Review Article

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A REVIEW ON PRONIOSOMES: A PRO-COLLOIDAL PARTICULATE DRUG CARRIER

P. V. Swamy *, Ch. Sucharitha and G. Surendra Babu
Department of Pharmaceutics, Shri Vishnu College of Pharmacy, Bhimavaram, West Godavari District, Andhra Pradesh, India

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*Corresponding author
E-mail: vspadavala@svcp.edu.in

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ABSTRACT

Colloidal particulate carrier systems are the systems which carry particulates in a nanometre size. These systems are substantially effective for transportation and distribution of variety of loaded drugs to desired site and increase efficacy and decrease toxicity, to provide therapeutic activity in a controlled manner for a prolonged period of time. One such new emerging colloidal systems is proniosomes which has capacity to improve the bioavailability and also permeation of drugs across the *stratum corneum* to provide a controlled release action and reduce toxic effects associated with drugs. These are the dry formulations of water-soluble non-ionic surfactant coated carrier systems which immediately on hydration form niosomes. They have the capacity to overcome the various problems associated with niosomes and liposomes, like instability, transportation, distribution, storage and dosing. They offer versatile drug delivery concept for both hydrophilic and hydrophobic drugs. They have the capacity to deliver drugs effectively through different routes at specific site to achieve controlled release action. This review concentrates on preparation, characterization, components, structure, types, evaluation parameters, proniosomes in drug delivery and targeting, toxicities associated with proniosomes, proniosomes versus niosomes, clinical applications, mechanism of vesicle formation in proniosomes and future trends associated with it. Also, drug delivery via different routes, such as oral, parenteral, topical and transdermal, ocular, vaginal, mucosal, pulmonary and intranasal were discussed.

KEY- WORDS: Nonionic vesicles, targeted drug action, proniosomes, skin permeation, surfactants, transdermal

INTRODUCTION

Novel drug delivery is a method of delivering medication to a patient in a manner of nanomedicine, which plans to employ nanoparticle-mediated drug delivery in order to combat the downfalls of conventional drug delivery. These nanoparticles are loaded with drugs and targeted to specific diseased tissue, thereby avoiding interaction with healthy tissue. [1,2] The conventional drug delivery system includes the absorption of the drug; the targeted release system releases the drug in a dosage form at the site of action. The advantages of the targeted release system are: having a more uniform effect of the drug and reach relative constant zero order kinetics, minimize the undesirable side-effects and reduce the fluctuations in drug levels. [3] The disadvantage of the system is high cost and also low ability to adjust the dosages. To meet these disadvantages novel drug delivery is emerging new delivery systems according to the prevailing trend. Different types of carriers are invented to meet this trend. One of such new carrier is the colloidal particulate drug carrier. Colloidal particulate delivery, also known as vesicular drug delivery system includes liposomes [4], niosomes [5], sphingosomes [6], transfersomes [7,8] etc.

Among all the vesicular systems liposomes are greatly attracted by the formulation scientists due to their special potential to enclose a wide variety of substances and drugs. Liposomes are unilamellar or multi-lamellar spheroid structures composed of phospholipids, assembled into bilayers. It encapsulates both hydrophilic and lipophilic compounds. [9] But there are some physical and chemical instabilities associated with them like aggregation, fusion or leakage upon storage, degradation of phospholipids by hydrolysis and oxidation in a dispersed aqueous system that makes them unfit for oral administration.[10] They have difficulties in sterilization and large-scale production; also, it is difficult to obtain large quantities of sterile product with defined and reproducible properties.

To avoid all these drawbacks of liposomes, niosomes were invented, which can be easily made in the laboratory. Niosomes are the special drug delivery systems that can enhance the bioavailability of encapsulated drug by various mechanisms and provide a therapeutic activity for a longer period of time. These are the lipid vesicles made from safe and biocompatible nonionic surfactants with or without cholesterol in which hydrophilic drugs can be incorporated as an inner core and lipophilic drugs as an outer lipid bilayer. [11,12] Niosomes are different from liposomes by low cost, more stability, entrapment of more substances, ease of handling formulations and storage. However, they suffer from leaking, sedimentation of vesicles, and difficulty in sterilization; so, to overcome these problems, a newer approach was employed which is known as pro-colloidal particulate drug carriers. [13]

The pro- colloidal particulate system has evolved to decrease the stability issues pertaining to liposomes and niosomes. Pro-colloidal particulate systems are composed of water-soluble porous powder as a carrier, which entrap phospholipids/non-ionic surfactants and drugs dissolved in organic solvents. The resulted dry free-flowing granular product which is formed on hydration gives the aqueous colloidal carriers (liposome or niosome). [14] These systems can avoid various problems associated with aqueous colloidal systems. [15]

The new colloidal particulate drug delivery system includes a) pro-liposomes, b) pro-niosomes and c) pro-transfersomes.

Here, in this review, we are concentrating more on proniosomes and their usage in the drug delivery system. Proniosomes are anhydrous free-flowing formulations or liquid crystals with jelly-

like consistency of water-soluble carrier. [16,17] These are coated with suitable niosome-forming surfactants which on hydration form niosomes. Proniosomes, also called 'dry niosomes' can diminish physical and chemical instabilities associated with niosomes, also provide convenience of transportation, distribution, maintain systemic circulation, provide controlled release, enhanced penetration in the targeted areas and reduced the toxic effects. [12]

These systems can encapsulate both hydrophilic and hydrophobic drugs and also not require any specific conditions for storage. Proniosomes provide a novel solution for poorly soluble drugs. [14]

This review will predominantly focus on structure, types, components, preparation, mechanism of vesicle formation in proniosomes, optimization parameters, proniosomes versus niosomes, proniosomes in drug delivery and targeting, toxicities associated with proniosomes, clinical applications and future trends associated with it; drug delivery via different routes, such as oral, parenteral, topical/ transdermal, ocular, vaginal, mucosal, pulmonary and intranasal.

STRUCTURE OF PRONIOSOMES

Proniosomes are microscopic lamellar structures. In aqueous media, they combine anionic surfactant and cholesterol accompanied by hydration. The surfactant molecule guides itself in such a way that the non-ionic surfactant's hydrophilic ends are directed outward, while the hydrophobic ends form the bilayer in the opposite direction.

Both liposomes and proniosomes are bilayer based, although the bilayer of the liposome is phospholipid-based, while bilayer proniosomes are non-ionic surface-active agents. The method of preparation also depends on the formation of the unilamellar or multi-lamellar proniosomes. With hydrophilic ends exposed on the outside and inside of the vesicles, the niosome is made of a surfactant bilayer while the hydrophobic chains (both) face each other inside the bilayer. [18] For this function, hydrophilic as well as hydrophobic drugs are kept in the proniosomes. In the space enclosed in the vesicle, hydrophilic drugs are held, and the hydrophobic drugs embedded within the bilayer (Figure 1).

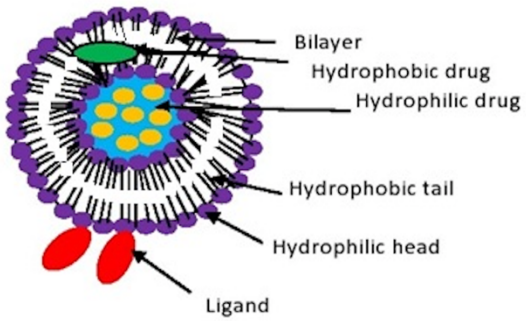

Figure 1: Structure of proniosomes (courtesy-Shutterstock)

Proniosomal gel is found in a gel structure that is transparent, translucent or semisolid. Due to the minimal presence of solvents, the formed proniosomes are in a variety of liquid crystal phases such as lamellar, hexagonal and cubic. The lamellar phase shows surfactant sheets arranged in bilayer, hexagonal phase demonstrating the hexagonally arranged cylindrical compact structure, while the cubic phase consists of curved continuous bilayer lipid extended to three dimensions. [19]

TYPES OF PRONIOSOMES

Proniosomes may be classified as dry granular proniosomes and liquid crystalline proniosomes.

Dry Granular Proniosomes

The Water soluble carrier such as sorbitol and maltodextrin is coated with surfactant. It is essential to prepare colloidal particulate carrier system at a temperature above the transition temperature of the non-ionic surfactant being used in the formulation. These are further categorized as sorbitol based proniosomes and maltodextrin based proniosomes.

Sorbitol based proniosomes is a dry formulation which involves sorbitol as the carrier, which is coated with non-ionic surfactant and is formed as niosomes within minutes by addition of hot water followed by agitation. On the sorbital powder the surfactant mixture prepared in organic solvent is sprayed and the solvent is evaporated. A very thin surfactant coating is formed on the carrier, hydration of coating forms multi-lamellar vesicles as the carrier dissolves.

Maltodextrin based proniosomes has potential application in delivery of hydrophobic and amphiphilic drugs. The particles formed from this preparation have high surface area and high mass ratios of surfactant to carrier, can be formed, which means that the amount of carrier to support surfactant can be easily adjusted. [20,21]

Liquid Crystalline Proniosomes

These act as a reservoir for transdermal drug delivery. The surfactant molecules when kept in contact with water, there are three ways through which lipophilic chains of surfactants can be transformed into a liquid state called lyotrophic liquid crystalline state (neat phase). These three ways are increasing temperature at kraft point (Tc), addition of solvent which dissolves lipids and using both temperature and solvent.

Neat phase or lamellar phase contains bilayer arrangement of sheets over one another intervening aqueous layer in between them. These types of structures give typical patterns under X-ray diffraction and thread-like birefringent structures under polarized microscope. These proniosomes are used in designing transdermal patches. The transdermal patch involves aluminium foil as a backing material along with plastic sheet. The gel is spread on the circular plastic sheet followed by covering with a nylon mesh. [22,23]

COMPONENTS OF PRONIOSOMES

Surfactants: Surfactants are the surface-active agents which have both water-insoluble hydrophobic (lipophilic) and hydrophilic (lipophobic) water-soluble groups, as of amphiphilic in nature. They act as solubilizers, wetting agents, emulsifiers and permeability enhancers. Nonionic surfactants are the most common type of surface-active agent used in preparing proniosomes for their stability, compatibility, and non-toxicity, compared to anionic, amphoteric or cationic. They are chosen for their less toxic, less hemolytic and less irritating to cellular surfaces and maintain the near physiological pH in solution. They have a property useful for enhancing drug absorption in several tissues, i.e., they are P-glycoprotein inhibitors. Alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids are the most commonly used non-ionic amphiphiles for the proniosome formation. Nonionic surfactants comprise both polar and nonpolar segments. Proper surfactant is selected based on three

factors: HLB value, phase-transition temperature (Tc) and critical packing parameter (CPP).

The HLB value of a surfactant plays a key role in controlling drug entrapment efficiency as shown in Table 1. [24,25]

Phase-transition temperature (Tc): Phase is a part of a system which determines physical state, chemical composition and internal structure. The study of surfactant phase helps in the determination of the number, composition and structure of phases formed by surfactant systems at specific conditions like pressure, temperature and system composition by following Gibbs phase rule. By analysis of phase diagrams one can predict the transition temperatures. [26]

As the transition temperature of surfactants increases, increase in the entrapment efficiency and decrease in the permeability takes place. Spans with highest phase transition temperature provide the highest entrapment for the drug and those with low phase transition temperature give low entrapment (Figure 2). The drug leaching from the vesicles can be reduced due to a high-phase transition temperature and low permeability. The Span 60 with a high Tc exhibits the highest entrapment efficiency. [27]

Critical packing parameter (CPP): It is defined as the relationship between the structure of the surfactant (size of hydrophilic head group and chain length of hydrophobic group) in the formation of vesicles. The structure also affects the entrapment efficiency of the drug (Table 2). Estimation of CPP helps in determining the surfactants molecular packing and structure such as micelles, cylindrical micelles, bilayers or inverted micelles etc [28] as shown in Figure 3 and Table 3. The CPP values of non-ionic surfactants in decreasing order is as follows: Span 60 (C18) > Span 40 (C16) > Span 20 (C12) > Span 80 (C18).

Membrane stabilizer: Cholesterol and lecithin are used as membrane stabilizers.

Cholesterol: It is a naturally occurring steroid which suppresses the tendency of surfactants to form aggregates by repulsive steric or electrostatic effects. It enhances the stability of vesicles by transition of the gel state to liquid phase in niosome system. If the cholesterol content is increased, there is increase in entrapment efficiency (%). It is only up to certain limit, further increase results in a significant decrease in entrapment efficiency. When surfactant monomers are assembled into bilayers to form niosomal membranes it accommodates itself as "vesicular cement" in the molecular cavities and this results in the increase of rigidity, decrease of permeability of cholesterol-containing membranes compared to cholesterol-free membranes. Effect of cholesterol concentration is as follows: One of them is mentioned here, entrapment into Span 20 has no significant action, while in Span 80, a significant increase in entrapment is found. It is due to unsaturation present in oleate sidechain.

Lecithin: According to their source of origin, it is named soya lecithin which is from soya beans and egg lecithin which is from egg yolk. The vesicle composed of soya lecithin is of larger size than vesicle composed of egg lecithin. The phosphatidylcholine is a major component of lecithin. It has low solubility in water and can form bilayer sheets, micelles or lamellar structures depending on hydration and temperature. It acts as permeation enhancer and prevents the leakage of drug from vesicles. As cholesterol, lecithin also helps in enhancement of drug entrapment due to high Tc (phase transition temperature). [29] Soya lecithin helps in enhancement of drug entrapment as it contains unsaturated fatty acids, oleic and linoleic acids but the egg lecithin contains the saturated fatty acid. Lecithin provides lesser stability as compared to cholesterol.

Carrier: The commonly used carriers in the preparation of proniosomes are spray-dried lactose, maltodextrin, lactose monohydrate, sorbitol, mannitol, glucose monohydrate and sucrose stearate.

A good carrier should possess the following characteristics: It should be safe and non-toxic, free flowing; possess poor solubility in the loaded mixture solution; possess good water solubility for ease of hydration; should increase the surface area and gives efficient loading; should be flexible and it mainly depends on the ratio of surfactant and other component that is incorporated. [30]

Solvent: The solvent which is selected for the preparation has a great effect on vesicle size and drug permeation rate; so careful selection of solvent is required. If we take different alcohols, the aqueous solubility decreases with the increase of their molecular size and their aqueous solubility in decreasing order is: ethanol > propanol > butanol > isopropanol.

As we see above ethanol and propanol have greater solubility in water which leads to formation of largest size of vesicles, whereas butanol and isopropanol of lower solubility in water form smallest size of vesicles due to branched chain present in them but they are easily formed due to faster phase separation. [31]

Aqueous phase selection and pH maintenance: The main components used in this preparation as aqueous phase are phosphate buffer (pH - 7.4), 0.1% glycerol, and hot water. The pH also plays an important role as it influences the tactness (skin permeation) of proniosomes, thus affecting their entrapment efficiency. [32]

Drug: The drug should be selected based on the following characteristics such as high frequency of administration, short elimination half-life and low aqueous solubility. [33]

METHODS OF PREPARATION

Slurry method [34]

The carrier and surfactant solution are taken in a round-bottom flask and are passed into the rotary flash evaporator which then forms a dry and free-flowing powder which is stored in tightly closed container under refrigeration in a light-resistant container. Due to the uniform coating on carrier, it protects the active ingredients and surfactants from hydrolysis and oxidation. The higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient. Carrier material (e.g., maltodextrin, a polysaccharide) is readily water-soluble, hence it is easy to coat the carrier particles by simply adding surfactant in organic solvents to dry carrier particles. But the method is time-consuming and involves specialized equipment with vacuum and nitrogen gas.

Spray coating method [35]

Surfactant is sprayed onto the carrier. A 100 ml round-bottom flask containing desired amount of carrier, surfactant (diacetyl phosphate) and cholesterol are evaporated by rotary evaporator. Then the round bottomed flask is kept in the rotating flask which is rotated in a water bath under vacuum at 65-70 ^{o}C for 15-20 min. Process is repeated until all the surfactant solution has been applied. The evaporation is continued until the powder becomes completely dried. We can see formation of multi-lamellar

vesicles. The material is further dried in desiccators under vacuum at room temperature overnight. This dry preparation is referred to as "proniosome". This is a simple method and suitable for hydrophobic drug without concerns of instability or susceptibility of active pharmaceutical ingredient to hydrolysis (caution: if the coating of surfactant solution is applied too quickly, the sorbitol particles would degrade, and sample becomes viscous slurry).

Coacervation phase-separation method [36]

In this method drug, lipid, cholesterol, phosphatidylcholine and surfactants are taken in a dry wide-mouthed glass beaker followed by the addition of solvent (caution: only minimum amount of suitable alcohol is taken, or else micelle formation takes place). Surfactant: alcohol: aqueous phase in 5:5:4 w/w/w ratios are selected. These ingredients are mixed well and warmed-over water bath at 60–70 °C for 5 min till surfactants are dissolved completely. Finally, the aqueous phase is added to the mixture and warmed on water bath, limited amount of aqueous phase is added so that gel formation can take place and not the dispersion, for example, diluted glycerol solution, isotonic buffer solution, and phosphate buffer or saline solution. The resultant solution is cooled overnight to obtain proniosomal gel and preserved in the glass tube in dark place. This method is easy and not time consuming. Specialized instrument is not required, and it is specially adopted for gel preparation.

Preparation of Niosomes from Proniosomes by Hydration

The prepared proniosome powder is weighed and filled in vials with screw caps. Water or saline is added at 80 °C and the vials are scrapped. The vials are connected for 2 min to a vortex mixer and agitated to obtain niosomal suspension (Figure 4).

Optimization of proniosomes

For optimization of proniosomes the following parameters are evaluated:

Measurement of angle of repose

This method is used for proniosomal powder and is done by funnel method and cylinder method. [37,38] In the first method, the funnel is fixed at a position and the powder, is poured into it (the outlet orifice of the funnel is 10 cm above the level of surface). The powder is flowed down from the funnel; it forms a cone shape on the surface. Then angle of repose is calculated by measuring the height of the cone and the diameter of its base. In the latter, the powder placed in a cylinder, which has a transparent side. Then, the cylinder is rotated at a fixed speed. The powder moves and rotates within the cylinder to a maximum angle, which is considered the angle of repose.

Surface morphology and particle-size distribution [39-41]

Following are the techniques used for measuring surface morphology and size distribution:

Scanning electron microscopy (SEM): A double-sided tape was affixed on aluminum stubs; powder is spread on it. The stub is placed in a vacuum chamber of scanning electron microscope. The samples are observed for morphological characterization using current induced in the gaseous secondary electron detector. The other detectors like current detector (grounded stage in the ion) or a photomultiplier that detects light emission from the gas (gas luminescence detector) may be used (working pressure: 0.8 torr, acceleration voltage: 30 kV).

Transmission electron microscopy (TEM): It is a technique in which a beam of electrons is transmitted through a specimen to form an image which is formed due to the interaction of the electrons with the sample.

Optical microscopy: The proniosomes after dilution are mounted on glass slides and viewed under a microscope with magnification of x1200. The photomicrograph of the preparation is obtained from the microscope by using a digital single lens reflex (SLR) camera.

Measurement of vesicle size [40,42]

Beckman Coulter submicron size analyzer: The vesicles are diluted about 100 times in the same medium (which is used for their preparation); then vesicle size is measured. The apparatus consists of a He-Ne laser beam of 632.8 nm focused with a minimum power of 5Mw. It consists of a Fourier lens which is used to point at the center of multi-element detector and a small volume of sample holding cell. The samples are stirred with a stirrer before vesicle size is determined.

Malvern mastersizer: The Mastersizer uses the technique of laser diffraction by measuring the intensity of light scattered as a laser beam passes through a dispersed particulate sample. According to the scattered pattern the size of the particles are analyzed.

Entrapment efficiency [43,44]

Dialysis method: The formulation is hydrated to develop the corresponding colloidal particulate carrier system. The process includes addition of 10 ml distilled water with mechanical stirring for 30 min. The colloidal particulate carrier system obtained by removal of drug by centrifugation, the pellet is collected and resuspended in 0.9% saline followed by addition of 1:1 ratio of absolute alcohol: propylene glycol mixture to lyse the vesicles. The resulting colloidal particulate carrier system is subjected to 30 min of bath sonication. Immediately incubated in a dialysis sac and dialysed against 100 ml of 40% v/v ethanol in water for 4 h. The colloidal particulate carrier system obtained after removal of unentrapped drug by dialysis is then resuspended in 30% v/v of PEG-200 and 1ml of 0.1% v/v Triton X- 100 solution is added to solubilize vesicles. This dialysis fluid is selected to ensure sink conditions. The amount of the drug found in the dialysate is taken as a measure of the free drug. The percentage of drug entrapped is calculated.

Centrifugation method: The suspension is taken into dialysis tube attached with osmotic cellulose membrane. The dialysis tube is suspended in 100 ml saline buffer at some pH, which is stirred on magnetic stirrer.

Using the osmotic cellulose membrane, the niosomal suspension and the unentrapped substances are isolated into the medium. Optical density values are noted after 6 h of exhaustive dialysis and the calculation of the trapped drug is carried out. Entrapment efficiency is calculated using the formula:

$$\text{Entrapment efficiency (\%)} = [(C_t - C_f)/ C_t] \times 100$$

Where C_t is the total concentration of the drug and C_f is the concentration of the free drug.

In-vitro release studies

The *in-vitro* studies can be performed by using Franz diffusion cell. Proniosomes are placed in the donor chamber of a Franz

diffusion cell fitted with a cellophane membrane. The proniosomes is then dialyzed against suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable method (UV spectroscopy, HPLC etc.). The maintenance of sink condition is essential. Any one or more of the following mechanisms may be involved in drug release from proniosomes derived from niosomal vesicles: vesicle surface desorption or drug diffusion from bilayer membranes; or combination mechanisms of desorption and diffusion.

Stability studies

Stability studies are carried out by storing the prepared proniosomes for a period of 1 month to 3 months at different temperature conditions such as refrigeration temperature (2-8 °C), room temperature (25 ± 0.5°C) and elevated temperature (45± 0.5°C). Drug content and variation in the average vesicle diameter are periodically monitored. Drug content and difference in the mean diameter of the vesicles are regularly tracked. [45]

Drug content

Proniosomes equivalent to 100 mg are taken in a standard volumetric flask. They are lysed with 50 ml methanol by shaking for 15 min. The solution is diluted to 100 ml with methanol. Then 10 ml of this solution is diluted at a certain pH to 100 ml with saline phosphate buffer. Aliquots are extracted and absorbance is measured at a given wavelength and using the calibration curve further, determined the drug content. [46]

XRD analysis

X-ray diffraction (XRD) is used to evaluate the crystallinity characteristics of the proniosome powders. XRD showed that crystals are detected as sharp and distinctive peaks when evaluated before dissolving the drug in chloroform or even after treating them in the rotary evaporator (simulating the process by which proniosomes were formulated). Hence, using XRD, there was no apparent effect of the organic solvent on the crystallinity characteristics of powder. Furthermore, studies on proniosomes showed no distinctive peaks in the proniosome formulations. [47]

Zeta potential analysis

For the determination of the colloidal properties of the prepared formulations, Zeta potential analysis is performed. The properly diluted niosome dispersion derived from proniosome is calculated using a zeta potential analyzer based on the method of electrophoretic light scattering and laser doppler velocimetry. The temperature is set at 25 ºC. Charge on vesicles and their mean Zeta potential values are derived directly from the measurement with a standard deviation of 5 measurements.

Mechanism of colloidal particulate drug carrier formation

The formation of colloidal particulate drug carrier in proniosomes depends on the ability of a nonionic surfactant to form bilayer colloidal particulate drug carrier rather than micelles. The formation of colloidal particulate drug carrier depends on three factors, viz., HLB values of surfactant, chemical arrangement of the constituent elements and parameter for critical packing (CPP).

Proniosomes have a vesicle shape propensity that is similar to ni osomes. The relationship between the surfactant structure, including the size of the hydrophilic head group and the length of the hydrophobic alkyl chain in the ability to form vesicles, can be described as CPP.

It is defined as: $CPP = V/ l_c \times a_o$

Where, V = volume of the hydrophilic group, lc = length of the critical hydrophobic group and ao = hydrophilic head group area. After measuring CPP, it shows that the surfactant is likely to form vesicles [48] when the value of CPP is between 0.5 and 1.

This means that it is possible that the surfactant may form vesicles at a CPP below 0.5 (indicating a large volume of the hydrophilic head group) is said to give spherical micelles, and a CPP above 1 (indicating a large volume of the hydrophobic group) is said to generate inverted micelles that give precipitation at subsequent stages.

For this reason, all grades of Spans are most frequently used in the proniosomal preparation. Essentially, all Spans have the same group of heads, but a particular chain of alkyls. As per the literature, as the alkyl chain length increases, the capture efficiency of the formulation increases as follows: Span 60 (C18) > Span 40 (C16) > Span 20 (C12) > Span 80 (C18).

Spans 60 and 80 have the same head group, but the alkyl chain varies (Span 80 has an unsaturated alkyl chain). The paraffin chain of Span 80 causes a marked increase in permeability, due to the presence of a double bond, resulting in low trapping power. In the formulation, the addition of cholesterol suppresses the propensity of surfactants to form aggregates and also offers stability to the bilayer membranes by increasing the vesicle's gel-liquid transfer temperature, as well as attributing higher HLB and lower essential packaging parameters. [49]

Proniosomes versus niosomes

Vesicular systems have been used as drug delivery carriers for several purposes for decades, such as targeted delivery of drugs, enhanced transport of drugs via various biological barriers and controlled release of drugs. Systems of vesicular drug delivery include liposomes, niosomes, ethosomes, transfersomes and others.

Such systems are comparable to traditional liposomes, but the structure and functions differ. Liposomes and niosomes have different types of applications in drug distribution but they encountered a lot of demerits, such as instability due to degradation and accumulation of phospholipids, fusion and drug leakage. Proniosomes have the ability to solve these disadvantages since they can be sterilised, kept at room temperature and can be immediately hydrated before administration to form niosomal dispersion. Proniosome powders have major benefits and are often favoured as the drug properties are altered by lyophilization over lyophilized powders. The superiority of proniosomes over niosomes has been stated by several published studies (Table 4).

A comparative analysis performed on niosome and proniosome stability studies showed that proniosomes can be stored effectively at room temperature and that the drug leakage from the proniosome vesicles was reduced, which is the main concern when stored at room temperature with niosomes.

Similarly, the safety of proniosomes can be seen by the evaluation of tenoxicam-containing proniosomal formulations for three months. The results of stability studies showed higher capture efficiency and retention and no substantial change was observed in mean particle size over a period of 90 days compared to newly

prepared sucrose stearate niosome. In addition, as opposed to niosomes, a proniosomal gel emerged as a propitious device to deliver estradiol effectively via the transdermal route with improved skin permeability. The increased estradiol permeation through the skin is due to the fact that proniosomes contain nonionic surfactants and lecithin that has penetration-enhancing properties. [50-52]

CLINICAL APPLICATIONS

Anti-neoplastic Treatment

Serious side effects are caused by most anti-neoplastic medications. Niosomes will alter the metabolism and extend the drug's circulation and half-life, thus reducing the drug's side-effects. Doxorubicin and methotrexate niosomal trapping (in two different studies) showed beneficial effects over untrapped drugs, such as decreased tumour proliferation rate and increased plasma levels followed by slower removal.

Niosome-Utilizing Transdermal Drug Delivery Systems

One of the most beneficial features of niosomes is that they significantly facilitate drug absorption through the skin. The delivery of transdermal drugs using niosomal technology is commonly used in cosmetics; it was also one of the niosomes' first applications. The topical use of niosome trapped antibiotics is done to treat acne. Relative to untrapped medications, the penetration of the drugs into the skin is dramatically increased. [53]

Transdermal vaccines using niosomal technology are also being examined recently. An analysis performed by P.N. Gupta et al., [54] showed that niosomes (along with liposomes and transfersomes) can be used with tetanus toxoid for topical immunisation. The current technology in niosomes, however, makes only a poor immune response, and thus further research in this field needs to be done.

Application in cardiology

For the treatment of hypertension, proniosomes are used as carriers for the transdermal delivery of captopril. The study shows that prolonged release of the drug in the body is caused by the proniosomal system. Sorbitan esters, cholesterol and lecithin are used to encapsulate the compound.

Therapy of hormones

Study was done on the proniosome-based transdermal delivery of the emergency contraceptive levonorgestrel. The composition of the niosome was a compact fluid crystalline hybrid. Particle size, encapsulation performance, stability tests, *in vivo* and *in vitro* studies were conducted in the device. A bioassay was also performed for progestational activity. It included endometrial assay and blockade of corpora luteal production.

Application in diabetes

The furosemide proniosome skin permeation study was performed using Span, soy lecithin, diacetyl phosphate and cholesterol. All results indicate that the proniosomes function as non-invasive furosemide delivery.

Delivery of drugs with peptides

The delivery of oral peptide drugs has the downside of bypassing the enzymes that would break down the peptide and protein bonds. To successfully protect the peptides from gastrointestinal peptide degradation, niosomes have been used. Oral delivery of the vasopressin derivative trapped in niosomes showed that drug trapping greatly enhanced the peptide's stability. [55]

Uses in immune response research

Because of their immunological selectivity, low toxicity and greater stability, the immune response was studied using niosomes. Niosomes and proniosomes are used to study the essence of the antigens-provoked immune response.

Niosomes as haemoglobin carriers

Blood has several protein carriers present in it. Niosomes can be used in the blood as carriers for haemoglobin. The niosomal or proniosomal vesicle is oxygen-permeable and therefore functions as a haemoglobin carrier in patients.

Drug Targeting

Their ability to target drugs is one of the most valuable aspects of niosomes. To target drugs to the reticulo-endothelial system, niosomes can be used. Niosome vesicles are preferentially taken up by the reticulo-endothelial system (RES). Circulating serum factors called opsonins regulate the absorption of niosomes. These opsonins are identified for clearance by the niosome. Such drug localization is used to treat tumours in animals known to metastasize to the spleen of the liver. [12]

It is also possible to use this translation of drugs to treat parasitic liver infections. It is also possible to use niosomes to target drugs to organs other than RES. To attack particular organs, a carrier mechanism (such as antibodies) may be added to niosomes (as immunoglobulin attaches readily to the lipid surface of the niosome). Many cells also have the intrinsic ability to recognise and bind particular determinants of carbohydrates, and niosomes can exploit this to direct carrier systems to particular cells.

Sustained Release

After the liver cells take up niosomes, Azmin et al., [56] suggested the role of the liver as a depot for methotrexate. Sustained release action of niosomes can be added to medicines with a low therapeutic index and low aqueous solubility, since niosomal encapsulation could be used to retain them in circulation.

Localized Drug Action

Localized drug activity increases the effectiveness of the drug's efficacy and simultaneously decreases its systemic toxic effects, e.g., mononuclear cells take up antimonial encapsulated in niosomes, resulting in drug localization, increased potency and thereby decreased both the dose and toxicity. The advancement of niosomal drug delivery technology is still at an early stage, but in cancer chemotherapy and anti-leishmanial therapy, the type of drug delivery system has shown promise.

Patents on Proniosomes: A number of patents on proniosomal/niosomal formulations have been granted (Table 5). [57-61]

Toxicities

It is inferred from the above discussion that the protection profile of proniosomes is very good due to the healthy and biocompatible materials used to make them. While surfactants are expected to demonstrate toxicities when used for the production of drug delivery systems, there are however, practically inadequate data on the toxicities associated with proniosomes.

Proniosomes, when given via oral and parenteral routes, do not produce any signs of toxicity. The toxicity of lornoxicam (NSAID) is proportional to the dosage when administered at the target site of action. Oro-dental mucoadhesive proniosomal gel is a favourable solution that increases the protection of lornoxicam in dental applications. Ocular irritancy screening for proniosomes of lomefloxacin had been shown to have elevated ocular tolerability and do not cause redness in the eye and inflammation. Another study showed that nonionic surfactants can harm the corneal and conjunctival epithelium and cause ocular irritation, redness and discharge, whereas common excipients used in non-ionic surfactant vesicles (NSVs), such as Span 60 and cholesterol have been reported to be safe and do not produce any ocular toxic signs.

Non-ionic surfactant vesicles like proniosomes are therefore healthy and do not contain any ciliotoxicity and cytotoxicity, as shown in a study to test the safety of topical delivery of NSVs. For the safety evaluation of intranasal formulations, the ciliotoxicity model is used, while the cytotoxicity model is used for the distribution of skin. Both models have shown that NSVs are healthy because of their physicochemical properties in all respects. [62,63]

Table 1: HLB values and their corresponding entrapment efficiencies

HLB Value	Entrapment efficiency
Between 4 & 8	Good
8.6	Highest
14-17	Not suitable for non-ionic surfactant
> 6	Cholesterol must be added to the surfactant in order to form a bilayered vesicle

Table 2: Surfactants and their corresponding entrapment efficiencies

Surfactants	Entrapment Efficiency
Non-Ionic Surfactants	Higher entrapment efficiency
Stearyl (C18) chains	
Lauryl (C12) chains	Lower than stearyl chains
Tweens+ cholesterol (1:1)	Highest entrapment efficiency of water-soluble drugs.

Table 3: Critical packing parameter (CPP) values and their micelles formation

CPP	Surfactants formation
0.5 and 1	Good micelles formation
below 0.5	Give spherical micelles
above 1	Produce inverted micelles

Table 4: Some of the drugs with their route, effect and composition

Drug	Category, composition, route of administration and effect/merits
Vinpocetine	Anti-epileptic drug, Span60/sorbitol/cholesterol, oral route, improved bioavailability and GI absorption
Flurbiprofen	NSAID, Span 80,Span 60/sorbitol/cholesterol, parenteral and transdermal route, sustained anti-inflammatory activity, reduce dosing frequency, improve solubility and permeation
Terconazole	Anti-fungal drug, Span 60/lecithin/cholesterol, vaginal route, enhanced mucoadhesive properties, high drug output and fine particle fraction
Doxycycline HCl and metronidazole	Antibiotic, Span 60/maltodextrin/cholesterol, oral route, improved combination therapy and patient compliance
Simvastatin	HMG-COA reductase inhibitors, Tween 20/ lecithin, transdermal route, enhanced bioavailability and hypocholesterolemic effect
Benzocaine	Local anaesthetic, Span 60/ cholesterol, oral mucosal and dental route, improved local anaesthesia by controlled release
Valsartan	Anti-hypertensive, Span 60/maltodextrin/cholesterol, oral route, improved oral bioavailability and enhanced permeation
Lacidipine	Diuretic, Cremophor RH 40/ cholesterol/soya lecithin, transdermal route, improved transdermal delivery, absorption and permeation
Risperidone	Antipsychotics, Span 60/cholesterol/ phospholipid G90, transdermal route, increased skin permeability and bioavailability
Mefenamic acid	NSAID, Span 60/soya lecithin/cholesterol, transdermal route, improved transdermal delivery and anti-inflammatory activity
Pioglitazone	Antidiabetic, Span 60/maltodextrin/cholesterol, oral route, improved hypoglycaemic effects by controlled release of drug
Cromolyn sodium	Mast cell stabilizers, sucrose stearate/cholesterol/stearylamine, pulmonary route controlled drug release and improve aerosolization
Nateglinide	Antidiabetic, Span 60/maltodextrin/cholesterol, oral route, improved oral bioavailability
Tenoxicam	NSAID, Tween 20/ cholesterol, transdermal route, improved patient compliance and drug safety
Levonorgestrel	Contraceptive agent, Span 20/40/60/80/ cholesterol/soya lecithin, trans-dermal route, bearing levonorgestrel results in the inhibition of formation of corpora lutea, which is the consequence of inhibition of LH
Captopril	Anti-hypertensive, Span 20/40/60/80/ cholesterol/soya lecithin, trans-dermal route, effective means of delivering the drug through the oral route
Estradiol	Female hormone, Span/Tween/lecithin/cholesterol, transdermal route, modulated drug transfer across skin.

Table 5: Some of the patents and inventors

Patent No./Year	Inventors	Composition/ Nature of Patent	References
US 4830857A (1989)	RM. Handjani, A. Ribier, G. Vanlerberghe, A. Zabotto, J. Griat	Cosmetic and pharmaceutical compositions.	57
US 6051250 A (2000)	A. Ribier, JT. Simonnet.	Composition for topical application containing stabilized niosomal vesicles	58
US 06576625B2 (2003)	A. Singh, R. Jain	Targeted vesicles constructions for cytoprotection and treatment of *H.Pyroli* infections.	59
US 06951655B2 (2005)	Y. Cho, K. H. Lee	Pro-micelle pharmaceutical compositions.	60
WO/2010/12346 (2010)	Madhavan N, Eva-Kathrin S, Madanagopal K	Vesicular Systems and Uses	61

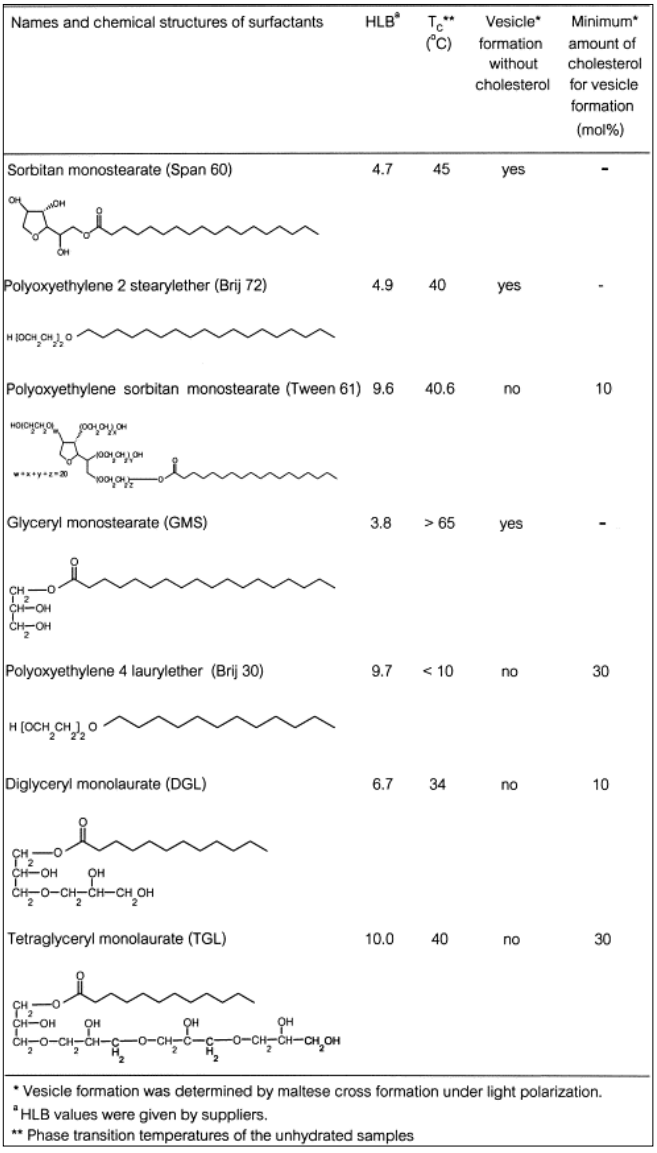

Figure 2: Vesicle formation ability, HLB values, phase transition temperatures of various non-ionic surfactants (courtesy-Shutterstock)

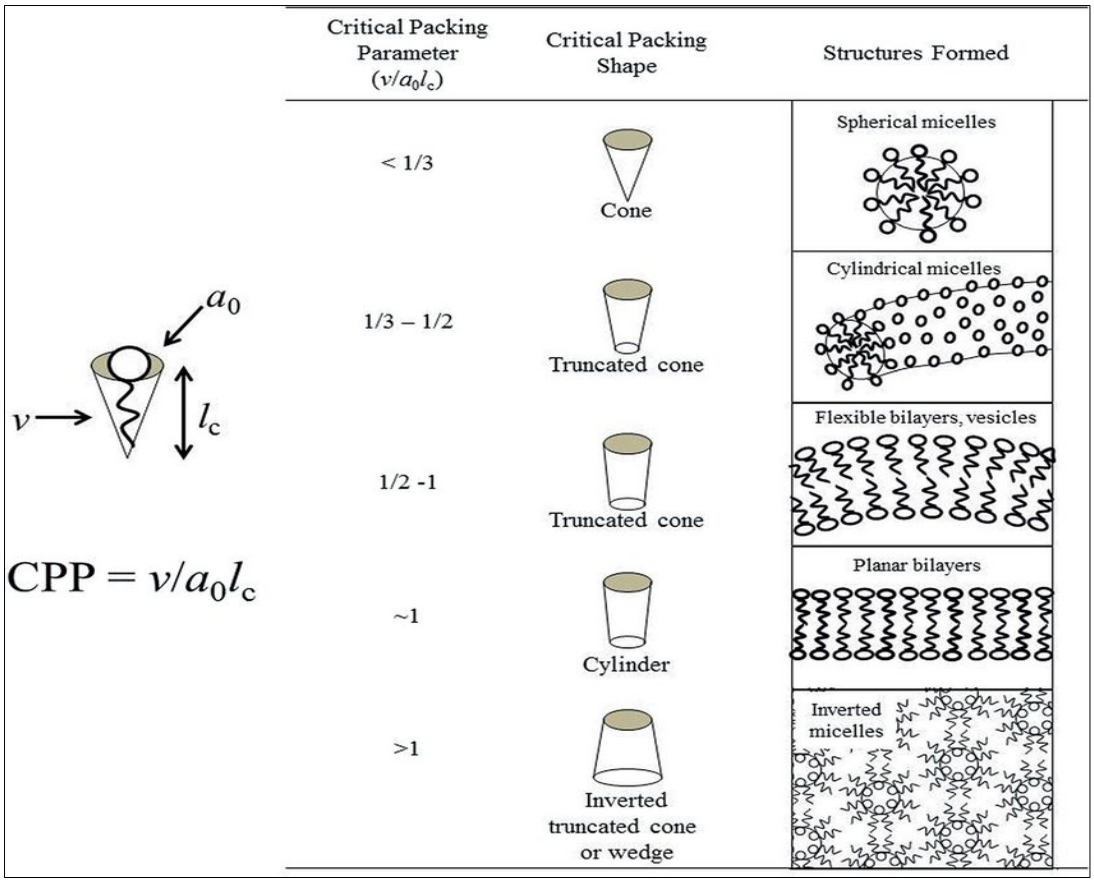

Figure 3: Critical packing parameter values and their structures (v = the hydrophilic group volume, l_c = critical hydrophobic group length and a_o = area of the hydrophilic head group) (courtesy-Shutterstock)

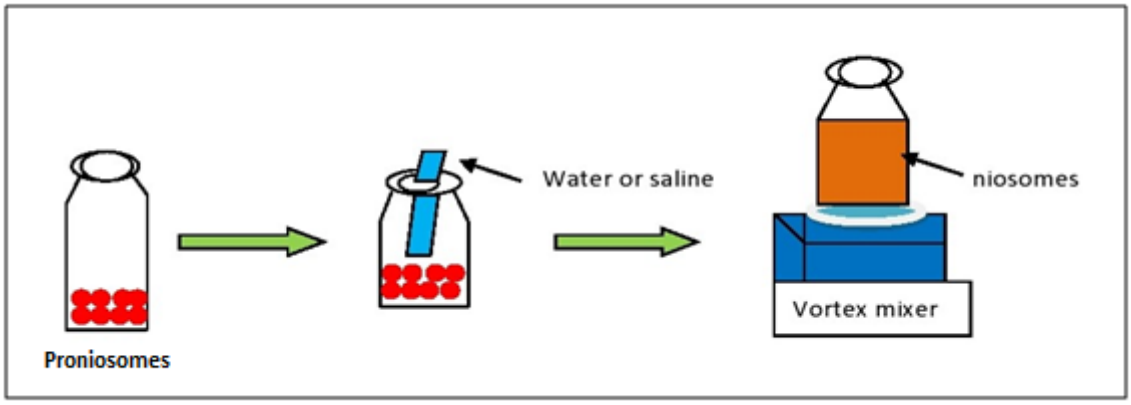

Figure 4: Formation of niosomes from proniosomes (courtesy-Shutterstock)

CONCLUSION

Proniosomes are promising transdermal drug delivery systems with their effectiveness based on their composition. Proper selection of the components can lead to better utilisation of such formulations.

Proniosomes are a flexible method for drug delivery compared with other drug delivery carriers, such as liposomes and niosomes; they have a variety of benefits. Proniosomes are the ones that are dry formulations which form niosomes promptly upon hydration. In terms of stability, niosomes developed from proniosomal technology are superior to conventional niosomes and the hydration of dry proniosomes is extremely simple than the extensive shaking process involved in the standard method of film hydration.

They have the potential to mitigate class II and IV drug solubility and permeability problems and have scalable properties and unit dosage forms, including tablets, beads and capsules can be developed from dry powder proniosomes.

They further benefit from transportation, distribution, storage and dosing. Extensive research on proniosomes has revealed their efficacy in drug delivery and targeting. Proniosomes are an appropriate carrier system for delivering a wide range of medicines through various routes, such as oral, parenteral, dermal, transdermal, ocular, vaginal, pulmonary mucosal and nasal routes efficiently. Proniosomes are employed extensively in oral and transdermal delivery of a broad range of medications. They are used mainly to enhance bioavailability and absorption from the gastrointestinal tract.

Moreover in transdermal delivery, they have a promising role; permeation enhancing properties, non-toxicity and opioid release modulation properties due to their penetration; although they received considerable attention in mucosal drug delivery.

In the field of pharmaceutical sciences, they present new aspects for other active drug agents, like anticancer drugs, narcotics, vaccines and genes.

Colloidal particulate drug carrier systems of non-ionic surfactants are a modern and novel method. These are effective drug delivery strategy. They have a membrane, composed primarily of non-ionic surfactants and cholesterol. There is normally a buffer solution in the enclosed interior at appropriate pH. Such formulations are becoming valuable for different delivery methods/ dosage types. They can be prepared by different approaches and depending on drug's properties, sum of cholesterol and form of surfactants. They do not need the special conditions of storage as liposomes. From administration point of view, proniosomes are an efficient drug targeting method and can provide better therapy than traditional drug delivery systems.

FUTURE PERSPECTIVES

Proniosomes are promising drug carriers for the future. These systems have been found to be more stable during sterilization and storage than niosomes. Proniosomes are thought to be better candidates of drug delivery as compared to liposomes and niosomes due to various factors like cost, stability etc. The use of proniosomal carrier results in delivery of high concentration of active agent(s), regulated by composition and their physical characteristics. Dry powder form of proniosomes makes them suitable for preparing unit dosage forms such as tablets, capsules and beads. There is lot of scope to investigate new carrier material for preparation of proniosomes and their potential remains to be investigated to the full extent.

New aspects of proniosome related niosomes have been introduced in pharmaceutical science over the last few decades, and the most approved by research scientists to target particular organs or tissues for better therapeutic effects have been introduced. The modern term that opens the door for pharmaceutical research is proniosomes. For potential use in the manufacture of proniosomes, various new carrier materials can be studied that are biocompatible and suitable for proniosomes.

In addition, proniosomes among vesicular systems are becoming promising drug delivery carriers, but they need to be investigated in the field of nutraceuticals, herbal compounds and cosmetics. As peptides undergo enzymatic degradation when administered by oral route due to the presence of enzymes and acidic environment, proniosomes may prove to be promising carriers for the delivery of peptides. Higher peptide stability could be achieved by proniosomal technology. In addition, they are convenient for vaccines and antigens to be administered and could work better in introducing the antigens to cells for antigen detection.

In addition, proniosomal carriers can efficiently distribute medications that have pronounced adverse effects to improve their therapeutic efficacy by minimizing side-effects. Proniosomes might also be used to carry haemoglobin to the blood since they are oxygen-permeable and can also be used effectively as a carrier for anemia treatment. Therefore, comprehensive research is needed to explore them through the creation of pilot plant scale-up studies in industrial establishments. Nevertheless, there are many problems that need to be analyzed in the industrial system and show their suitability for the distribution of a wide variety of medicines and natural products.

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