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DEVELOPMENT AND EVALUATION OF PRONIOSOMES AS A PROMISING DRUG CARRIER TO IMPROVE TRANSDERMAL DRUG DELIVERY

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ABSTRACT
Drug delivery systems using colloidal particulate carriers such as liposomes and niosomes have distinct advantages over conventional dosage forms. However, there remain significant problems like instability in the general application of liposomes and niosomes for drug delivery. Proniosome have the potential to become a promising drug carrier in order to give stability to niosomal drug delivery system without interfering it,s meritorious properties.
Proniosomes is dry formulation using suitable carrier coated with non ionic surfactants and can be converted into niosomes immediately before use by hydration.
This article describes the detail of formulation and evaluation of Proniosome including morphology, particle size, particle size distribution and drug release and their advantages over noisome. In all parameters proniosome are better than conventional niosomes.
Keywords: Niosomes, Proniosomes, Stability, Drug release studies, Controlled drug delivery systems

INTRODUCTION

Basic goal of drug therapy is to provide therapeutic amount of drug to proper site in body to promptly achieve and then maintain desired drug concentration in order to produce desired effect. Recently in the field of pharmaceutical sciences great efforts are being directed towards the refabrication of existing drugs and drug delivery system in to solve the problem related to poor solubility, poor bioavailability, dosing problem, stability, toxicity etc. This technique of working has lead to development of new drug and new drug delivery system in a more perfect form

Non ionic surfactant vesicles known as niosomes are gaining great attention as an alternative potential drugs delivery system to conventional liposomes. Niosomes have shown advantages as drug carriers, such as being cheap and chemically stable alternative to liposomes, but they are associated with problems related to physical stability, such as fusion, aggregation, sedimentation and leakage on storage [1-2]. The proniosome approach minimizes these problems by using dry, free flowing product, which is more stable during sterilization and storage[3].

Comparison of Proniosome with Niosome

Niosomes or non-ionic surfactant vesicles are microscopic lamellar structure formed on admixture of non ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media.

Proniosomes are dry formulations of surfactant coated carrier vesicles. Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media.

Limitations of niosomes which can be avoided by use of proniosomes[4].

1. Liposomes and niosomes are dispersed aqueous systems and have a problem of degradation by hydrolysis
2. Liposomes and niosomes require special storage and handling.
3. In liposome purity of natural phospholipids is also variable
4. Difficulty in sterilization, transportation, distribution, storage uniformity of dose and scale up
5. Use of unacceptable solvents of the preparation
6. Incomplete hydration of the lipid/surfactant film on the walls during hydration process.
7. Sedimentation, aggregation or fusion on storage is usually seen

Proniosomes minimize the problems using dry, free flowing product which is more stable during storage and sterilization and it has additional merits of easy of transfer, distribution, measuring and storage.

Ideal properties of Drug to develop Proniosomes

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 reactions drugs.

Mechanism of drug transport through skin

The exact mechanism of penetration of drug in the vesicles through the skin is not yet explored, but this is necessary that proniosomes should be hydrated to form niosomal vesicles before the drug is released and permeates across the skin. Penetration depends on nature and type of the drug used, vesicles formed and hydration temperature for the conversion of proniosomes to niosomes. Proniosomes contain both non-ionic surfactant and phospholipids both can act as penetration enhancer and useful in increasing permeation enhancing. The lipids used in the preparation of proniosomes, act as carrier that will form depot at the site of action and hence sustains the action. The rate-limiting step in the penetration of drug through the transdermal drug delivery is the lipid (ceramides) part of stratum corneum, which packed tightly as bilayer by hydrogen bonding. The hydrogen bonding will strengthen and stabilize the lipid bilayer and as a result will impart the barrier property of stratum corneum. Proniosomes will hydrate to niosomes when applied to skin. On to the skin surface, the niosomes formed adsorbs fuses and loosens the ceramides by competitively breaking the hydrogen bond network leading to high thermodynamic activity at the interface (figure 1). This will increase the increases the concentration gradient and hence increases the diffusion pressure for the driving of drug through the stratum corneum[5].

Composition of proniosome

Main components of Proniosome formulation are following (Figure 2)

1. Surfactants

The term surfactant is a blend of surface active agent. Surfactants are usually organic compounds that are ampiphilic, meaning they contain both hydrophobic groups (their tails) and hydrophilic groups (their heads). Therefore, a surfactant molecule contains both a water

insoluble (and oil soluble component) and a water soluble component. Selection of surfactant should be done on the basis of HLB value. Any surfactant, having Hydrophilic Lipophilic Balance HLB number in between 4 and 8 was found to be compatible with vesicle formation. The encapsulation efficiency of Tween is relatively low as compared to Span[6].

Nonionic sufactants:

Examples-Fatty alcohols, Cetyl alcohol, Stearyl alcohol, Cetostearyl alcohol, Oleyl alcohol, Polyoxyethylene glycol alkyl ethers e.g. Octaethylene glycol monododecyl ether, pentaethylene glycol , Glucoside alkyl ethers eg. Decyl glucoside, Lauryl glucoside, Polyoxyethylene glycol alkylphenol ethers e.g. Nonoxynol-9, Glycerol alkyl esters: eg.Glyceryl laurate .

2. Cholesterol

Steroids are important components of cell membranes and their presence in membrane brings about significance changes with regard to bilayer stability, fluidity, and permeability. Cholesterol a natural steroid is the most commonly used membrane additive and can be incorporated to bilayers at high molar ratios. It does not form bilayer vesicles but preven vesicle aggregation by the inclusion of molecules that stabilize the system against the formation of aggregate by repulsive steric or electrostatic effects. It leads transition from the gel state to liquid phase in noisome systems. As a result niosomes becomes less leaky [7].

3. Drug

Entrapment of drug in niosomes increases vesicle size, mainly by interaction of solute with surfactant head groups thus increases the charge and mutual repulsion of the surfactant bilayers and so increases vesicle size[7].

4. Aqueous Phase

Phosphate buffer pH 7.4, 0.1% glycerol, hot water are used as aqueous phase in preparation of proniosomaes[8].

5. Solvent

Alcohol used in Proniosomes has a great effect on vesicle size and drug permeation rate

Solubility of alcohol in water increases the size in the following order[8].

Ethanol > Propanol > Butanol > Isopropanol

6. Phosphatidyl choline

It acts as stabilizing agent as well as penetration enhancer. The commonly used PC is lecithin i.e. soya lecithin, egg lecithin[9].

Method of Preparation

1. Slurry method

Proniosomes can be prepared from a stock solution of surfactants and cholesterol in suitable olvent. The required volume of surfactant and cholesterol stock solution per gram of carrier and drug should be dissolved in the solvent in 100 ml round bottom flask containing the carrier (maltodextrin or lecithin). Additional chloroform can be added to form the slurry in case of lower surfactant loading. The flask has to be attached to a rotary flash evaporator to evaporate solvent at 50- 60 rpm at a temperature of 45±2^0 C and a reduced pressure of 600mm Hg until the mass in the flask had become a dry, free flowing product. Finally, the formulation should be stored in tightly closed container under refrigeration in light[10].

2. Coacervation phase separation method

Accurately weighed or required amount of surfactant, carrier (lecithin), cholesterol and drug can be taken in a clean and dry wide mouthed glass vial (5 ml) and solvent should be added to it. All these ingredients has to be heated and after heating all the ingredients should be mixed with glass rod. To prevent the loss of solvent, the open end of the glass vial can be covered with a lid. It has to be warmed over water bath at 60-700 C for 5 minutes until the surfactant dissolved completely. The mixture should be allowed to cool down at room temperature till the dispersion get converted to a proniosomal gel[11].

3. Slow spray coating method

A 100 ml round bottom flask containing desired amount of carrier can be attached to rotary flash evaporator. A mixture of surfactants and cholesterol should be prepared and introduced into round bottom flash on rotary evaporator by sequential spraying of aliquots onto carrier's surface. The evaporator has to be evacuated and rotating flask can be rotated in water bath under vacuum at 65-70oC for 15 – 20 min. This process has to be repeated until all of the surfactant solution had been applied. The evaporation should be continued until the powder becomes completely dry[12].

Formation of Niosomes from Proniosomes

The niosomes can be prepared from the proniosomes this can be achieved by two ways[13].

Hydration by skin: The hydration is achieved by skin itself i.e. the water in the skin is used to hydrate the proniosome formulation and conversion to niosomes.

Hydration by solvents: Aqueous systems i.e. purified water, saline solution and buffers are used to convert proniosomes to niosomes with or without agitation and sonication (Figure 3).

Evaluation of Proniosomes

1. Stability Studies

Stability studies carried out by storing the prepared proniosomes at various temperature conditions like refrigeration on (2-8˚C) room temperature (25˚±0.5˚C) and elevated temperature (45˚±0.5˚C) from a period of one month to 3 months. Drug content and variation in the average vesicle diameter were periodically monitored. ICH guidelines suggests stability studies for dry proniosomes powder meant for reconstitution should be studied for accelerated stability at 75% relative humidity as per international climatic zones and climatic conditions[14].

2. Vesicle Size Determination

It was carried out using an optical microscopy with a calibrated eyepiece micrometer. About 200 niosomes were measured individually, average was taken, and their size range, mean diameter were calculated[15].

3. Drug Content

Proniosomes preparation equivalent to 40 mg is taken into a standard volumetric flask. Then they were lysed with 100ml of propane-1-ol by shaking. Then 1ml of this was subsequently diluted with phosphate buffer (pH 7.4). The absorbance was measured by UV spectrophotometer[16].

4. Shape and surface morphology

Surface morphology means roundness,smoothness and formation of aggregation. it was studied by screening electron microscopy, optical microscopy, transmission electron microscopy[16].

5. Separation of Free Unentrapped Drug

The encapsulation efficiency of proniosomes is determined after separation of the un- entrapped drug using these techniques:

A. Dialysis

The aqueous niosomal dispersion is dialysed tubing against suitable dissolution medium at room temperature then samples are withdrawn from the medium at suitable time interval centrifuged and analysed for drug content using UV spectroscopy[17].

B. Gel Filtration

The free drug is removed by gel filtration of niosomal dispersion through a sephadex G50 column and separated with suitable mobile phase and analysed by suitable analytical techniques[18].

C. Centrifugation

The niosomal suspension is centrifuged and the surfactant is separated after this the pellet is washed and then re-suspended to obtain a niosomal suspension free from unentrapped drug[18].

6. Drug Entrapment efficiency of proniosomes

Entrapment efficiency of niosomes can be determined by exhaustive dialysis method. The measured quantity of niosomal preparation can be taken into a dialysis tube to which osmosis cellulose membrane

was securely attached on one side. The dialysis tube was suspended in 100ml phosphate buffer (pH 7.4), which was stirred on a magnetic stirrer. The unentrapped drug will get separated from the niosomal suspension into the medium through osmosis cellulose membrane. At every hour entire medium (100ml) was replaced with fresh medium (for about 9-12hrs) till the absorbance reached a constant reading indicating no drug is available in unentrapped form. The niosomal suspension in the dialysis tube was further lysed with propane-1-ol and estimated the entrapped drug by UV spectrophotometric method. The entrapment efficiency was calculated using following equation[19].

$$\% \text{ Entrapment} = \frac{\text{Total drug} - \text{Diffused drug}}{\text{Total drug}} \times 100$$

7. Measurement of Angle of repose

Proniosomes powder was poured into a funnel which was fixed at a position so that the 12mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows down from the funnel to form a cone on the surface. Angle of repose was then calculated by measuring the height of the cone and the diameter of its base[20].

8. Rate of hydration (Spontaneity)

Spontaneity of niosomes formation is described as number of niosomes formed after hydration of proniosomes for 15 min. Proniosomes were transferred to the bottom of a small stoppered glass tube and spread uniformly. One ml saline (0.154 M NaCl) was added carefully along the walls of the test tube and kept aside without agitation. After 15-20 min a drop of aqueous layer was withdrawn and placed on Neubaur's chamber. The number of niosomes eluted from proniosomes was counted[20].

9. Zeta Potential determination

Zeta potential can be analysed to measure the stability of niosomes by studying its colloidal property. The zeta potential of indomethacin proniosomes was measured by a zeta potential probe. Zeta potential analysis is a measure of net charge of niosomes. The higher charge on the surface of vesicles produce repulsive force between the vesicles which made them stable, devoid of agglomeration and faster settling, providing an evenly distributed suspension[21].

10. In-vitro drug release and skin permeation studies

This can be performed by following technique

(I). Franz Diffusion Cell

This franz diffusion cell has a donor chamber fitted with a cellophane membrane.the proniosomes are placed in it and dialysed against a suitable dissolution medium at room temperature the drug content is analyzed using suitable method (UV spectroscopy, HPLC) maintenance of sink conditions is essential[22].

(II). Dialysis Tubing

This apparatus has prewashed dialysis tubing which can be hermatically sealed.the proniosomes are placed in it and then dialyzed against a suitable dissolution medium at a room temperature the samples are withdrawn from the medium at suitable intervals. centrifuged and analyzed for drug content using suitable method (UV spectroscopy, HPLC[23].

(III). Reverse Dialysis

In this apparatus a no of small dialysis tubes containing 1 ml of dissolution medium are placed. Then proniosomes then displaced into the dissolution medium.the direct dilution of the proniosomes is possible with this method. But the rapid release can not be quantified using this method[23].

11. Drug Release Kinetic Data Analysis

The release data obtained from various formulations can be studied for their fitness of data in different kinetic models like Zero order, Higuchi's and Peppa's[24].

1. Zero order kinetics

$$Q_t = Q_0 + K_0 t$$

Where, Q_t = amount of drug dissolved in time t,
Q_0= initial amount of drug in the solution,
K_0= Zero order release constant.

2. First order kinetics

$$\text{Log } Q_t = \log Q_0 + K_1 \, t/2.303$$

Where, Qt = amount of drug released in time t,
Q_0= initial amount of drug in the solution,
K_1= first order release rate constant

3. Higuchi model

$$Q_t = K_H . \, t_{1/2}$$

Where Qt = amount of drug released in time t, KH= Higuchi dissolution constant.

4. Korsemayer and Peppas release model

$$M_t / M_\infty = K.t_n$$

Where, M_t / M_∞ = fraction of drug release,
K = release constant, t = release time,
n = Diffusion exponent for the drug release that is dependent on the slop of the matrix dosage forms.

CONCLUSION

Proniosomes are water soluble carrier particles that are coated with surfactant and can be hydrated to form a niosomal dispersion immediately before use on brief agitation in hot aqueous media. Compared to liposome and niosome suspension, proniosome represents a significant improvement by eliminating physical stability problems, such as aggregation or fusion of vesicles and leaking of entrapped drug's during long term storage. Proniosome are convenient to store, transport and for unit dosing since proniosome have similar release characteristics as conventional niosomes, it may offer improved bioavailability of some drugs with poor solubility controlled release formulations or reduced adverse effects of some drugs. Because proniosome are a dry powder, further processing is possible. To provide convenient unit dosing, the proniosome powder may be processed to make beads, tablets or capsules. The hydration of proniosome powder is much easier than the long shaking process required to hydrate surfactant in the conventional dry film.

However, future experiments should explore the suitability of proniosomes with wide variety of drugs having designed drawbacks for improved and effective intended therapy. So, that proniosomes are represented as promising drug carriers and promising drug delivery module.

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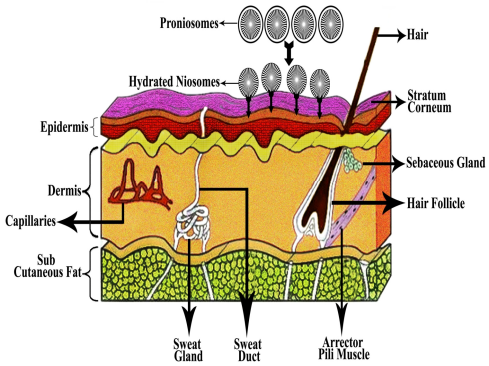

Figure1: Mechanism of drug transport from Proniosome through skin

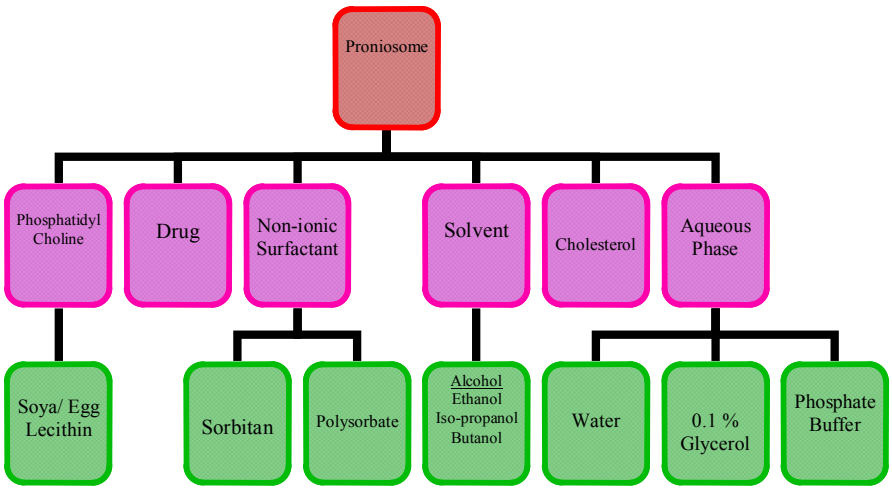

Figure 2: Composition of Proniosome

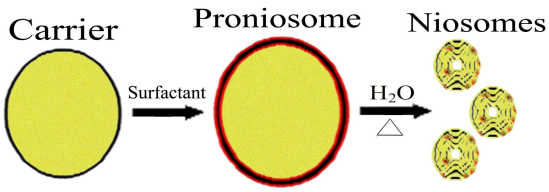

Figure 3: Proniosome conversion to Niosome