Review Article

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PRONIOSOMES: A SURROGATED CARRIER FOR IMPROVED TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT
Proniosomes is dry formulation using suitable carrier coated with non ionic surfactants and can be converted into niosomes immediately before use by hydration. These 'proniosomes' minimize problems of niosome physical stability such as aggregation, fusion and leaking, and provide additional convenience in transportation, distribution, storage, and dosing. These proniosomes-derived niosomes are as good as or even better than conventional niosomes. The focus of this review is to bring out different aspects related to proniosomes preparation, characterization, entrapment efficiency, in vitro drug release, applications and merits.
KEYWORDS: Niosomes; Proniosomes; Characterisation; *in-vitro* drug release, Stability.

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INTRODUCTION

From early 1980s, niosomes have gained wide attention by researchers for their use as drug targeting agents, drug carriers to have variety of merits while avoiding demerits associated with the conventional form of drugs[1, 2]. Niosomes without incorporation are microscopic lamellar structures, which are formed on the admixture of non-ionic surfactants with or of cholesterol or other lipid[3]. Niosomes are widely studied as an alternative to liposomes. These vesicles appear to be similar to liposomes in terms of their physical properties. From a technical point of view, niosomes are promising drug carriers as they possess greater stability and lack of many disadvantages associate with liposomes such as high cost and the variable purity problems of phospholipids[4].The additional merits with niosomes are low toxicity due to non ionic nature, no requirement of special precautions and conditions for formulation and preparation[5]. Moreover it is the simple method for the routine and large scale production of niosomes without the use of unacceptable solvents[6]. However, stability is a prime concern in the development of any formulation and even though, niosomes have shown advantages as drug carriers, such as being low cost and chemically stable as compared to liposomes[7].They too, are measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes[8].The resulting niosomes are very similar to conventional niosomes and more uniform in size[9] .The proniosomes approach minimizes these problems by using dry, free-flowing product, which is more stable during sterilization and storage[9, 10, 11]. Ease of transfer, distribution, measuring, and storage make proniosomes a versatile delivery system with potential for use with a wide range of active compounds[8].

But the advancements in the delivery systems are necessary to produce the better characteristics and simplification of the formulation process. The advancement in the niosomes leads to the evolution of proniosomal delivery systems[11, 12 13]. Proniosomes are non-ionic based surfactant vesicles, which may be hydrated immediately before use to yield aqueous niosome dispersions. Proniosomes are nowadays used to enhance drug delivery in addition to conventional niosomes[14].

These vesicular delivery systems have attracted considerable attention in topical/transdermal drug delivery for many reasons. These penetration enhancers are biodegradable, non-toxic, amphiphilic in nature, and effective in the modulation of drug release properties. Their effectiveness is strongly dependent on their physiological properties, such as composition, size, charge, lamellarity and application conditions[15]. The active ingredients present in the formulation of drugs and

cosmetics/cosmeceuticals permeate through the intercellular lipid matrix, i.e. intercellular and transcellular. However, vesicular delivery systems use three pathways for permeation of drugs in the tissues and they are, a) hair follicle associated with sebaceous glands, b) through sweat glands and c) across the continuous stratum corneum (SC) layer[16, 17].

In general a limited number of studies are available which deal with the preparation and evaluation of proniosomes[6, 8, 9, 10, 11, 12, 13, 18, 19, 20]. These studies mostly focused on the utilization of proniosomes in transdermal drug delivery. This article briefly reviews the trends and the future perspective in the development of proniosomal drug delivery systems.

Advantages of Proniosomes

Liposomes and noisomes are well known drug/cosmetic delivery systems. But these delivery systems have been reported to have many disadvantages in terms of preparation, storage, sterilization, etc. The disadvantages of liposome's and noisomes are given below, which can be overcome by proniosomes[13, 14, 21].

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

TYPES OF PRONIOSOMES [22]

Dry Granular Proniosomes

According to the type of carrier and method of preparation of dry granular proniosomes are

I. Sorbitol based proniosomes
II. Maltodextrin based proniosomes

Sorbitol based proniosomes is a dry formulation that involves sorbitol as a carrier, which is further coated with non ionic surfactant and is used as a noisome within minutes by addition of hot water followed by agitation. These are normally made by spraying surfactants mixture prepared in organic solvent on to the sorbitol powder and then evaporating the solvent. Since the sorbital carrier is soluble in organic solvent, the process is required to be repeated till the desired surfactant coating has been achieved. In Sorbitol based proniosomes size distribution is very uniform. It is usefull in case where the active ingredient is susceptible to hydrolysis. The residual sorbitol decreases the entrapment efficiency to less than one half of that observed without sorbitol. These necessitate reduction in proportion of carrier in final niosomal suspension. The difficulty lies in testing of sorbitol particles because sorbitol is solubale in chloroform and organic solvents. It is prepared by slow spraying method.

Maltodextrin based proniosomes prepared by fast slurry method. Time required to produce proniosomes by slurry method is independent of the ratio of surfactant solution to carry out. Proniosomes of high surface to carriers ratio can be prepared. The method of obtaining niosomes from such a proniosomes for the drug deliver is very simple. An analogue process with the sorbitol results in a solid, surfactant/sorbitol cake. Since maltodextrine morphology is preserved, hollow blown maltodextrin particles can be used for significant gain in surface area. The higher surface area results in thinner surfactant coating, which makes the rehydration process efficient. This preparation has potential of application in delivering of hydrophobic and amphiphilic drugs[9, 10, 11].

Liquid Crystalline Proniosomes

When the surfactant molecule are kept in contact with water, there are three ways trough which lipophilic chains of surfactants can be transformed into a disordered, liquid state called lyotropic liquid crystalline state(neat phase). These three ways are increasing temperature at Kraft point (Tc), addition of solvent which dissolve lipids; and use of both temperature and solvent. Neat phase or lamellar phase contains bilayers arranged in a sheet over one another within intervening aqueous layer. This type of structure gives typical X-ray diffraction and thread like birefringent structure under polarized microscope. For ternary lecithin, non-ionic surfactants as monoglyceride and alcohol system, lamellar liquid crystals are formed at Kraft temperature in presence of alcohol. The lamellar crystalline phase is converted into dispersion of niosomes at higher water concentration. The organization of lipid/ethanol/water mixture into lamellar structure can be conveniently utilized for transdermal of drugs. The liquid crystalline proniosomes and proniosomal gel act as reservoir for transdermal delivery of drug. The transdermal patch involves aluminium foil as a baking material along with the plastic sheet (of suitable thickness stuck to foil by means of adhesive). Proniosomal gel is spread evenly on the circular plastic sheet followed by covering of nylon mesh[13, 18, 23].

This method avoids the use of pharmaceutically unacceptable solvents and it is easy to scale up. This system may directly be formulated into transdermal

patch; upon hydration with water from skin it may be converted into niosomes. As the formulation is in direct contact with skin, it itself act as a penetration enhancer. Liquid crystalline proniosomes display a number of advantages:

I. Stability.
II. Higher entrapment efficiency.
III. As a penetration enhancer.
IV. There is no disruption of membrane properties of stratum corneum.
V. Easy to scale up as no lengthy process is involved; moreover it avoids the use of pharmaceutically unacceptable additives.
VI. Amenable to direct fabrication of transdermal patch and does not require dispersion of vesicle into polymer matrix.

PREPARATION OF PRONIOSOMES

Here are number of components present in proniosomes with non ionic surfactants and cholesterol, lecithin being the main ingredient. Desirable characteristics of the selected carrier that could be used in the preparation of proniosomes [24]. These include; safety and non-toxicity, free flowability, poor solubility in the loaded mixture solution and good water solubility for ease of hydration[19]. Different carriers and non ionic surfactants and membrane stabilizers used for the proniosomal preparation are shown in table 1. Three different methods were reported for the preparation of proniosomes.

Slurry Method

Maltodextrin powder 10 g as carrier is added to a 250-mL round-bottom flask and the entire volume of surfactant solution (14.5 mL) was added directly to the flask to form slurry. If the surfactant solution volume is less, then additional amount of organic solvent can be added to get slurry. The flask was attached to the rotary evaporator and vacuum was applied until the powder appeared to be dry and free flowing. The flask was removed from the evaporator and kept under vacuum overnight. Proniosome powder was stored in sealed containers at 4°C. The time required to produce proniosomes is independent of the ratio of surfactant solution to carrier material and appears to be scalable[8, 10, 11, 23].

Advantages

1) Maltodextrin is a polysaccharide easily soluble in water and it is used as carrier material in formulation, it was easily coat the maltodextrin particles by simply adding surfactant in organic solvent to dry maltodextrin.
2) Due to uniform coating on carrier it protects the active ingredients and surfactants from hydrolysis and oxidation etc.
3) The higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient.

Disadvantages

1. Method is time consuming and involves specialized equipment with vaccum and nitrogen gas.
2. The thin film approach allows only for a predetermined lot sizes so material often wasted so small quantities or small dose batch can be tedious one.

Coacervation Phase Separation Method

This method is widely adopted to prepare proniosomal gel. Precisely weighed amounts of surfactant, lipid and drug are taken in a clean and dry wide mouthed glass vial of 5.0 ml capacity and alcohol (0.5 ml) is added to it. After warming, all the ingredients are mixed well with a glass rod; the open end of the glass bottle is covered with a lid to prevent the loss of solvent from it and warmed over water bath at 60-70°C for about 5 min until the surfactant mixture is dissolved completely. Then the aqueous phase (0.1% glycerol solution) is added and warmed on a water bath till a clear solution was formed which is then converted into proniosomal gel on cooling[12, 13].Diagrametic representation as shown in figure no.1.

Advantages

a. Method is simple and without time consumable so it does required any specialized equipment.
b. Specially adopted for gel preparation
c. Small quantities or small dose formulation can be prepared on lab scale.

Slow Spray-Coating Method

This method involves preparation of proniosomes by spraying surfactant in 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 loading has been achieved. The surfactant coating on the carrier is very thin and hydration of this coating allows multilamellar vesicles to form as the carrier dissolves[25, 26]. The resulting niosomes are very similar to those produced by conventional methods and the size distribution is more uniform. It is suggested that this formulation could provide a suitable method for formulating hydrophobic drugs in a lipid suspension without concerns over instability of the suspension or susceptibility of the active ingredient to hydrolysis[9]. This method was reported to be tedious since the sorbitol carrier for formulating proniosomes is soluble in the solvent used to deposit the surfactant. Sorbitol is also found to interfere with the encapsulation of certain drugs

Advantages

1. Simple method and suitable for hydrophobic drug without concerns of instability or susceptibility of active pharmaceutical ingredient to hydrolysis.

Disadvantages

1. If the coating of surfactant solution was applied too quickly, the sorbitol particles would degrade and sample becomes viscous slurry.
2. Sorbitol is found to interefere with encapsulation efficiency of drug
3. This method was reported to be tedious since the sorbitol carrier for formulating proniosomes is soluble in the solvent used to deposit the surfactant.

VESICLE FORMATION IN PRONIOSOMES

The ability of non-ionic surfactant to form bilayer vesicles instead of micelles is not only depends on the hydrophilic-lipophilic balance (HLB) values of the surfactant and the chemical structure of the components, but also on the critical packing parameter (CPP) . In proniosomes the vesicle-forming tendency is similar to niosomes. The relationship between the structure of the surfactant including size of hydrophilic head group, and length of hydrophobic alkyl chain in the ability to form vesicles is described as

$CPP = \upsilon / l_c a$

Where υ = hydrophobic group volume, l_c = the critical hydrophobic group length and a = the area of the hydrophilic head group. A CPP of between 0.5 and 1 indicates that the surfactant is likely to form vesicles. A CPP of below 0.5 (indicating a large contribution from the hydrophilic head group area) is said to give spherical micelles and a CPP of above 1 (indicating a large contribution from the hydrophobic group volume) should produce inverted micelles, the latter presumably only in an oil phase, or precipitation would occur[27, 28, 29].

Addition of cholesterol suppresses the tendency of the surfactants to form aggregates and also provides greater stability to the bilayer membranes by increasing the gel liquid transition temperature of the vesicle and also attributes to the higher HLB and smaller critical packaging parameters. Cholesterol addition also enables more hydrophobic surfactants to form vesicles. Apart form this addition of cholesterol also influences membrane permeability, encapsulation efficiency and bilayer rigidity[27].

Stabilization and permeability can also be enhanced by the addition of lecithin and by the addition of charged molecules like, diacetyl phosphate (DCP) and stearyl amine (SA) to the bilayer.

Preparation of Niosomes from Proniosomes by Hydration

Prepared proniosome powder is weighed and filled in screw cap vials. Water or saline at 80°C is added and the vials are capped. The vials are attached to a vortex mixer and agitated for 2 minutes to get niosomal suspension[10, 11] as shown in figure no.2.

Conversion of Proniosome Gel into Niosomes

Proniosome gel is an intermediate state of formation of niosome. Minimum quantity of continuous phase, leads to the formation of liquid crystalline compact mass of proniosomes. Proniosome gel thus obtained has some advantages over conventional niosomes due to their compact gel nature, which helps in degradation, transportation and stability. The conversion of proniosome gel into niosomes can be achieved in two ways.

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

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

The proniosome gel system is directly being formulated in the patch for used in dermal and transdermal applications without the requirement of polymeric matrix for dispersion. The formulation takes water from the skin and converts into niosomes. The addition of aqueous phase from outside also leads to the formation of niosomes. After the addition of aqueous phase, agitation and sonication leads to formation of niosomes with small size vesicles. The addition of water into compact mass of proniosome leads to the swelling of bilayers as well as vesicles due to the interaction of water with polar groups of the surfactant. Due to the inclusion of water in the bilayers, the stacked structures tend to separate. Above a limiting concentration of solvent bilayers tends to form spherical structure which gives rise to unilamellar to multilamellar vesicular structures. Addition of shaking step in hydration process leads to complete hydration and formation of niosomes[6, 13, 14].

CHARACTERIZATION OF PRONIOSOMES

Proniosomes are characterized for vesicle size, size distribution, shape, surface morphology, aerodynamic behavior, spontaneity are enlisted in table 2.

Separation Free (Unentrapped) Drug

The encapsulation efficiency of proniosomes is determined after separation of the unentrapped drug from entrapped drug using techniques like centrifugation[6, 9, 10, 12, 18, 19] and by using cellophane dialysis tubing D-9777

and dialyzing exhaustively against 400 mL saline at 4°C for 24 hours [8, 13].

Determination of Entrapment Efficiency (Measurement of Partitioning)

The vesicles 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 was added to solubilize vesicles[19]. The resulting clear solution is then filtered and analysed for drug content.

The vesicles obtained after removal of drug by centrifugation, the pellet was collected and resuspended in 0.9% saline followed by addition of 1:1 ratio of absolute alcohol: propylene glycol mixture to lyse the vesicles[13].

The percentage of drug entrapped is calculated using the following formula[19, 30].

EE%= ED/TD ×100

Where EE% is the entrapment efficiency percent, ED is the entrapped drug concentration and TD is the theoretical drug concentration

***In Vitro* Drug Release from Proniosomal Vesicles**

In vitro drug release and skin permeation studies for proniosomes were determined by different techniques like Franz diffusion cell[18], Keshary-Chien diffusion cell [13], Cellophane dialyzing membrane[6, 12], USP Dissolution apparatus Type I[19], Spectrapor© molecular porous membrane tubing[19].

In vitro skin permeation studies have been carried out female albino rat[6], female albino rat (Sprauge-Dawley strain), flank skin[13] and Wister rat skin (7-9 weeks old)[18]. Drug release from proniosome derived niosomal vesicles can follow any one or more of the following mechanisms; desorption from surface of vesicles or diffusion of drug from bilayered membrane or a combined desorption and diffusion mechanism.

Stability Studies on Proniosomes

Stability studies were carried out by storing the prepared proniosomes at various temperature conditions like refrigeration temperature (2°-8°C), room temperature (25° ± 0.5°C) and elevated temperature (45° ± 0.5°C) from a period of one month to three months. Drug content and variation in the average vesicle diameter were periodically monitored[12, 13, 19]. ICH guidelines suggests stability studies for the dry proniosome powders meant for reconstitution should be studied for accelerated stability at 40°C/75% relative humidity as per international climatic zones and climatic conditions (WHO, 1996). For long term stability studies the temperature is 25°C/60% RH for the countries in zone I & II and for the countries in Zone III & IV the temperature is 30°C/65% RH. Product should be evaluated for appearance, colour, assay, pH, preservative content, particulate matter, sterility and pyrogenicity.

APPLICATIONS

Proniosomal gel system is a step forward to niosomes, which can be utilized for various applications in delivery of actives at desired site. Proniosomes are easily hydrated using aqueous phase or by skin itself if used topically. Their incorporation into base gel/cream/ointment along with other ingredients leads to form a cosmetic preparation. These cosmetic formulations can be used for topical/transdermal applications for various functions. Proniosomal gel formulation shows advantages in controlled drug delivery, improved bioavailability, reduced side effects and entrapment of both hydrophilic and hydrophobic drugs. Proniosome gel has an affinity towards biological membranes which helps in enhancing the permeation of actives through skin. A brief compilation related to wide range of actives including therapeutic agents and cosmetic agents are given in table which have been reported to be utilized for various applications. Various application of proniosomes as shown in table 3.

FUTURE TRENDS

Studies on proniosome gel formulation indicate that it has become a useful dosage form for drug permeation into the skin, especially due to their simple, scaling-up production procedure and ability to modulate drug delivery across the skin. There is a strong need for exploring the proniosomal delivery systems for cosmetics, herbal actives and nutraceuticals. Use of proniosome in the cosmetic formulation will lead to prolong action, better absorption along with many advantages. To get the desired characteristics of a particular proniosome gel formulation, it is important to select the surfactant of suitable HLB in the formulation of proniosome gel. Hence, a more extensive study should be undertaken to find out the optimal proniosome formulation for drug/cosmetic permeation into the skin.

CONCLUSION

Proniosomes are promising drug carriers for the future with greater physical and chemical stability and potentially scalable for commercial viability. The delivery system holds promise for the effective drug delivery for amphiphilic drugs. Proniosomes has attracted a great deal of attention for the delivery of drugs through transdermal route because of the advantages like non-toxicity and penetration enhancing effect of surfactants and effective modification of drug release properties. The findings of the studies on proniosomes till date, opens the door for the future use of different carrier materials with biocompatibility and suitability for the preparation of proniosomes.

Proniosomes in dry powder form makes the possibility of convenient unit dosing as the proniosome powder can further be processed to make beads, tablets or capsules. However, future experiments should explore the suitability of proniosomes with more drugs having defined drawbacks for improved and effective intended therapy. Studies should be explored to assess the ability of different carrier materials to formulate proniosomes and the ability of proniosomes to deliver the drugs meant for administration through various routes.

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Table 1: Non-ionic surfactants and coating carriers used for the preparation of proniosomes

S. No.	Non ionic surfactants used
1 2 3 4 5 6 7 8	Span 20[6, 13] Span 40[13, 18] Span 60[10, 11, 13] Span 80[12, 13] Span 85[18] Tween 20[6, 18] Tween 60[18] Tween 80[18]
	Coating materials investigated
1 2 3 4 5 6 7	Sucrose stearate[19] Sorbitol[9, 12] Maltodextrin (Maltrin M500)[10, 11] Maltodextrin (Maltrin M700)[10, 11] Glucose monohydrate[19] Lactose monohydrate[19] Spray dried lactose[19]
	Membrane stabilizers used
1 2	Cholesterol[8, 12, 19] Lecithin[6, 12, 18]

Table 2: Methods for the characterization of proniosomes

S. No.	Parameter	Instrument/Method Employed
1	Vesicle size determination and size distribution	1. Malvern Mastersizer[19] 2. Optical microscopy[12] 3. Laser diffraction particle size analyzer[8, 9] 4. Coulter submicron size analyzer[18]
2	Shape and surface Morphological characterization	1. Optical microscopy[12] 2. Transmission electron microscopy[19] 3. Scanning electron microscopy[6]
3	Aerodynamic behavior	Twin-Stage Impinger[19]
4	Angle of repose	Funnel method[19]
5	Spontaneity (Rate of hydration)	Using Neubaur's chamber[13]

Table 3: Various application of Proniosomes

Name of therapeutic agent	Therapeutic category	Route of delivery	Delivery system
Levonorgestrel[13]	Contraceptive agent	Transdermal	Proniosome gel
Flurbiprofen[14]	NSAID	Transdermal	Proniosome gel
Captopril[12]	Antihypertensive	Transdermal	Proniosome gel
Estradiol[18]	Female hormone	Transdermal	Proniosome gel
Ketorolac[6]	NSAID	Transdermal	Proniosome gel
Frusemide[20]	Diuretic	Transdermal	Proniosome gel
Losartan potassium[31]	Antihypertensive	Transdermal	Proniosome gel
Chlorpheniramine Maleate[32]	Anti-histamine	Transdermal	Proniosome gel
Pseudo-ceramide[33]	Anti-wrinkle	Topical	Liquid crystal
Benzophenone-4/octyl methoxycinnamate[34]	Sunscreen agent	Percutaneous	Liquid crystal
Vitamin A[35]	Antioxidant	Topical/ Transdermal	Liquid crystal
Cosmetic composition[16]	Skin cleansing agent	Topical	Liquid crystal

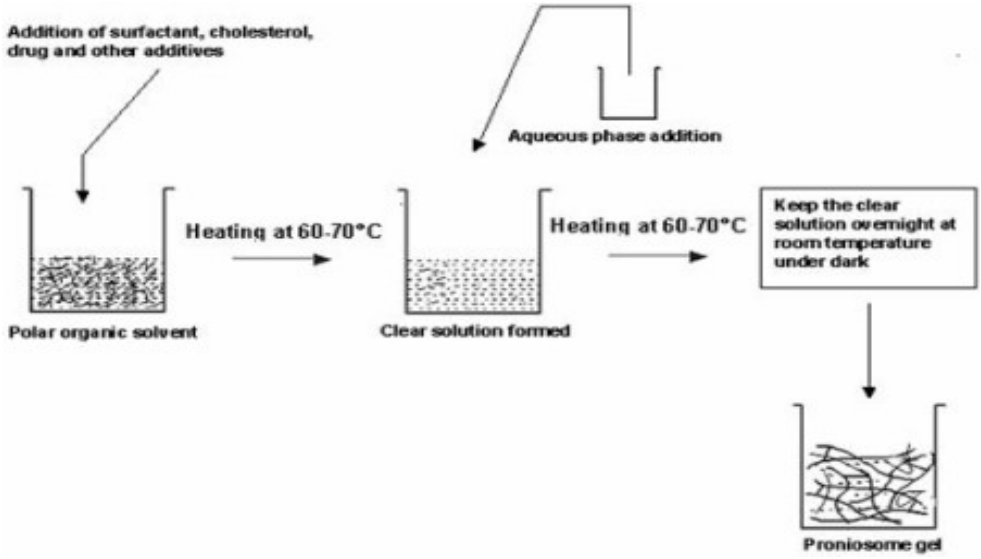

Fig 1: Diagrammatic representation for preparation of proniosome gel

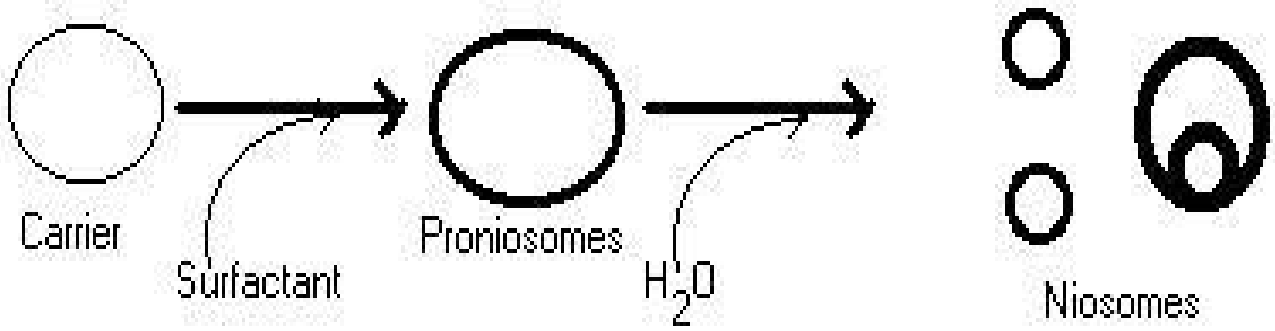

Fig 2:Formation of niosome from proniosomes