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# PRONIOSOMAL GEL: A NOVEL THERAPEUTIC TOPICAL / TRANSDERMAL DRUG DELIVERY SYSTEM

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**Keywords:**

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**ABSTRACT:** Today, Nanotechnology is widely used for leading new dosage forms. Vesicular drug delivery system is expanding as one of advanced nanotechnology. Delivery of drugs using colloidal particulate carriers and liquid crystalline compact niosomal hybrid such as niosome and proniosomes has peculiar advantages over conventional dosage forms. Proniosomes is a dry formulation using suitable carrier coated with non-ionic surfactant and can be converted into niosome immediately before use by hydration. These vesicles are amphiphilic molecules having capability of entrapping both hydrophilic and hydrophobic drugs. Vesicular systems are lamellar structures composed of amphiphilic molecules surrounded by an aqueous environment. The non-ionic surfactants are preferred in the proniosomes preparation than cationic, anionic, and ampholytic surfactants because they have the ability to increase solubility which helps in increasing solubility and bioavailability of poorly water soluble drugs. The versatile vesicular drug delivery through the transdermal route is advantageous due to the vesicles tendency to attach and adhere to the cell surface and causes increased permeation rate. However, the major pathways for drug permeation in the tissues is through sweat glands, stratum corneum layer, and hair follicle associated with sebaceous glands. Primarily, proniosomal gel is a compact semi-solid liquid crystalline (gel) product of non-ionic surfactants easily prepared on dissolving the surfactant in a minimal amount of acceptable solvent and the least amount of aqueous phase. This article provides an overview of the formulation, evaluation, and application of proniosomal gel as a carrier for topical drug delivery.

**INTRODUCTION:** The transdermal route is acceptably used nowadays as it is appropriate over the conventional dosage forms. The transdermal route bypasses the GI tract; hence the gastric irritation is avoided, reduces the number of doses, improved patient compliance, and improved bioavailability, and can preserve suitable plasma concentration.

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In recent years it has been shown that the skin is a useful route for drug delivery to the system circulation. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation *via* the skin. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to the desired site of action with little or no interaction with non-target tissue [1].

In niosome, the vesicles forming amphiphile are a non-ionic surfactant such as Span-60, Span 40, which is usually stabilized by the addition of cholesterol and a small amount of anionic surfactant such as dicetyl phosphate [2-3].

The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L'Oreal. Proniosomes are non-ionic-based surfactant vesicles that may be hydrated instantly before use to yield aqueous niosome dispersions. Proniosomes are currently used to enhance drug delivery in addition to conventional niosomes. They are converted into niosomes respectively upon simple hydration or by the hydration of skin itself after application [4].

**Proniosomes:** Proniosomes are vesicular systems in which the vesicles are made up of non-ionic-based surfactants, cholesterol, and other additives. Semisolid liquid crystal gel (proniosomes) ready by dissolving the surfactant in a minimal quantity of an acceptable solvent, namely ethanol, and then hydration with the slightest amount of water to form a gel. These structures are liquid crystalline dense niosomes hybrids that can be converted into niosomes upon hydration or used as such in the topical/transdermal applications. Proniosomal gels are generally present in transparent, translucent, or white semisolid gel texture, which makes them physically stable throughout storage and transport [5]. The surfactant molecule directs themselves such that the hydrophilic ends of the non-ionic surfactant face outward, while the hydrophobic ends are in the opposite direction to form the bilayer [6].

Proniosomes are dry formulations of the surfactant-coated carrier, which can be measured out as needed and rehydrated by brief agitation in hot water. These "proniosomes" minimize problems of niosomes such as physical stability such as aggregation, fusion, and leaking and provided additional convenience in transportation, distribution, storage, and dosing. The stability of dry proniosomes is expected to be more stable than a pre-manufactured niosomal formulation. In release studies, proniosomes appear to be equivalent to conventional niosomes. Size distributions of proniosome- derived niosomes are somewhat better than those of conventional niosomes, so the release performance in more critical cases turns out to be superior. Proniosomes are dry powder, which makes further processing and packaging possible. The powder form provides optimal flexibility; unit dosing, in which the proniosome powder is provided in the capsule, could be beneficial. This Proniosomal drug delivery has attracted towards transdermal drug delivery because surfactants themselves act as penetration enhancers and are biodegradable, non-toxic, amphiphilic, possess the property of encapsulation, and they can entrap both hydrophilic and lipophilic drugs [7] as shown in **Fig. 1.** Both phospholipids and nonionic surfactants act as penetration enhancers. The ratio between the nonionic surfactant and cholesterol could affect on release characteristics as well as the entrapment efficiency of the incorporated drugs [8].

A proniosome formulation based on malt dextrin was recently developed that has potential applications in the delivery of hydrophobic or amphiphilic drugs. The better of these formulations used a hollow particle with an exceptionally high surface area. The principal advantage with this formulation was the amount of carrier required to support the surfactant could be easily adjusted, and proniosomes with very high mass ratios of surfactant to carrier could be prepared. Because of the easy method of production of proniosomes using the malt dextrin by slurry method, hydration of surfactant from proniosomes of a wide range of compositions can be studied [9].

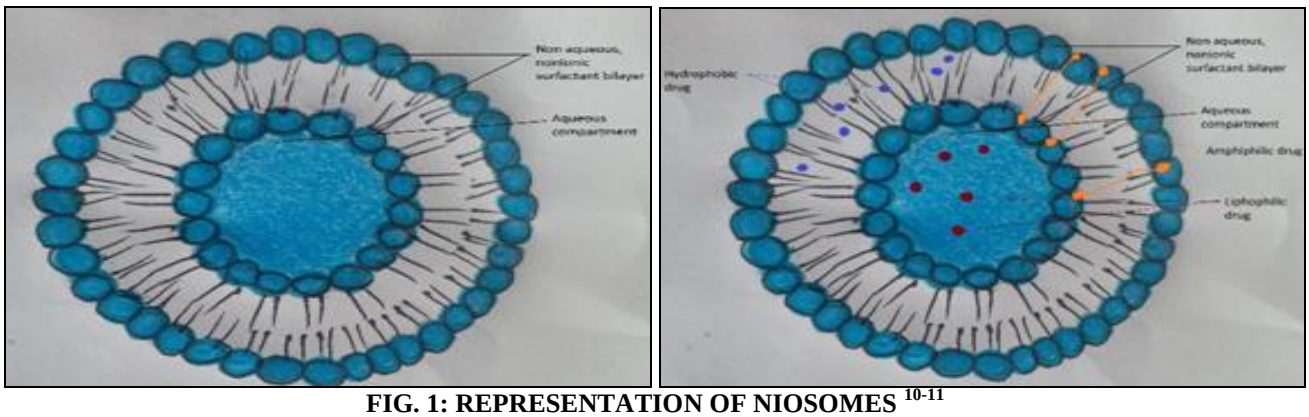


**FIG. 1: REPRESENTATION OF NIOSOMES [10-11]**

**Structure of Proniosomes:** Proniosomes are present in transparent, translucent, or a semisolid gel structure. Because of limited solvent presence, formed proniosomes are a mixture of phases of liquid crystal-like lamellar, hexagonal, and cubic, as shown in **Fig. 2**. Here, the lamellar phase showed sheets of surfactant arranged in a bilayer, hexagonal phase showed the compact cylindrical structure arranged in a hexagonal manner, whereas the cubic phase consists of a curved continuous lipid bilayer extending to three dimensions. While formulating this gel, in the beginning, a less viscous composition is formed in some cases, but the addition of water leads to interaction between water and a polar group of surfactant, resulting in swelling of bilayers. If the amount of solvent is increased further, then a spherical structure is formed, *i.e.*, multilamellar, multi-vesicular. Complete hydration leads to the formation of 'niosomes' [12].

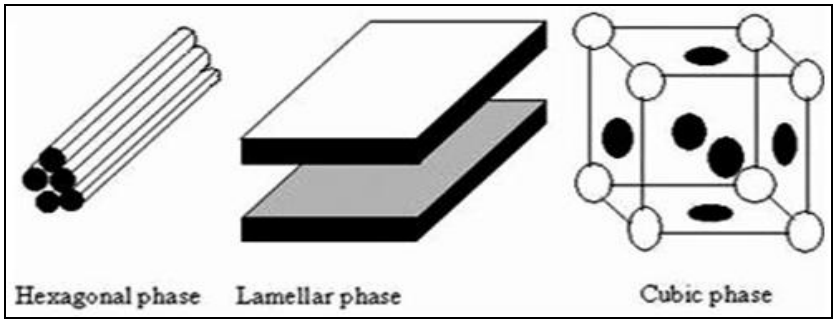


**FIG. 2: SCHEMATIC REPRESENTATION OF VARIOUS LIQUID CRYSTALLINE PHASES**

**Advantages of Proniosomal Gel: [13, 14]**

- Proniosomes have the potential for entrapping a wide range of active compounds.
- Easy for transportation, sterilization, distribution, storage, and dosing.
- Degradation by hydrolysis or oxidation problems is avoided.
- No special conditions required for storage and handling.
- Sedimentation, aggregation or leakage is not seen.
- Uses acceptable solvents in minimum quantity in the preparation.
- It shows controlled targeted and sustained release of drugs due to depot formation[15]

**Suitability of Drug to the Proniosomes: [16]**

Different categories of drugs selections for proniosomes formation based upon the below-mentioned points;

- ✓ Low Aqueous solubility drugs.
- ✓ High dosage frequency drugs.
- ✓ Low half-life.
- ✓ Controlled drug delivery suitable drugs.
- ✓ Higher adverse drug reactions drugs.

**Composition of Proniosomes: [8, 13]**

**1. Surfactants:** Selection of surfactant should be done on the basis of HLB value. As Hydrophilic Lipophilic Balance (HLB) is a good indicator of the vesicle forming ability of any surfactant, HLB number in between 4 and 8 was found to be compatible with vesicle formation. It is also reported that the hydrophilic surfactant owing to high aqueous solubility on hydration, does not reach a state of concentrated systems in order to allow free hydrated units to existing aggregates and coalesced to form lamellar structure. The water-soluble detergent polysorbate 20 also forms niosomes in the presence of cholesterol. This is despite the fact that the HLB number of this compound is 16.7 degrees of entrapment is affected by the HLB of a surfactant. The transition temperature of surfactants also affects the entrapment of drugs in vesicles. Spans with the highest phase transition temperature provide the highest entrapment for the drug and vice versa. Span 40 and Span 60 produces vesicles of larger size with higher entrapment of drug. The drug leaching from the vesicles is reduced due to high phase transition temperature and low permeability. The high HLB value of Span 40 and 60 results in a reduction in surface free energy, which allows

forming vesicles of larger size hence large area exposed to the dissolution medium and skin. No significant difference is observed in the skin permeation profile of the formulation containing Span 60 and Span 40 due to their higher phase transition temperature that is responsible for their lower permeability. The encapsulation efficiency of Tween is relatively low as compared to Span. The geometry of the vesicle to be formed from surfactants is affected by its structure, which is related to critical packing parameters. On the basis of critical packing parameters of Surfactants can predicate geometry of vesicle to be formed.[17] Critical packing parameters (CPP) can be defined using the following equation,

$$CPP = V / l c \times a^0 \quad \text{----------Equation 1}$$

$$CPP \leq 0.5 \text{ micelles form}$$

$$CPP = 0.5 – 1 \text{ spherical vesicles form}$$

$$CPP = 1 \text{ inverted vesicles form}$$

V = hydrophobic group volume, lc = the critical hydrophobic group length, a0= the area of hydrophilic head group. A CPP value below 0.5 indicates a large contribution from the hydrophilic head group area and is said to give spherical micelles and a CPP of above 1 indicates a large contribution from the hydrophobic group volume should produce inverted micelles [13]. The drug leaching from the vesicles can be reduced due to high phase transition temperature and low permeability. Span 60 is the good surfactant because it has CPP value between 0.5 and 1 [14]. Non-ionic surfactants are used as solubilizers, wetting agents, emulsifiers and permeability enhancers [18]. They (nonionic surfactants) are also strong P-glycoprotein inhibitors, a property useful for enhancing drug absorption and for targeting to specific tissues [19].

**2. Stabilizers:**

**i. Cholesterol:** Cholesterol is an essential component of vesicles. Incorporation of cholesterol influences vesicle stability and permeability. The concentration of cholesterol plays an important role in the entrapment of drugs in vesicles. There are reports that entrapment efficiency increase with increasing cholesterol content and by the usage of span 60, which has higher transition temperature. It was also observed that very high cholesterol content had a lowering effect on drug entrapment to the vesicles.

This could be due to the fact that cholesterol beyond a certain level starts disrupting the regular bi-layered structure leading to loss of drug entrapment [20]. Cholesterol is also known to prevent leakage by abolishing gel to liquid phase transition [21]. It prevents accumulation by the inclusion of molecules that stabilize the system against the formation of an aggregate by repulsive steric or electrostatic effects [22].

**ii. Phosphatidyl Choline:** Phosphatidylcholine is such a major component of lecithin. Phosphatidyl choline has low solubility in water. In an aqueous solution, its phospholipids can form either liposomes, bilayer sheets, micelles or lamellar structures, depending on hydration and temperature. This results in a type of surfactant that is usually classified as amphipathic. They are a major component of biological membranes and can be easily obtained from a variety of readily available sources such as egg yolk or soybeans. Depending upon the Source from which they are obtained they are named egg lecithin and soya lecithin. The incorporation of lecithin in proniosomes is justified as it acts as permeation enhancers. Incorporation of lecithin further enhanced the percent drug entrapment to 96.1% and leads to vesicles of smaller size due to increase in hydrophobicity which results in a reduction of vesicle size. There is probably the formation of more compact, well-organized bi-layers which prevent the leakage of a drug. It is found that vesicles composed of soya lecithin are of larger size than vesicle composed of egg lecithin, possibly due to difference in the intrinsic composition [12].

**3. Carriers:** Maltodextrin is a polysaccharide. It has minimal solubility in organic solvent. Thus it is possible to coat maltodextrin particles by simply adding surfactant in organic solvent. The use of malt dextrin as a carrier in Proniosomes preparation permitted flexibility in the ratio of surfactant and other components which can be incorporated. Coating sorbitol results in solid cake-like mass.[23]

**4. Solvent and Aqueous Phase:** Alcohols have profound effects on vesicle size and drug permeation rate. Different alcohols produce different sized vesicles and thus follow the order.

Ethanol >butanol>isopropanol Ethanol has greater solubility in water and form the highest size of vesicles compared to isopropanol which forms the smallest vesicles due to the branched-chain present. Phosphate buffer pH 7.4, 0.1% glycerol, and hot water is used as an aqueous phase in preparation of proniosomes [20].

**5. Miscellaneous:**

**i. Dicetyl Phosphate (DCP):** Dicetyl phosphate is a charged lipid that induces a negative charge to vesicles. Proniosomal formulation containing DCP in-corporate slightly greater amount of drug as compare to formulation containing surfactant and cholesterol only but much less than those formulation containing egg/soya lecithin. It is also reported that drug release was maximum for the formulation containing DCP perhaps due to the charge present in the DCP containing bi-layers, which is responsible for the increase in the curvature and decrease vesicle size, DCP decreases the entrapment efficiency of the drug into niosomal vesicle.

**ii. Stearyl amine (SA):** Stearyl amine is also a charged lipid used to impart positive charges on niosomal vesicles. It is reported that SA decreases entrapment efficiency.

**iii. Solulan:** Solulan C24 (poly-24 oxyethylene cholesteryl ether) must be added to the formulation to ensure a homogenous formulation devoid of aggregates.

**TABLE 1: INGREDIENTS USED FOR THE PREPARATION OF PRONIOSOMAL GEL [20]**

| S. no. | Ingredients used | Example | Use |
|---|---|---|---|
| 1. | Surfactants (Non-ionic) | Spans 20, 40, 60, 80, 85, Tween 20,40, 60, 80 Brij 30, 52, 56, 58, 72,76 | Act as permeation enhancers. |
| 2 | Stabilizers - Cholesterol | Cholesterol | Give strength to the formulation and prevent leakage. |
| 3 | Stabilizers Lecithin | Lecithin | Forming stable vesicles. Penetration enhancer |
| 4 | Solvent | Ethanol, methanol | For solubilizing drug |
| 5 | Carriers: Maltodextrin | Maltodextrin | Impart flexibility |
| 6 | Sorbitol | Sorbitol | Alters the drug distribution |

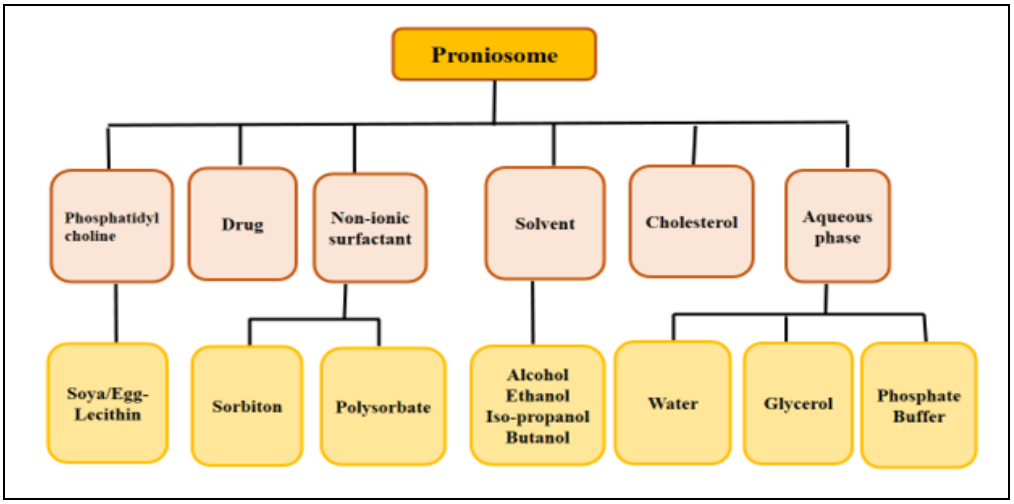


**FIG. 3: COMPOSITION OF PRONIOSOME**

**Strategies for Preparation of Proniosomes:** Proniosomes are the product of non-ionic surfactants easily prepared by dissolving the surfactant in a minimal amount of an acceptable solvent and the least amount of water. Typically, proniosomes may contain various non-ionic surfactants like span 20, 40, 60, 80, and 85, tween 20, 40, 80; lecithin, alcohol (ethanol, methanol, isopropyl alcohol), and chloroform.

The chemical structure of surfactants influences drug entrapment efficiency. Increasing the alkyl chain length is leading to higher entrapment efficiency. It had also been reported that spans having the highest phase transition temperature provide highest entrapment for the drug and vice-versa. The drug can be entrapped into proniosomes composed of tweens; however, the encapsulation efficiency was relatively low as compared to those

composed of spans. Most of the surfactants used to make non-ionic surfactant vesicles have a low aqueous solubility. However, freely soluble non-ionic surfactants such as tween can form the micelles on hydration in the presence of cholesterol. Cholesterol concentration into proniosomal formulations could affect vesicle stability and permeability. In addition, non-ionic surfactant and cholesterol can be combined with lecithin in these preparations.

Formulations containing lecithin increase the entrapment efficiency of drugs compared to a formulation containing cholesterol only. However, the incorporation of lecithin into formulation requires special treatment during preparation and storage, which makes the product less stable and highly expensive. As stated earlier, proniosomes require minimal amount of acceptable solvents like ethanol, methanol, isopropyl alcohol, and chloroform for dissolving surfactants.

**Types of Proniosomes:** [9]

There are two types of proniosomes

- ✓ Dry granular proniosomes
- ✓ Liquid crystalline proniosome

**I. Dry granular Proniosomes:** These involve the coating of the water-soluble carrier such as sorbitol and maltodextrin with surfactant resulting in the formation of a dry formulation in which each water-soluble particle is covered with a thin film of surfactant.

**a) Sorbitol Based Proniosomes:** It is a dry formulation that involves sorbitol as a carrier .these are made by spraying a surfactant mixture prepared in the organic solvent into sorbitol powder and then evaporating the solvent .useful in the case where the active ingredient is susceptible to hydrolysis.

**b) Maltodextrin Based Proniosomes:** These are prepared by the slurry method. Maltodextrin is a polysaccharide easily soluble in water and is used as a carrier material in the formulation, and its morphology is preserved.

Hollow-blown maltodextrin particles are used to increase in gain in surface area. The higher surface area results in thinner surfactant coating, which is suitable for the rehydration process.

**II. Liquid Crystalline Proniosomes:** When surfactant molecules are made in contact with water, there are three ways in which the lipophilic chains of surfactants are being transformed into a disordered liquid state. The three ways are as follows;

1) Increasing temperature at Kraft's point
2) Addition of solvents
3) Using both temperature and solvent

**Formation of Niosomes from Proniosomes:** [23-26]
The niosomes can be prepared from the proniosomes by adding the aqueous phase with the drug to the proniosomes 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

**Action of Proniosomes:** Proniosomes show their action after they are converted to niosome on hydration. The hydration may occur either by the skin or by the addition of aqueous solvents. Proniosomes can entrap both hydrophilic as well as lipophilic drugs.

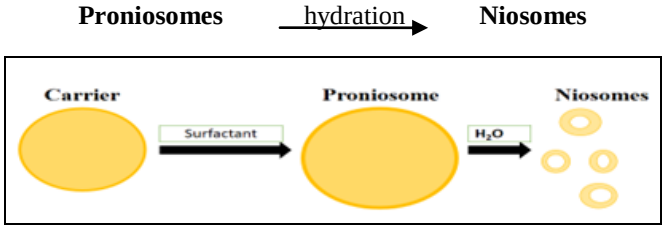


**FIG. 4: FORMATION OF NIOSOMES FROM PRONIOSOME**

**Preparation of Proniosomes:** [23, 24, 27]
**Preparation of Proniosomes:** The proniosomes can be prepared by,

- ➢ Spraying method.
- ➢ Slurry method.
- ➢ Coacervation phase separation method.

**1. Spraying Method:** (Hu and Rhodes *et al.* in 1999) prepared proniosomes by spraying the surfactant in an organic solvent onto sorbitol powder and then evaporating the solvent. Because

the sorbitol carrier is soluble in the organic solvent, it is necessary to repeat the process until the desired surfactant load has been achieved. The surfactant coating on the carrier comes out to be very thin and hydration of this coating allows multilamellar vesicles to form.

**2. Slurry Method:** (Almira.I and Blazek - Walsh *et al*. in 2001) developed slurry method to produce proniosomes using maltodextrin as a carrier. The time required to produce proniosome by this is independent of the ration of surfactant solution to the carrier material. In the slurry method, the entire volume of surfactant solution is added to maltodextrin powder in a rotary evaporator and vacuum applied until the powder appears to be dry and free-flowing. Drug containing proniosome-derived niosomes can be prepared in manner analogous to that used for the conventional niosomes, by adding the drug to the surfactant mixture prior to spraying the solution onto the carrier (sorbitol, maltodextrin) or by addition of the drug to the aqueous solution used to dissolve hydrate the proniosomes.

**3. Coacervation Phase Separation Method:** Accurately weighed or required amount of surfactant, carrier (lecithin), cholesterol, and the 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 have to be heated and after heating all the ingredients should be mixed with a glass rod. To prevent the loss of solvent, the pen end of the glass vial can be covered with a lid. It has to be warmed over a water bath at 60-70 ºC for 5 minutes until the surfactant dissolved completely. The mixture should be allowed to cool down at room temperature till the dispersion gets converted to a proniosomal gel.

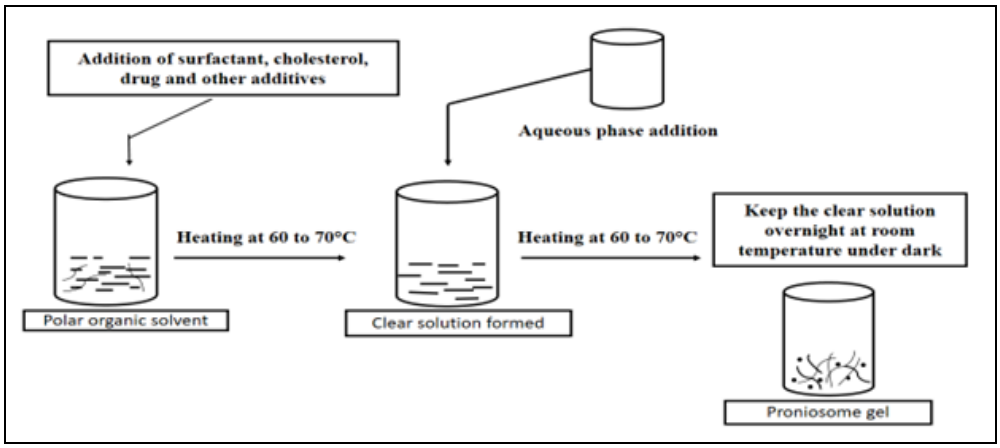


**FIG. 5: COACERVATION PHASE SEPARATION METHOD**

**Percutaneous Drug Absorption:**

**Fick's First Law of Diffusion:** [18] Percutaneous drug absorption can be defined by Fick's first law of diffusion as in Eqn. 1:

$$Dq / dt = Jss = Ks \times D / h \times \Delta Cv \times A$$

Where, dQ / dt = amount of drug diffused per unit time (i.e. drug flux), Jss = drug flux, Ks = partition coefficient, D = diffusion coefficient, h = diffusional path length (thickness of SC), ΔCv = concentration gradient of drug and A = skin surface area treated.

In order to achieve enhanced drug delivery, changes can be made at two basic levels. The first approach - Chemical modifications in drug molecules in order to increase drug flux through the production of derivatives with optimum lipid solubility, but a major setback to this technique is that it seems to be a failure when the candidate is protein or DNA. The second approach - Structural alterations made within the skin by suitable agents or drug carriers. In order to enhance the drug delivery through the transcellular route (a polar pathway) swelling of the intracellular protein matrix, alteration of protein structure within the corneocytes can be attempted. On the other hand, in the case of the intercellular route (lipoidal pathway or the aqueous pathway) of penetration of the drug could be enhanced by altering the crystallinity of the intercellular lipid bilayer through an increase in hydration of the lipid polar head groups. Instead,

the lipid hydrophobic tails could be disordered to pull off the same effect. Amplified drug partitioning could also be facilitated in the aqueous spaces between the lipid bilayers through a local enrichment of enhancer molecules. Finally, drug penetration can also occur through skin appendages such as hair follicles.

**Mechanism of Drug Transport through Skin: [8, 13]** As studies performed on the transdermal/topical application of vesicles have rendered conflicting results. It is still not clear which factors influence the vesicle skin interactions and play an important role in determining the efficiency of drug transport through the skin. But it is clear that Proniosomes should be hydrated to form niosomal vesicles before the drug is released and permeates across the skin. Many scientists proposed different theories/ mechanisms for vesicle skin interaction.

Two types of vesicle skin interactions were observed during in vitro studies using human skin, which may induce various effects on dermal or transdermal drug delivery.

- When vesicles come in contact with stratum corneum aggregate, fuse and adhere to the surface of the cell. It is believed that this type of interaction leads to a high thermodynamic activity gradient of the drug at the interface of the vesicle and stratum corneum, which is the driving force for penetration of the lipophilic drugs across the stratum corneum.

- This type of interaction involves the ultra-structural changes in the intercellular lipid regions of the skin and its deeper layers at a maximum depth of about 10 mm as revealed by Freeze Fracture Electron Microscopy (FFEM) and Small Angle X-ray Scattering (SAXS). In addition to these two, several other mechanisms could explain the ability of vesicles to modulate drug transfer across the skin, including:

- ❖ Nature of drug.
- ❖ The lipid bi-layers of niosomes act as a rate limiting membrane barrier for drugs.
- ❖ Dehydration of vesicles.
- ❖ The vesicles act as penetration enhancers to. Reduce the barrier properties of the skin.
- ❖ Size and composition of vesicles.
- ❖ Biophysical factors.

**TABLE 2: EVALUATION / CHARACTERIZATION OF PRONIOSOMES**

| Parameter | Instrument / Method used |
|---|---|
| Vesicle morphology | Scanning electron microscopy, Laser microscopy |
| Shape and surface morphology | Optical microscopy, Scanning microscopy |
| Angle of repose | Funnel method |
| Encapsulation efficiency | Centrifugation method, Dialysis method |
| *In-vitro* drug release studies | Franz diffusion cell, Dialysis membrane |

**Separation of Unentrapped Drug: [13, 20, 23]** The removal of unentrapped solute from the vesicles can be accomplished by various techniques, which include.

**1. Dialysis:** The aqueous niosomal dispersion is dialyzed in dialysis tubing against a suitable dissolution medium at room temperature. The samples are withdrawn from the medium at suitable time intervals, centrifuged, and analyzed for drug content using a suitable method (U.V. spectroscopy, HPLC, etc.).

**2. Gel Filtration:** The unentrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and eluted with a suitable mobile phase and analyzed with suitable analytical techniques.

**3. Centrifugation:** The proniosome derived niosomal suspension is centrifuged, and the supernatant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from the unentrapped drug.

**Measurement of Angle of Repose:** The angle of repose of dry proniosomes powder was measured by a funnel method (Lieberman *et al.* 1990). The proniosomes powder was poured into a funnel which was fixed at a position so that the 13 mm outlet orifice of the funnel is 5 cm above a level black surface. The powder flows down from the funnel to form a cone on the surface, and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

**Scanning Electron Microscopy:** Particle size of proniosomes is a very important characteristic. The

surface morphology (roundness, smoothness and formation of aggregates) and the size distribution of proniosomes were studied by Scanning Electron Microscopy (SEM). Proniosomes were sprinkled onto the double-sided tape that was affixed on aluminum stubs. The aluminum stub was placed in the vacuum chamber of a scanning electron microscope (XL 30 ESEM with EDAX, Philips, Netherlands). The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).

**Optical Microscopy:** The niosomes were mounted on glass slides and viewed under a microscope (Medilux- 207RII, Kyowa-Getner, and Ambala, India) with a magnification of 1200X for morphological observation after suitable dilution. The photomicrograph of the preparation was also obtained from the microscope by using a digital SLR camera.

**Measurement of Vesicle size:** The vesicle dispersions were diluted about 100 times in the same medium used for their preparation. Vesicle size was measured on a particle size analyzer (Laser diffraction particle size analyzer, Sympatec, Germany). The apparatus consists of a He-Ne laser beam of 632.8 nm focused with a minimum power of 5 mW using a Fourier lens [R-5] to a point at the centre of multielement detector and a small volume sample holding cell (Su cell). The sample was stirred using a stirrer before determining the vesicle size. Hu C. and Rhodes 7 in 1999 reported that the average particle size of proniosomes derived niosomes is approximately 6 μm while that of conventional niosomes is about 14 μm.

**Entrapment Efficiency:** Entrapment efficiency of the niosomal dispersion can be done by separating the unentrapped drug by dialysis, centrifugation or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug.

***In-vitro* Methods for the Assessment of Drug Release from Proniosomes:** *In-vitro* drug release can be done by (Chen DB *et al.*, 2001).

- Dialysis tubing
- Reverse dialysis
- Franz diffusion cell

**Dialysis Tubing:** Dialysis tubing Muller *et al.* 35 in 2002 studied in-vitro drug release could be achieved by using dialysis tubing. The proniosomes is placed in prewashed dialysis tubing, which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged, and analyzed for drug content using a suitable method (U. V. spectroscopy, HPLC, *etc*.). The maintenance of sink condition is essential.

**Reverse Dialysis:** In this technique, a number of small dialysis containing 1 ml of dissolution medium are placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method; however, the rapid release cannot be quantified using this method.

**Franz Diffusion Cell:** The *in-vitro* diffusion 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 are then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals and analyzed for drug content using a suitable method (U.V spectroscopy, HPLC, *etc*.).The maintenance of sink condition is essential.

**Drug Release Kinetic Data Analysis:** The release data obtained from various formulations were studied further for their fitness of data in different kinetic models like Zero-order, Higuchi's, and peppa's. In order to understand the kinetic and mechanism of drug release, the result of in-vitro drug release study of Niosome was fitted with a various kinetic equation like zero-order (Equation 1) as cumulative % release vs. time, higuchi's model (Equation 2) as cumulative % drug release vs. square root of time. r and k values were calculated for the linear curve obtained by regression analysis of the above plots

$$C = k0t \text{ …..(1)}$$

Where k0 is the zero-order rate constant expressed in units of concentration/time and t is time in hours.

$$Q = kHt1/2 \text{ .....(2)}$$

Where kH is higuchi's square root of time kinetic drug release constant To understand the release mechanism, in-vitro data was analyzed by peppa's model (Equation 3) as log cumulative % drug release *vs*. log time, and the exponent n was calculated through the slope of the straight line.

$$Mt / M\infty = btn \text{ .....(3)}$$

Where Mt is the amount of drug release at time t, M∞ is the overall amount of the drug, b is constant, and n is the release exponent indicative of the drug release mechanism. If the exponent n = 0.5 or near, then the drug release mechanism is Fickian diffusion, and if n has a value near 1.0 then it is non-Fickian diffusion.

**Osmotic Shock:** The change in the vesicle size can be determined by osmotic studies. Niosomal formulations are incubated with hypotonic, isotonic, hypertonic solutions for 3 h. Then the changes in the size of vesicles in the formulations are viewed under optical microscopy.

**Stability Studies:** To determine the stability of proniosomes, the optimized batch was stored in airtight sealed vials at different temperatures.

Surface characteristics and percentage drug retained in proniosomes and parameters for evaluation of the stability, since instability of the formulation would reflect in drug leakage and a decrease. In the percentage drug retained. The proniosomes were sample at regular intervals of time (0, 1, 2, and 3 months ), observed for colour change, surface characteristics, and tested for the percentage drug retained after being hydrated to form niosomes and analyzed by suitable analytical Methods(UV spectroscopy, HPLC methods, *etc*.).

**Zeta Potential Analysis:** Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted proniosome derived niosome dispersion was determined using zeta potential analyser based on electrophoretic light scattering and laser Doppler velocimetry method (Zeta plus™, Brookhaven Instrument Corporation, New York, USA). The temperature was set at 25 °C. Charge on vesicles, and their mean zeta potential values with a standard deviation of 5 measurements were obtained directly from the measurement.

**Factors Affecting the Formulation of Proniosome:** [28, 29] Various processing and formulation variables affect the proniosomes characteristics. They include surfactant chain length, cholesterol content, drug concentration, total lipid concentration, a charge of lipids, pH of the dispersion medium, and type of alcohol used in the preparation.

**1. Surfactant Chain Length:** Spans are commonly used in the preparation of proniosomes. All span types have the same head group and different alkyl chains. Increasing the alkyl chain length is leading to higher entrapment efficiency. The entrapment efficiency followed the trend Span60 (C18) >Span40 (C16)>Span20 (C12)>Span80 (C18). Span 60 and Span 80 have the same head groups, but Span 80 has an unsaturated alkyl chain. De Giere demonstrated that the introduction of double bonds into the paraffin chains causes a marked enhancement of the permeability of liposomes, possibly explaining the lower entrapment efficiency of the Span 80 formulation.

**2. Cholesterol Content:** Cholesterol increases or decreases the percentage encapsulation efficiency depending on either the type of the surfactant or its concentration within the formulae.

**3. pH of the Hydration Medium:** The percentage encapsulation efficiency of niosomes prepared by hydration of proniosomal gels of Span 60 / cholesterol (9:1) was found to be greatly affected by the pH of the hydrating medium. For example, the fraction of flurbiprofen encapsulated was increased to about 1.5 times as the pH decreased from pH 8 to 5.5. The increase in the percentage encapsulation efficiency of flurbiprofen by decreasing the pH could be attributed to the presence of the ionizable carboxylic group in its chemical structure. Decreasing the pH could increase the proportions of the unionized species of flurbiprofen, which have higher partitioning to the bilayer lipid phase compared to the ionized species.

**4. Total lipid Concentration:** The percentage encapsulation efficiency of flurbiprofen was increased as the lipid concentration was increased

from 25 to 200 mol/ml, respectively. The increase in percentage encapsulation efficiency of flurbiprofen as a function of total lipid concentration was linear. On the other hand, the amount of flurbiprofen entrapped was decreased on increasing the lipid concentration from 25 to 200mol/ml, respectively. This leads to the fact that the fraction of lipid taking part in encapsulation decreases as the concentration of lipid increases.

**5. Drug Concentration:** Increasing flurbiprofen concentration from 25 to 75mg/mmol lipids in the Proniosomes prepared from Span 60 / cholesterol (9:1) showed an increase in both percentage encapsulation efficiency and the amount of drug encapsulated per mol total lipids upon hydration and formation of niosomes.

**6. Charge of the Lipids:** Incorporation of either Dicetyl phosphate (DCP), which induces negative charge or stearylamine (SA) which induces positive charge decreased the percentage encapsulation efficiency of flurbiprofen into niosomal vesicles.

**Applications of Proniosomes:** [28, 30, 31] The application of niosomal technology is widely varied and can be used to treat a number of diseases. The following are the few uses of niosomes that are either proven or under research.

**Drug Targeting:** One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticulo-endothelial system. The reticuloendothelial system (RES) preferentially takes up noisome vesicles.

The uptake of niosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosome 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. Niosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to niosomes (as immunoglobulin bind readily to the lipid surface of the niosome) to target them to specific organs. Many cells also possess the intrinsic ability to recognize and bind specific carbohydrate determinants, and this can be exploited by niosomes to direct carrier systems to particular cells.

**Anti-neoplastic Treatment:** Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half-life of the drug, thus decreasing the side effects of the drugs. Niosomal entrapment of Doxorubicin and Methotrexate (in two separate studies) showed beneficial effects over the unentrapped drugs, such as decreased rate of proliferation of the tumor and higher plasma levels accompanied by a slower elimination

**Delivery of Peptide Drugs:** Oral peptide drug delivery has long been faced with the challenge of bypassing the enzymes which would breakdown the peptide. The use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated.

In an *in-vitro* study conducted by Yoshida et al., oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.

**Uses in Studying Immune Response:** (Brewer and Alexander in 1992) studied niosomes are used in studying immune response due to their immune-logical selectivity, low toxicity, and greater stability. Niosomes are being used to study the nature of the immune response provoked by antigens.

**Niosomes as Carriers for Haemoglobin:** (Moser P. and Marchand Arvier M. in 1989) reported that niosomes can be used as carriers for haemoglobin within the blood. The niosomal vesicle is permeable to oxygen and hence can act as a carrier for hemoglobin in anemic patients

**Transdermal Drug Delivery Systems Utilizing Niosomes:** One of the most useful aspects of niosomes is that they greatly enhance the uptake of drugs through the skin. Transdermal drug delivery utilizing niosomal technology is widely used in cosmetics; In fact, it was one of the first uses of the niosomes. Topical use of niosome entrapped antibiotics to treat acne is done. The penetration of the drugs through the skin is greatly increased as compared to the un-entrapped drug.

Recently, transdermal vaccines utilizing niosomal technology is also being researched. A study conducted by P. N. Gupta *et al.* has shown that

niosomes (along with liposomes and trans-ferosomes) can be utilized for topical immunization using tetanus toxoid.

However, the current technology in niosomes allows only a weak immune response, and thus, more research needs to be done in this field.

**Sustained Release:** Azmin *et al.* suggested the role of liver as a depot for methotrexate after niosomes are taken up by the liver cells. Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation *via* niosomal encapsulation.

**Localized Drug Action:** Drug delivery through niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects *e.g*. Antimonial encapsulated within niosome are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity. The evolution of niosomal drug delivery technology is still in the infancy stage, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.

**Cosmetics Formulation:** [2] Now a day's large numbers of cosmetic preparations available in the market are utilizing niosomes and liposomes as a carrier for the delivery of actives. Liposomes were prepared using unacceptable organic solvents, whose traces in the final preparation can cause harm to the skin. It is proved that proniosomes are as effective as noisome and liposomes, but their preparation, handling, storage, and transportation make them superior to others. The therapeutic agents which can be utilized for incorporation into proniosomal carrier systems include moisturizing, nutritional, anti-wrinkle, anti-aging, cleansing, sunscreen particles, *etc*.

**NSAID Application:** Non-steroidal anti-inflammatory drugs like Ketorolac tromethamine (KT) administered intramuscularly and orally in divided multiple doses for short-term management of postoperative pain.

Therefore, an alternative, non-invasive mode of delivery of the drug is needed. So, that, Transdermal route of delivery is an unconditionally attractive route of administration to maintain the drug blood levels of KT for an extended period of time.

**TABLE 3: DIFFERENT STUDIES RELATED TO THE APPLICATIONS OF PRONIOSOME DERIVED NIOSOMES**

| S. no. | Drug | Formulation (Vesicle type) | Category | Reference |
|---|---|---|---|---|
| 1. | Levonorgestrel | Proniosomal gel, patch | Contraceptive agent | 14 |
| 2. | Captopril | Proniosomal Gel | | 32 |
| 3. | Piroxicam | Proniosomal Gel | NSAIDs | 33 |
| 4. | Aceclofenac | Proniosomal Gel | NSAIDs | 34 |
| 5. | Meloxicam | Proniosomal Gel | NSAIDs | 35 |
| 6. | Lisinopril Dihydrate | Proniosomal Gel | NSAIDs | 36 |
| 7. | Miconazole | Niosomes | Antifungal | 37 |
| 8. | Metformin | Proniosomal Gel | Anti-hyperglycemic agent | 38 |
| 9. | Clotrimazole | Proniosomal Gel | Antifungal | 39 |
| 10. | Nystatin | Proniosomal Gel | Antifungal | 40 |
| 11. | Naproxen | Proniosomal Gel | NSAIDs | 41 |
| 12. | Fluconazole | Proniosomal Gel | Antifungal | 42 |
| 13. | Ornidazole | Proniosomal Gel | Antibacterial | 43 |
| 14. | Ketoconazole | Proniosomal Gel | Antifungal | 44 |
| 15. | Carvidilol | Proniosomal Gel | Antihypertensive | 45 |
| 16. | Terconazole | Proniosomal Gel | Antifungal | 46 |
| 17. | *Capecitabine* | Proniosomal Gel | Anticancer | 47 |
| 18. | Clarithromycin | Proniosomal Gel | Antibacterial | 48 |
| 19. | Ritonavir | Proniosomal Gel | Antiretroviral | 49 |
| 20. | Ciclopirox | Niosomes | Antifungal | 50 |
| 21. | Tolterodine Tartrate | Proniosomal Gel | Anticholinergic | 51 |

**Marketed Products:** Lancôme has come out with a variety of anti-aging products which are based on niosomes Formulations. L'Oreal is also conducting research on anti-aging cosmetic products. The first product, 'Niosome' was introduced in 1987 by Lancôme [4, 52].

**CONCLUSION:** Proniosomes have advantages of controlled and sustained release action, stability, and versatility as a drug carrier. Proniosomes are propitious drug carriers for the future with greater physical, chemical stability and potentially expandable for commercial feasibility. Proniosomal delivery system holds effective delivery for amphiphilic drugs. Due to the advantages of nontoxicity & penetration enhancing the effect of surfactants & effective modification of drug release, proniosomes have attracted a greater deal of attention for delivering drugs through the transdermal route. Proniosomes in dry form make the possibility of suitable unit dosing as they are further converted into beads, tablets, capsules. The findings of the studies on proniosomesopens the door for the future, use of different carrier's materials with biocompatibity and suitability for the preparation of proniosomes. The future experiments would explore the suitability of proniosomes with more drugs having defined drawbacks for improved & effective intended therapy.

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