maltodextrin based proniosomes prepared by slurry method. Maltodextrin is a polysaccharide easily soluble in water and it is used as carrier material in formulation.

Liquid crystalline proniosomes

When the surfactant molecule are kept in contact with water, there are three ways through which lipophilic chains of surfactant can be disordered in to a liquid state called as lyotropic liquid crystalline state. These three ways are

1. Increasing temperature at kraft point (Tc),
2. Addition of solvent which dissolve lipids,
3. Use of both temperature and solvent.

The liquid crystaliine proniosomes and proniosomal gel act as reservoir for transdermal delivery of drug[5].

COMPONENTS OF PRONIOSOMES

Surfactant

Surfactants are the surface active agent usually they contains both a water insoluble (lipophilic) and a water soluble (hydrophilic) component. They are used in variety of purposes like acting as solubilizers, wetting agents, emulsifiers and permeability enhancers. The most common non-ionic amphiphiles used for vesicle formation are alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids.

CARRIER MATERIAL

The carrier when used for preparation of proniosomes permits the flexibility in the ratio of surfactant and other components that are incorporated. And it increases the surface area and. To whom correspondence should be hence efficient

loading. The carriers should be safe and non-toxic, free flowing, poor solubility in the loaded mixture solution and good water solubility for ease of hydration[6].

MEMBRANE STABILIZER

Cholesterol and lecithin are mainly used as membrane stabilizer. Steroids are important components of cell membrane. Cholesterol is a naturally occurring steroid used as membrane additive. It prevents aggregation by the inclusion of molecules Phosphatidyl choline is a major component of lecithin. Depending upon the source they are obtained and are named as egg lecithin and soya lecithin. It acts as stabilising as well as penetration enhancer.

SOLVENT AND AQUEOUS PHASE

Alcohol used as solvent in Proniosome formulation which are having pronounced effect on vesicle size and drug permeation rate. Vesicles formed from different alcohols are having different size and they follow the order: Ethanol > Propanol > Butanol > Isopropanol. Ethanol has a greater solubility in water hence leads to formation of highest vesicles size instead of isopropanol which forms smallest size of vesicle[7].

DRUG

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

METHODS OF PREPARATION OF PRONIOSOMES

Proniosome preparation mainly comprised of nonionic surfactants, coating carriers and membrane stabilizers. The formulation may be prepared by following methods.

Spraying method

This method involves preparation of proniosomes by spraying surfactant in organic solvent onto the carrier and then evaporating the solvent. It is necessary to repeat the process until the desired surfactant loading achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows vesicles to form as the carrier dissolves. The resulting niosomes have uniform size distribution similar to those produced by conventional methods.

Slurry method

Proniosomes were produced by slurry method by using a different carrier. In slurry method, the whole volume of surfactant solution is added to maltodextrin powder in a rotary evaporator and vacuum is applied until the powder appears to be dry and free flowing product. Drug containing proniosomes-derived niosomes can be prepared in manner similar to that used for the conventional niosomes, by adding drug to the surfactant mixture prior to spraying the solution on the carrier (sorbitol, maltodextrin, and mannitol) or by addition of drug to the aqueous solution used to hydrate the proniosomes.

Coacervation phase separation method

In this method, accurately weighed amount of carrier, cholesterol, surfactant and drug are taken in a clean and dry wide mouthed glass vial (5 ml) and solvent to be added to it by simple mixing. In order prevent the loss of solvent, open end of the glass vial can enclosed by a lid and heated on water bath at 60-70ºC for 5 min. The mixture should be allowable to cool at room temperature the dispersion gets converted to a proniosomes[5,4].

FORMATION OF NOISOME BY PRONIOSOME

The niosomes can be prepared from the proniosomes by adding the aqueous phase with the drug to the proniosmes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant.

$T > Tm$

Where,

T = Temperature

Tm = Mean phase transition temperature

REVIEVE OF LETRETURE

Akhilesh Dubey *et al.*, developed Lornoxicam loaded Maltodextrin based proniosomes by slurry method with different surfactant to cholesterol ratio. They reported proniosomal formulation showed higher entrapment efficiency and *in-vitro* release and release follows super case II transport diffusion[9].

Parthibarajan *et al.*, reported Methotrexate entrapped Proniosomes by slurry method using cholesterol, the non-ionic surfactant span 80 and the carrier maltodextrin. They reported proniosomes exhibited a prolonged release over a period of 24hrs and concluded that the encapsulation of Methotrexate Proniosomes could be meant for targeted drug delivery thereby reduces the toxicity associated with conventional dosage forms[10].

Akhilesh *et al,*. Investigated Glipizide loaded sorbitol, maltodextrin and mannitol based proniosomes by slurry method with different surfactant to cholesterol ratio. The proniosome formulations were evaluated for FT-IR study, angle of repose and scanning electron microscopy. They reported, formulation based maltodextrin showed higher entrapment efficiency of 82.64 ± 1.25 and *in-vitro* release of 98% at the end of 24hrs and zero order kinetics release[11].

Raja K *et al.*, have reported Glipizide loaded maltodextrin based proniosome with different surfactant to cholesterol ratio. They used slurry method to prepare proniosomes. Their results showed that the release was followed by the zero order kinetics with super case II transport diffusion. They reported the proniosome formulation showed appropriate stability[12].

Sandeep Loona *et al.*, prepared proniosomes of Metformin hydrochloride using different ratios of span 60 span and span 40, they characterized the proniosomes for their encapsulation efficiency, size, zeta potential analysis, *in vitro* drug release, vesicular stability at different storage conditions. They have concluded that formulation with 9:2:9 ratio of span 60, cholesterol, lecithin give maximum encapsulation efficiency, good zeta potential and lowest drug release percent after 24 hrs[13].

APPLICATION OF PRONIOSOMES

- Drug targeting
- Anti-neoplastic treatment
- Leishmaniasis
- Delivery of peptide drugs
- Uses in studying immune response
- Proniosomes carriers for haemoglobin
- Proniosomes carrier for cardiac disorders
- Sustained release
- Localized drug action
- Hormonal therapy
- Nsaid application.

Drug Targeting

One of the most useful aspects of proniosomes is their ability to target drugs. Proniosomes can be used to target drugs to the reticule-endothelial system. The reticule-endothelial system (RES) preferentially takes up proniosomes vesicles. The uptake of proniosomes is controlled by circulating serum factors called poisonings. These poisonings mark the proniosomes for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of 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 immunoglobulin bind readily to the lipid surface of the noisome) to target them to specific organs[14].

Anti-neoplastic Treatment

Most antineoplastic drugs cause severe side effects. Noisome can alter the metabolism; prolong circulation and half-life of the drug, thus decreasing the side effects of the drugs. Noisome entrapment of Doxorubicin and Methotrexate (in two separate studies) showed beneficial effects over the entrapped drugs, such as decreased rate of proliferation of the tumor and higher plasma levels accompanied by slower elimination. Podophyllotoxin- (PPT-DPPC) dipalmitoyl phosphatidyl choline proliposomes (PPT-DPPC-PL) for improvement of the stability of PPT-DPPC[15].

Leishmaniasis

Leishmaniasis is an illness it caused by parasite of the genus Leishmania invades the cells of the liver and spleen. Commonly prescribed drugs for the treatment of Leishmaniasis is (antimonials) derivatives of antimony, which in higher concentrations can cause cardiac, liver and kidney damage. Use of pronoisome in assessments conducted showed that it was possible to administer higher levels of the drug[16].

Delivery of Peptide Drugs

Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which breakdown the peptide. Use of proniosomes intended to successfully protect the peptides breakdown from gastrointestinal tract. In a study, oral delivery of a vasopressin derivative entrapped in proniosomes showed highest entrapment of the drug and significant increase in the stability of the incorporated peptide.

Used in Studying Immune Response

Proniosomes are used to study the immune response due to their immunological selectivity, low toxicity and greater stability. Niosomes are being used to study the nature of the immune response provoked by antigens[17].

Proniosomes as Carriers for Haemoglobin

Using a photo initiator, such as eosin and visible light. These hydrogel are constrained to surgical sites nearby to a light source as they form with difficulty after injection into the body. Ion-mediated gelation has been described for a number of polymers, e.g. chitosan/phosphate ions or alginates/calcium ions. The concentrations of the counter ion available under physiological situations are usually lacking for cross-linking of the above mentioned polymers. There are two important factors which limit the use of calcium-alginate. The first factor is their potential immunogenicity and the second one is longer time *in-vivo* degradability[18].

Proniosomes used in Cardiac Disorders

Proniosomal carrier system used for the treatment of hypertension for example captopril that is capable of efficiently delivering entrapped drug over an extended period of time.

Sustained release drug delivery

Sustained release action of proniosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via proniosomal encapsulation.

Localized drug action

Drug delivery through proniosomes is one of the approaches to achieve localized drug action, Localized drug action results in enhancement of efficacy of the drug and at the same time it will reduces its systemic toxic effects e.g. Antimonials[19].

Hormonal Therapy

A proniosome based transdermal drug delivery system of levonorgestrel (LN) was developed and widely characterized both in vitro and in vivo. The biological assay for progestational activity included endometrial assay and inhibition with the formation of corpora lutea[20].

NSAID application

Non-steroidal anti-inflammatory drug like Ketorolac tromethamine (KT) administered intramuscularly and orally in divided multiple doses for short-term management of postoperative pain. Therefore, an alternative noninvasive mode of delivery of the drug is needed. So that, Transdermal route of delivery is an unconditionally an attractive route of administration to maintain the drug blood levels of KT for an extended period of time.

Table No.1: List of common non-ionic amphiphiles used in proniosome formulation

S.No	Non-ionic Amphiphiles	Examples
1	Alkyl ethers and alkyl glycerylethers	Polyoxyethylene 4 lauryl ether (Brij30) Polyoxyethylene stearyl ethers (Brij 72,76) Polyoxyethylene cetyl ethers (Brij 52, 56, 58)
2	Sorbitan fatty acid Esters	Span 20, 40, 60, 80
3	Polyoxyethylene fatty acid esters	Tween 20, 40, 60, 80

Table No.2: Carriers used for the preparation of Proniosomes

S.No	Carrier materials investigated
1	Maltodextrin
2	Mannitol
3	Sorbitol
4	Sprayed lactose
5	Glucose monohydrate
6	Lactose monohydrate
7	Sucrose stearate

Table No.3: Proniosome as carrier of various drug molecules[8]

S.No	Name of therapeutic agent	Route of delivery	Therapeutic category	Result
1	Levonorgestrel	Transdermal	Contraceptive agent	The study demonstrated the utility of proniosomal transdermal patch bearing levonorgestrel for effective contraception.
2	Flurbiprofen	Transdermal	NSAID	The drug release rate from cholesterol free proniosomes was to be high.
3	Captopril	Transdermal	Antihypertensive	Prolonged release of captopril.
4	Estradiol	Transdermal	Female hormone	The non-ionic surfactant in proniosomal formulation helps in enhancement of drug permeation through the skin.
5	Losartan potassium	Transdermal	Antihypertensive	Enhanced bioavailability and skin permeation.
6	Chlorpheniramine Maleate	Transdermal	Anti-histamine	Span 40 proniosomes showed optimum stability, loading efficiency and particle size and release kinetics suitable for transdermal delivery of drug.
7	Ketorolac Tromethamine	Transdermal	NSAIDS	The drug entrapment was high within the lipid bilayers of vesicles.
8	Tenoxicam	Transdermal	NSAID	Tenoxicam loaded proniosomal formula proved to be non-irritant, with significantly higher anti-inflammatory and analgesic effects
9	Piroxicam	Transdermal	NSAIDS	Span 60 based lecithin vesicle showed significant decrease in paw swelling. There is a increased drug delivery from lipid vesicles
10	Vinpocetine	Transdermal	Cerebro-vascular and cerebral Degenerative diseases	Proniosomes were prepared to optimize the extent of drug permeation through the skin
11	Ketoprofen	Transdermal	NSAIDS	Demonstrat permeation enhancement of ketoprofen compared to plain gel.
12	Aceclofenac	Oral delivery	NSAIDS	The polynomial equation and contour plots developed by central composite design allowed to prepare proniosomes with optimum characteristic.
13	Indomethacin	Oral delivery	NSAIDS	The release rate of the drug from the vesicle was in the controlled manner.
14	Gliclazide	Oral delivery	Anti-diabetic	Higher surfactant concentration shows the higher entrapment efficiency.

Table No.4: Different evaluation parameters for Proniosome[6,7]

S.No	Parameter	Analytical Method/ Instruments
1	Vesicle morphology	Scanning electron microscopy Laser microscopy.
2	Shape and surface morphology	Scanning electron microscopy (SEM) transmission electron microscopy (TEM). Optical microscopy.
3	Zeta Potential Analysis	Zeta potential probe model.
4	Stability Studies on Proniosomes	ICH guidelines
5 6	Determination of entrapment efficiency of proniosomes	Dialysis tube
7	Angle of repose	Funnel method
8	*In vitro* drug release study	Franz diffusion cells Keshary-chein diffusion cells Cellophane dialyzing membrane USP dissolution apparatus-I *In vitro* skin permeation studies
9	Drug release kinetic data Analysis.	Higuchi's model, Peppa's model

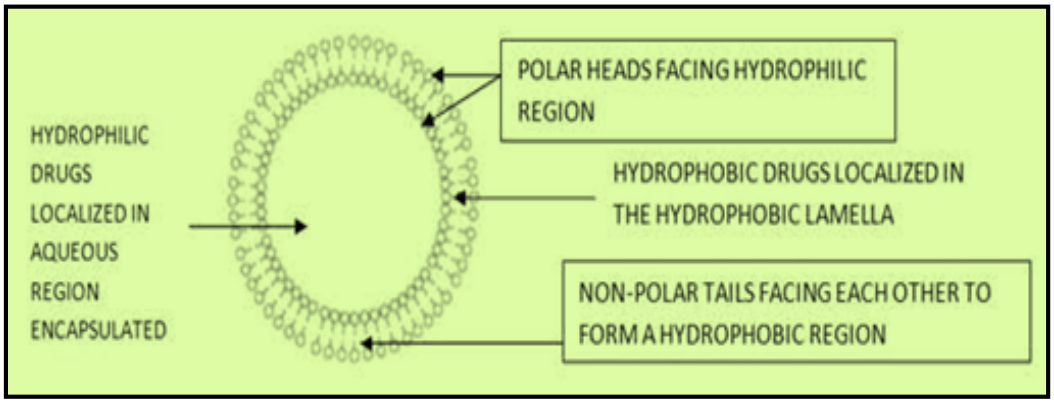

Figure No.1: Schematic representation of proniosomes

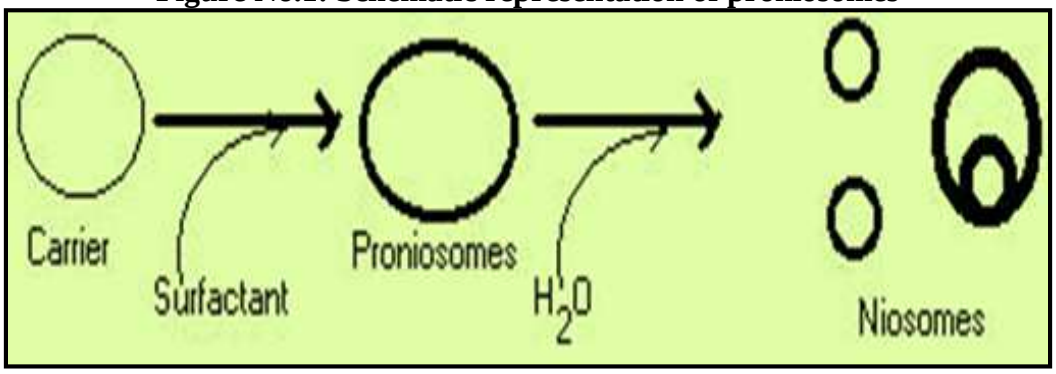

Figure No.2: Schematic representation of formation of niosomes by proniosome

CONCLUSION

From the above article concluded that the concept of including the drug into niosomes for a better targeting of the drug at proper tissue destination. Proniosomes based niosomes are thoughts to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Proniosomes have been tested to encapsulate lipophilic as well as hydrophilic drug molecules. The use of proniosomal carrier results in delivery of high concentration of active agent(s), regulated by composition and their physical characteristics.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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