Review Article

PRONIOSOMAL GEL AS A BETTER CARRIER SYSTEM - A REVIEW

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ABSTRACT

A Vesicular drug delivery system (VDDS) is the system like liposome, niosome, proniosomes, transferosome etc. in which encapsulation of active moieties in vesicular structure so that drug can be reached at predetermined time. One of the advancement in vesicular drug delivery is the preparation of proniosomes. Drug encapsulated in the vesicular structure of proniosomes prolong the presence of drug in the systematic circulation and boosts the penetration into target tissue. Proniosomal gel developed to stabilize niosomal drug delivery system without affecting its properties as promising drug carrier. Proniosomes are developed using appropriate carrier coated with surfactants and can be converted into niosomes immediately before use by hydration. These proniosomes derived niosomes are as worthy as or even better than conventional niosomes in terms of stability.

Keywords; vesicular drug delivery, niosomes, and proniosomes, gel, physical stability.

INTRODUCTION

In the Past few decades, significant attention has been concentrated on the development of new drug delivery system named controlled drug delivery system. These formulation gives continuous release of their active ingredients at a predetermined rate and predetermined time hence prolonged action. The important objective for the development of controlled release forms is the extend the duration of action, better safety of margin of high potency drugs due to enhanced control of plasma level, reduce fluctuation in plasma concentration, reduce the serious side effects. Recently different carrier system and technologies have been widely studied with the aim of controlling the drug release and improving the efficacy and selectivity of formulation.[1]

One of the ways to transform the original biodistribution of drug is to entrap them in submicroscopic drug carriers, they are particulate, polymeric, macromolecular and cellular. Particulate type carrier, also recognized as a colloidal carrier system, includes lipid particles, microspheres, polymeric micelle, nanoparticles, and vesicles. The vesicular systems are highly well-organized in one or several concentric lipids by layers, when certain amphiphilic building blocks are confronted with water.[2]

Vesicular carriers are colloidal particle in which a concentric bilayer made up of amphiphilic molecule surrounded by an aqueous compartment. These amphiphilic molecules formed by phospholipids, surfactant (non ionic, ionic or combination) are either present separately or in combination along with cholesterol as fluidity buffer.[3]

Vesicular shows a very promising role in improving the permeability and solubility enhancement therefore they can also improve bioavailability of drug by enhancing absorption, stability. Also targeting the site of action which is actually the resultant of improved solubility, stability and permeability.[4]

Drug delivery system using colloidal particulate carrier named liposome and niosome have proved to possess distinct advantages over conventional dosage forms because the particles can act as a drug reservoir as it can carry both hydrophilic drug and hydrophobic drugs via encapsulated in the interior aqueous compartment, latter by partitioning of drug in hydrophobic domain. Modification of the particle composition or surface can adjust the drug release and/or the affinity for the target site.

Chemical problem associated with degradation of these vesicles in the dispersed aqueous system is due to hydrolysis or oxidation as well as physical problem as sedimentation, aggregation or fusion of liposomes during storage.

The pro-vesicular concept has advanced to resolve the stability issues affecting the conventional vesicular systems i.e. liposome's and niosomes. These Pro-vesicular systems are composed of water soluble porous powder as a carrier upon which one may load phospholipids/non-ionic surfactants and drugs dissolved in organic solvent, resulting dry free-flowing granular product that can be hydrated immediately before use and can avoid many of the problems associated with aqueous vesicular dispersions.

The new concept has established which gives the potential in improving the oral bioavailability and permeation of drugs across the stratum corneum. Based on the investigations it was clear that pro-vesicular systems appear to be an alternate drug carrier for various routes of drug administration. It can avoid many problems associated with aqueous vesicular dispersions.[5]

To overcome the limitations (especially chemical and physical stability) of vesicular drug delivery systems, the pro-vesicular approach was introduced.

This includes-

A. Proliposomes
B. Pro-niosomes
C. Dry granular liposomes
D. Mixed micellar proliposomes
E. Pro-transferosomes.[6]

Proniosomes:

To overcome the disadvantage of niosomes, proniosomes are prepared and reconstituted into niosomes. Hu and Rhodes et al., described that proniosomes are dry formation of surfactant coated carrier, which can be measured out as needed and rehydrated by brief agitation in hot water.. Proniosomes derived niosomes are superior to conventional niosomes in ease of storage, transport and dosing. In release studies proniosomes appear to be equivalent to conventional niosomes along with the stability, it is expected to be more stable than a pre-manufactured niosomal formulation. size distribution of proniosomes derived niosomes are somewhat better than conventional niosomes so the release performance in more critical causes turns out be greater.[7,8,9]

The advantages of pro-niosomes are as follows:

1. Avoiding the problems of physical stability such as fusion, aggregation, sedimentation, and leakage on storage.
2. Avoiding the problem of chemical stability like hydrolysis of encapsulated drugs which limits
3. the shelf life of the dispersion.
4. Ease of storage and handling.
5. No difficulty in sterilization, transportation, distribution, storage uniformity of dose, and scale-up.
6. Drug delivery improves bioavailability and minimum side effects.
7. It shows controlled targeted and sustained release of drugs due to depot formation.
8. It can entrap both hydrophilic and hydrophobic drugs.
9. It is biodegradable, biocompatible, and non-immunogenic to the body.
10. The shape, size, composition, and fluidity of niosomes drug can be controlled when required.[10]

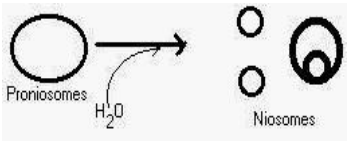
Action of proniosomes:

The conversion of proniosome formulation into niosomes can be done by two-ways.

1. Hydration by skin: The hydration is accomplished by using the water in the skin which hydrate the proniosome formulation and thus convert in to niosomes.
2. Hydration by solvents: using aqueous systems, i.e., purified water, saline solution, and buffers which convert proniosomes into niosomes with or without agitation and sonication.[11]

Formation of niosomes from proniosomes:

The niosomes can be prepared from the pro-niosomes by adding different types of aqueous phase with brief agitation.



Proniosomal gel:

Proniosomes are vesicular systems, where vesicles are made up of non-ionic based surfactants, cholesterol and other additives. Semisolid liquid crystal gel (proniosomes) prepared by dissolving the surfactant in a minimal quantity of an acceptable solvent, namely ethanol and then hydration with slightest amount of water to form a gel. These structures are liquid crystalline dense niosomes hybrids that can be converted into niosomes rapidly upon hydration or used as such in the topical/transdermal applications. Proniosomal gels are normally present in transparent, translucent or white semisolid gel texture, which makes them physically stable.[12]

Components of proniosomes:

A. Surfactant:
The term surfactant is a blend of surface active agent. Surfactant molecule contain both a water insoluble (and oil soluble components) and a water soluble component. Their functions including acting as a solubilizers, wetting agents, emulsifiers and permeability enhancers. Most commonly useds nonionic amphiphiles in vesicle formulation are alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids.

B. Membrane stabilizer:
Cholesterol and lecithin are mostly used as membrane stabilizer.
Cholesterol:
Steroids are important component of cell membrane and their presence in membrane brings about significance changes with regard to bilayer stability, fluidity and permeability. Cholesterol a natural steroid is the most frequently used membrane additive. It doesn't form bilayer vesicles but avoid vesicle aggregation by the inclusion of molecules that stabilize the system by repulsive steric or electrostatic effects.

Lecithin:
Phosphatidayl choline is a major part of lecithin. It has low solubility in water. Depending upon the source they are named as egg lecithin and soya lecithin. It acts as stabilizing and penetration enhancer. It is found that those vesicles composed of soya lecithin are of larger size than vesicle composed of egg lecithin probably due to the difference in the intrinsic composition.

C. Solvent and aqueous phase:
Alcohol has a great effect on vesicle size and drug permeation rate. Vesicles formed from different alcohols are of different size and they follow the order:
Ethanol> propanol> butanol> isopropanol.
Ethanol has greater solubility in water hence leads to formation of highest size of vesicles instead of isopropanol which forms smallest size of vesicles due to branched chain present. Phosphate buffer 6.8, 0.1% glycerol, hot water is used as aqueous phase in preparation of proniosomes.

D. Drug
Selection criteria could be based on the following assumptions

- Low aqueous solubility
- Higher dosage frequency
- Short half life.
- Controlled drug delivery
- Higher adverse drug reaction

Method of preparation:[13,14,15]
Proniosomal gel commonly prepared by Co-acervation phase separation method

Co-acervation phase separation method
This is the widely used method to prepare proniosomal gel. Weighed quantities of drug, lipid and surfactants are taken in a dry wide-mouthed glass beaker. The ingredients are mixed well along with solvent and warmed over water bath at 60–70^{0}C until the surfactant mixture dissolves completely. During the process care must be taken to prevent loss of any solvent due to evaporation. Then the aqueous phase is added to the mixture and warmed on water bath. The resultant solution is cooled overnight.

Characterization of proniosomal gel:
Measurement of pH:
The pH of proniosomal formulation was determined by using digital pH meter.1gm of gel was dissolved in 100ml of distil water and was placed for 2hr. the measurement of pH of each formulation was done in triplicate and average values were calculated.

Viscosity determination:
Brookfield viscometer was used for viscosity determination. The formulation (10g) was taken and it was allowed to calibrate for 5min before measuring the dial reading using spindle No 64 at 20 rpm.[16]

Vesicle size analysis:
The average size and size distribution measurement was carried out by dynamic light scattering with zetasizer (Malvern instruments Ltd) .[17]

Zeta potential:
Measurement of zeta potential of the liposomal formulation was done by using a Malvern nanozetasizer instrument. The zeta potential measurements were done at 250C.[18]

Spreadability:
The spreadability of the gel formulation was determined by taking two glass slides (14*5cm) of equal length. On one glass slide, 1gm gel was applied. To the other slide, weights are added and the time taken for the second glass slide to slip off from the first glass slide was determined.

Spreadability coefficient was determined by the formula

SC=M*l/t,

Where, SC=spreadability coefficient,
M= mass in gram,
l = length,
t = time in second.

Entrapment efficiency:
Percentage entrapment efficiency was studied by centrifuge method. 100mg of proniosomal formulation was weighed and dispersed in 10ml of PBS pH 6.8. The obtained proniosomes dispersion was centrifuged at 10000 rpm for 30 min. the clear fraction (supernatant) was used for the determination of the free drug. The drug concentration in the resulting solution was assayed by UV spectrophotometer at absorption maxima.
The percentage of drug encapsulation was calculated by the following:

%EE = [1-(Cf/Ct)]*100

Cf= unencapsulated drug
Ct = total drug taken.

Drug content:
The drug content was determined by dissolving 100 mg of proniosomal gel in 100 ml of PBS pH 6.8. From this 1ml solution is diluted up to 100ml of PBS pH 6.8. Then the absorbance is measured by UV spectrophotometer against blank at λ max and the drug content was calculated.

$$\text{Amount of drug} = \frac{\text{concentration from the standard graph} \times DF}{1000}$$

Where DF = dilution factor[19]

***In-vitro* drug permeation study:**
The in vitro drug release studies were conducted by using Franz diffusion assembly.10 mg equivalent proniosomal preparation was placed on dialysis membrane between donor and receptor compartment of diffusion cell assembly. The receptor compartment was filled with PBS pH 6.8, magnetically stirred at 200 rpm. The drug content was determined by collecting 2ml receptor fluid every hour. The volume withdrawn was replaced with equal quality of fresh buffer. After suitable dilution, the sample was analyzed spectrophotometrically at λmax.[20, 21]

***In vitro* drug release kinetics:**
The dissolution profile of all the batches was fitted to Zero order, First order and Higuchi to ascertain the kinetic modeling of the drug release. The results obtained from in vitro release studies were plotted in four kinetics models of data treatment as follows:

- Cumulative percentage drug release Vs. Time (zero order rate kinetics)
- Log cumulative percentage drug retained Vs. Time (first order rate kinetics)
- Cumulative percentage drug release Vs. √T (Higuchi classical diffusion equation)
- Log of cumulative percentage drug release Vs. log Time (Peppas exponential equation).

Stability studies:
The stability study of the proniosomal preparation was determined by drug content and entrapment efficiency. The selected batch was packed in tightly closed containers wrapped in aluminum foil and kept at 30±20C at (65±5%RH) for 90 days in a stability chamber and also at 8±20C temperature in a refrigerator.[23]

CONCLUSION
In the future Proniosomes are promising drug carriers. Proniosomes derived niosomes are better alternative to the liposomal vesicular system it's because of its greater physical, chemical stability and potentially scalable for commercial viability. Main advantage of proniosomal delivery system is that incorporation of Amphiphilic drugs. Proniosomes has attracted a greater deal of attention for delivery of drugs through transdermal route, due to its benefits like non-toxicity, penetration enhancing effect of surfactants and effective modification of drug release.

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