Songklanakarin J. Sci. Technol.
42 (6), 1171-1186, Nov. - Dec. 2020

http://www.sjst.psu.ac.th

Review Article

Proniosomes: An effective carrier for dermal and transdermal delivery

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Received: 10 May 2019; Revised: 7 August 2019; Accepted: 13 August 2019

Abstract

Proniosomes are non-ionic surfactant based vesicles that can be hydrated to yield an aqueous niosomal dispersion. The evolution of proniosomes has been motivated by development of niosomes to minimise the stability problems of niosomes and liposomes. Moreover, proniosomes can encapsulate both hydrophilic and lipophilic drugs. They are effective in enhancing skin penetration for transdermal delivery. This article describes key compositions of a proniosomal system, types of proniosomes, preparation techniques, and their characteristic properties including particle size, morphology, flow ability, entrapment efficiency, drug release, and permeability performance. The advantages of proniosomes, the mechanism of action in skin penetration, and the toxicity of proniosomes are discussed. Several categories of drugs formulated for a proniosomal system and topical or transdermal delivery are also reviewed.

Keywords: proniosomes, dermal delivery, transdermal delivery, application

1. Introduction

Niosomes have gained much attention as drug carriers that offer a variety of advantages, since their use began in the early 1980s. They are non-ionic surfactant vesicles with microscopic lamellar structure, formed by the admixture of non-ionic surfactants, with or without cholesterol, which are subsequently hydrated in aqueous media. Niosomes appear promising alternatives to liposomes, due to their ability to entrap both hydrophilic and lipophilic actives, providing greater stability than liposomes, and lacking the liposomal drawbacks including the high cost and the purity problem of phospholipids. Additionally, the use of non-ionic surfactants as drug carriers provides low levels of toxicity and no special conditions are required in the preparation process.

Although the niosomes offer many advantages over liposomes, they have some stability limitations manifesting in aggregation, fusion, leaking of the entrapped drug, and hydrolysis of encapsulated drugs, which would limit the shelf life of the dispersion. In order to address these problems and to provide additional convenience in transportation, distribution, storage, and dosing, proniosomes have been developed. The advancement of niosomes resulted in the evolution of proniosomal delivery systems. Proniosomes are non-ionic based surfactant vesicles that exist in two forms, namely as 1) dry granular proniosomes, and as 2) liquid crystalline proniosomes (proniosomal gel). They can be immediately converted into niosomal dispersion by rehydration in aqueous media within minutes before use. The niosomes obtained after the rehydration of proniosomes are very similar to conventional niosomes although with more uniform size distribution. Proniosomes can eliminate physical stability problems of niosomes, especially leaking, aggregation, and fusion. The encapsulation of actives in the vesicular structure of proniosomes can provide prolonged existence of the actives, improved penetration, and reduced toxicity after administration. The dry granular form of proniosomes makes them more stable during storage and sterilization, and more convenient to transfer, distribute, and measure. These benefits lead to potential uses with a wide range of active compounds. In addition, in the form of a proniosomal gel, it is possible to undergo rehydration by water in the skin under occlusive conditions, and to overcome the skin barrier by loosening the stratum corneum that is mainly useful for topical and transdermal applications. As carriers, proniosomes act as the

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reservoirs in controlled release of encapsulated actives by modification of their composition. The desired characteristics could be obtained by selecting suitable surfactants to the proniosome formulation. This article briefly reviews the preparation and evaluation of proniosomes, the toxicity of proniosomes, and the application of proniosomes in dermal and transdermal delivery.

2. Composition of Proniosomes

Proniosomes are generally composed of non-ionic surfactants formed as lamellar vesicles. Other components may be added to improve properties of the proniosomes. The proniosomes consist of various ingredients, as described below.

2.1 Surfactant

Non-ionic surfactants are the main structural components of proniosomes. The HLB value of the surfactant is very important for vesicle forming ability, because it is a good indicator of vesicle formation and entrapment efficiency. An HLB value between 4 and 8 was reported to be compatible with vesicle formation by proniosomes. Due to the high aqueous solubility of hydrophilic surfactants, it is quite difficult for the surfactants to reach a high concentration. Therefore, the ability of the free hydrated units to aggregate and coalesce to form the proniosomal lamellar structure would be absent. The gel to liquid phase transition temperature of surfactants also affects the entrapment efficiency of a drug in the vesicles. A high transition temperature surfactant is likely to form an orderly gel with less leaky bilayers and high entrapment efficacy. In contrast, a low transition temperature surfactant usually gives a less orderly liquid and low entrapment efficiency (Vora, Khopade, & Jain, 1998). Tweens ordinarily show lower entrapment efficacy than Spans (Yadav *et al*., 2010). A high transition temperature of the surfactant is also associated with reduced drug permeability through the skin, as observed in the study by Vora, Khopade, and Jain (1998). Proniosomes consisting of Span 60 with a high transition temperature (53°C) showed a lower permeation flux than those consisting of Span 80 with a low transition temperature (-12°C). Several non-ionic surfactants are usually employed in the preparation of proniosomes, in the studies listed in Table 1.

2.2 Cholesterol

Cholesterol is an essential component functioning as the vesicular cement of the surfactant monomers when they are assembled into the bilayer of the niosomal membrane. The space filling effect of cholesterol improves stability and rigidity of the niosomal membrane, and decreases drug permeation through the membrane when compared to a cholesterol-free membrane. Therefore, the entrapment efficiency of drugs in niosomes is improved. An increase in the concentration of cholesterol brings about increased entrapment efficiency, but this effect saturates. Then, any further cholesterol added would reduce the entrapment efficiency due to the competition between cholesterol and drugs to fill the bilayer (El-Laithy, Shoukry, & Mahran, 2011). As shown in the study by El-Laithy, Shoukry, and Mahran (2011), an increasing cholesterol content in the ratio of cholesterol: lecithin: sucrose laurate from 10:180:180 to 20:180:180 significantly increased entrapment efficiency from 74.25% to 85.37%. However, a further increase to 30:180:180 ratio significantly decreased entrapment efficiency to 79.91%.

2.3 Phosphatidylcholine

Phosphatidylcholine is usually used in a niosomal formulation as the membrane stabiliser and penetration enhancer. One well-known phosphatidylcholine that is generally employed in the formulations is lecithin, with examples including soy lecithin and egg lecithin. Some reports have shown that hydrogenated-type lecithins have benefits over not

Table 1. Different types of nonionic surfactant used to prepare proniosomes and their properties.

No.	Surfactant	Molecular formula	M.W. (g/mol)	HLB	Transition temperature	Reference
1.	Span 20 (Sorbitan monolaurate)	$C_{18}H_{34}O_6$	346.46	8.6	16°C	(Vora, Khopade, & Jain, 1998)
2.	Span 40 (Sorbitan monopalmitate)	$C_{22}H_{42}O_6$	402.57	6.7	42°C	(Fang, Yu, Wu, Huang, & Tsai, 2001; Vora, Khopade, & Jain, 1998)
3.	Span 60 (Sorbitan monostearate)	$C_{24}H_{46}O_6$	430.63	4.7	53°C	(Blazek-Welsh & Rhodes, 2001a, 2001b; Vora, Khopade, & Jain, 1998)
4.	Span 80 (Sorbitan monooleate)	$C_{24}H_{44}O_6$	428.62	4.3	-12°C	(Vora, Khopade, & Jain, 1998)
5.	Span 85 (Sorbitan trioleate)	$C_{60}H_{108}O_8$	957.49	1.8	-	(Fang, Yu, Wu, Huang, & Tsai, 2001)
6.	Tween 20 (Polyoxyethylene sorbitan monolaurate)	$C_{26}H_{50}O_{10}$	522.68	16.7	-	(Fang, Yu, Wu, Huang, & Tsai, 2001)
7.	Tween 60 (Polyoxyethylene sorbitan monostearate)	$C_{35}H_{68}O_{10}$	648.92	14.9	-	(Fang, Yu, Wu, Huang, & Tsai, 2001)
8.	Tween 80 (Polyoxyethylene sorbitan monooleate)	$C_{32}H_{60}O_{10}$	604.82	15.0	-	(Fang, Yu, Wu, Huang, & Tsai, 2001)

benefits over not hydrogenated lecithins, from increased rigidity of the cholesterol and reduced formation of leaky vesicles (Varshosaz, Pardakhty, Mohsen, & Baharanchi, 2005). The presence of double bonds in not hydrogenated lecithin allows the molecular chains to bend (conformational rotation), which prevents tight contacts with the adjacent molecules on forming the niosomal membrane. This results in low rigidity and high permeability of the membrane (El-Laithy, Shoukry, & Mahran, 2011; Fang, Yu, Wu, Huang, & Tsai, 2001).

2.4 Solvent

The solvent can act as a penetration enhancer. It also greatly affects the size of vesicles formed and the drug permeation rate of the niosomes. The commonly used alcohols include ethanol, propanol, butanol, and isopropanol. Some reports have revealed that the solubility of alcohol in water increases the particle size of the niosomes. Ethanol showed slow phase separation because of its greater solubility in water, leading to large sized vesicles and less spontaneity in the formation of the niosomes than with propanol, butanol, or isopropanol. Additionally, it was found that the drug penetration was maximized with isopropanol due to the branched structure of its molecules acting as a co-surfactant, loosening the bilayer packing, thereby achieving increased drug release rate (Ishii, Takamura, & Ishigami, 1995; Vora, Khopade, & Jain, 1998).

2.5 Aqueous phase

The aqueous phase that is commonly used in the preparation of proniosomes includes 0.1% glycerol, phosphate buffer solution (pH 7.4), and hot water.

2.6 Carriers (Coating materials)

The carriers employed in the preparation of proniosomes have the major task to hold the drugs. The carriers should be safe, non-toxic, free flowing, have poor solubility in the loaded mixture solution, but good solubility in water for ease of hydration. They should help prepare proniosomes by permitting flexibility in the ratio between surfactants and other incorporated components, increase the surface area, and enhance drug loading. The frequently used carriers include maltodextrin, sucrose stearate, sorbitol, glucose monohydrate, lactose monohydrate, and spray dried lactose. In the preparation process, coating with sorbitol, glucose monohydrate, or lactose monohydrate is quite difficult because of their solubility in the mixture solution, which upon application brings about viscous slurry samples. Meanwhile, maltodextrin provides a flexible ratio between surfactants and other incorporated components. Therefore, it is considered an effective carrier in proniosomes.

2.7 Other ingredients

There are some other ingredients that also help in the preparation of proniosomes; for example, Solulan™ (lanolin derivative), oleic acid, and stearylamine. Solulan™ helps prevent the aggregation of the proniosome formulation by steric hindrance (Yadav *et al.*, 2010). Oleic acid may be filled in the proniosome formulation to provide negative charge to the vesicles, and reduces both zeta potential and particle size (Zakir, Vaidya, Goyal, Malik, & Vyas, 2010). Stearylamine can be added to the proniosomal formulation to improve the entrapment efficiency because it produces strong electrostatic interactions between the negatively charged drug and the positively charged stearylamine (Abd-Elbary, El-laithy, & Tadros, 2008).

3. Types of Proniosomes

Proniosomes can be classified in two categories according to the type of carrier and the method of preparation, which are dry granular proniosomes and liquid crystalline proniosomes.

3.1 Dry granular proniosomes

The dry granular proniosomes are usually sorbitol-based or maltodextrin-based proniosomes. The first mentioned proniosomes are dry formulation proniosomes that employ sorbitol as a carrier and are further coated with a non-ionic surfactant. The second type, maltodextrin-based proniosomes, are also in a dry formulation, which can be prepared by the fast slurry method that is potentially scalable for the niosomal encapsulation of amphiphilic and hydrophobic drugs.

3.2 Liquid crystalline proniosomes

The liquid crystalline proniosomes are also known as proniosome gels. They are usually used as the reservoir in transdermal delivery of a drug. The principle of the proniosome gel preparation involves the formation of sol phase at a high temperature to completely dissolve the surfactant with no formation of micelles due to a very small amount of solvent. When a small amount of water is added to the above mixture, a W/O microemulsion is formed. The surfactants are bound at the interfaces of aqueous and oil domains. During cooling the solubilities of surfactant and cholesterol in the solvent decrease, and the affinity of the solvent-gelator is low due to limited solvent. Then, a proniosome gel is formed with lamellar micelles.

4. Techniques to Prepare Proniosomes

Three methods are commonly used to prepare proniosomes, as follows.

4.1 Slurry method

A carrier such as maltodextrin powder is added into a round-bottom flask. Then, the stock solution of surfactant and membrane stabilizer is added to form a slurry. If the surfactant solution volume is low, additional organic solvent can be added to get slurry. The flask is then attached to a rotary evaporator and a vacuum is applied at 50-60 rpm with a temperature of 45±2°C and reduced pressure of 600 mmHg, until the sample turns into dried and free-flowing powder. The sample is then kept in a desiccator overnight under a vacuum. This final preparation is known as proniosomes, which have to be stored in a tightly sealed container at refrigerated temperature until further evaluation (Blazek-Welsh & Rhodes, 2001a,

2001b). A schematic diagram of proniosome preparation by the slurry method is shown in Figure 1.

4.2 Slow spray-coating method

The slow spray-coating method is conducted by spraying a surfactant that is soluble in an organic solvent onto the carrier and then evaporating the solvent using a rotary evaporator that has to be evacuated and rotated in a water bath under controlled conditions at 65-70°C for 15-20 min (Sankar, Ruckmani, Durga, & Jailani, 2010; Mishra, Kapoor, & Bhar gava, 2011). The process is repeated until the desired surfactant loading has been achieved. The evaporation should be continued until the powder becomes completely dry. The hydration of the surfactant coated on the carrier brings about multilamellar vesicles when the carrier dissolves (Yoshioka, Sternberg, & Florence, 1994). This preparation method is reported to provide niosomes similar to the conventional niosome preparation method, but with more uniform particle size distribution (Kumar & Rai, 2011a*)*. However, there are some limitations to this method, related to the choice of carrier. The commonly used carrier in this approach is sorbitol, which interferes with encapsulation of the active drugs. A schematic diagram of proniosome preparation by the slow spray-coating method is shown in Figure 2.

4.3 Coacervation phase separation method

The coacervation method is the method of choice to prepare proniosome gel. In this method, precisely weighed amounts of drugs, surfactants, and cholesterol are placed in a clean and dry wide-mouthed glass vial. Then the solvent is added and warmed in a water bath at 60-70°C until the surfactant and cholesterol are completely dissolved. To prevent the loss of the solvent, the open end of the vial will be covered with a lid. The aqueous phase is then added and warmed in the water bath until a clear solution is obtained. The mixture is allowed to cool down to room temperature, during which the dispersion is converted to proniosome gel (Vora, Khopade, & Jain, 1998*)*. The diagram of proniosome preparation by coacervation phase separation method is shown in Figure 3.

5. Preparation of Niosomes from Proniosomes by Hydration

A proniosome powder can be converted to niosomes by hydration, which is conducted by adding an aqueous solvent such as water or saline solution to the proniosome powder. The temperature of the aqueous solvent might be ambient or warm. Vortex mixing or other agitation is also required to obtain the niosomal suspension.

6. Characterisation of Proniosomes

The techniques for the characterisation of prepared proniosomes include:

1) Particle size or its distribution can be determined by various techniques including optical microscopy, Coulter counter, laser diffraction particle size analyzer, or photon correlation spectroscopy, depending on vesicle size of the proniosome. The sample might be diluted to a suitable concentration and stirring might be applied during the measurement.

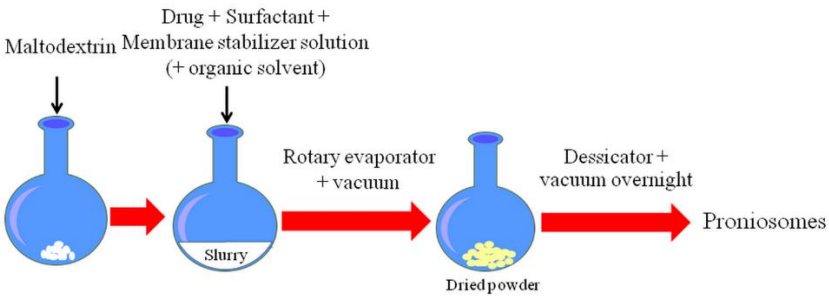

Figure 1. A schematic diagram of the slurry method to prepare proniosome

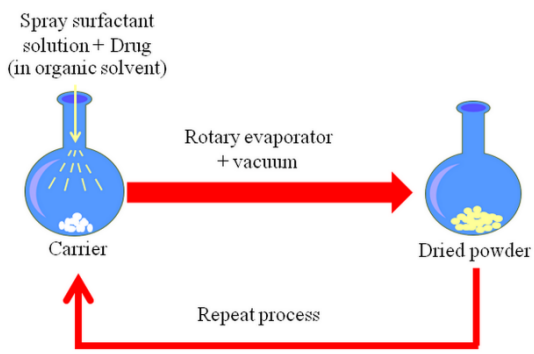

Figure 2. A schematic diagram of the slow spray-coating method for proniosome preparation

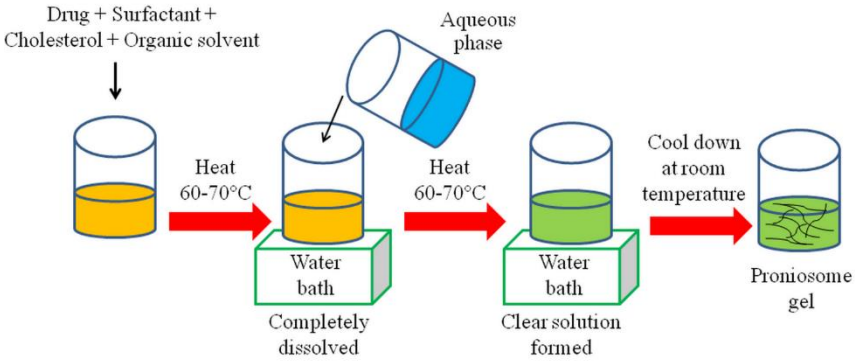

Figure 3. A schematic diagram of the coacervation phase separation method for proniosome preparation

2) Shape and surface morphology can be evaluated by optical microscopy, scanning electron microscopy (SEM), or transmission electron microscopy (TEM). SEM provides the surface morphology of proniosome vesicles, whereas TEM provides information on the inner structure of proniosome vesicles.

3) Entrapment efficiency is evaluated by separating the not entrapped drugs from the niosomal suspension by centrifugation. Suitable quantitative assays to determine the amount of drugs are UV spectrophotometry, high performance liquid chromatography, or gas chromatography. The entrapment efficiency can be calculated using the formula given in Equation 1.

$$\text{Entrapment efficiency} = \frac{\text{Amount of entrapped drug}}{\text{Total amount of drug}} \times 100 \qquad \text{(Eq. 1)}$$

4) *In-vitro* release and skin permeation can be determined by various techniques including Franz diffusion cell, Kesary-Chien diffusion cell, cellophane dialyzing membrane, United States Pharmacopeia (USP) dissolution apparatus type I, or Spectrapor molecular porous membrane tubing. A skin permeation study can use skin of humans or of animals such as rabbits, rats, or pigs. The release of the active ingredients from the proniosomes, and their permeation through the skin, may involve various mechanisms including (i) desorption from the surface of the vesicles, (ii) diffusion from the bilayered membranes, and (iii) a combination of desorption and diffusion mechanisms.

5) Flow ability is determined by measuring the angle of repose with the funnel method. The funnel is in a fixed position and proniosome powder is poured into it. The orifice of the funnel is 10 cm above the surface level. The powder will flow downward through the outlet orifice of the funnel to form a cone on the surface. The angle of repose is calculated from Tan α, determined by measuring the height and the diameter of the cone, as shown in Equation 2.

$$\text{Tan } \alpha = h/r \qquad \text{(Eq. 2)}$$

where α is the angle of repose; h is height of the cone, and r is radius of the cone's base.

6) Stability can be evaluated by storing the prepared proniosomes at various temperatures, such as refrigerated (2-8°C), room (25°C), or elevated temperature (45°C) for a period of 1 to 3 months. The physicochemical characteristics, such as particle size and drug content of the proniosomes, are monitored. The ICH guidelines on stability suggest that the stability of dried proniosome powders has to be tested for the reconstitution property at accelerated conditions (40°C/75% RH) based on international climatic zones and climatic conditions.

7. Mechanism of Action of Proniosomes on Skin Penetration

The precise mechanisms by which the drugs from the vesicles can penetrate through the skin have not yet been predicated. The penetration usually depends on the nature and type of drug, on vesicles formed, and on hydration temperature to convert the proniosomes to niosomes. The stratum corneum is the main barrier layer of the skin. It consists of corneocytes surrounded by a lipid matrix, and is considered the rate-limiting barrier for drug permeation. The lipid domain is modeled as a bilayer composed of ceramides, free fatty acids, cholesterols, cholesterol esters, and cholesterol sulfate. These lipids are organized in two coexisting lamellar phases with 6 nm period (Short periodicity phase: SPP) and 13 nm period (Long periodicity phase: LPP). Especially the LPP and crystalline lateral packing are considered to play essential roles in the skin barrier function. Ceramides account for approximately 50% of the total stratum corneum lipid mass. Their structures include a sphingolipid tail linked to a fatty acid tail. The ceramides form tight packing with strong hydrogen bonds between amide and hydroxyl groups in the ceramide head groups, which are responsible for the strengthening, integrity, and barrier properties of the lipid bilayer in the stratum corneum. Additionally, the cholesterol and cholesterol esters in the intercellular lipid lamellae likely reduce fluidity of the lamellae and stabilize the stratum corneum (Couvreur, Fattal, & Andremont, 1991). Water is absolutely essential for normal function of the skin. The retention of water in the stratum corneum is dependent on two major components: (1) an intracellular hygroscopic and hydrosoluble substance called natural moisturizing factor (NMF) in the corneocyte, and (2) the stratum corneum intercellular lipids arranged orderly to form a barrier hindering

transepidermal water loss (TEWL). Proper water content in stratum corneum is necessary for proper maturation and skin desquamation.

Proniosomes will be hydrated to niosomes when applied to the skin due to skin hydration. On the skin, the formed niosomes absorb, fuse, and loosen the ceramides by competitively breaking the hydrogen bond network, with a high thermodynamic activity at the interface. The concentration gradient of the drug increases, and thus the diffusion pressure increases to drive the drug through the stratum corneum (Yadav *et al.*, 2010). The lipids employed in proniosomal preparation act as the carrier by forming the depot at the site of action to provide sustained release. Skin hydration is also an essential factor that helps convert proniosomes to niosomes. Sufficient hydration of the skin is associated with appropriate conversion of the proniosomes to niosomes, and with prolonged drug release from the niosomes for desired timing.

8. Proniosomal Applications for Dermal and Transdermal Delivery

Proniosomes are considered an attractive delivery system that can facilitate the administration of drugs through the skin. They easily penetrate the stratum corneum owing to the presence of non-ionic surfactants and can control the percutaneous drug release. The application of proniosomes can be designed to provide either topical or transdermal effects depending on the therapeutic intentions. For topical effects, the desirable localised action depends on vesicular size and low penetrability of the carrier that would allow drug localisation at the site of administration, enhancing local efficacy and reducing systemic side effects. Meanwhile, transdermal effects depend on ability of the proniosomes to maintain and deliver the encapsulated drug to systemic circulation by improving drug permeability. Various therapeutic moieties are formulated as proniosomes for either topical or transdermal delivery. In this review, the therapeutic moieties encapsulated in proniosomes are classified by their pharmacological effects to either topical or transdermal types, depending on the therapeutic intentions. The effects on the delivery aspects of the proniosomes have been reviewed, as shown in Table 2.

9. Toxicity of Proniosomes

Similar to niosomes, proniosomes are nonionic surfactant vesicles, but they usually present in dry or gel state. Generally, the physical forms of niosomes and proniosomes do not influence their toxicity, when comparing liquid crystal and gel formulations, according to the study by Medda, Mukhopadhyay, and Basu (1999). However, the surfactants used in the formulation may show toxicity. The research on toxicity of niosomes or proniosomes is still limited. One study on the toxicity of surfactant types of the niosomal formulation evaluated effects on human skin keratinocytes. The results showed that ester type surfactants were less toxic than ether type surfactants, owing to the enzymatic degradation of ester bonds (Hofland *et al*., 1991). Hofland *et al*. (1992) also studied the toxicity of alcohol ethoxylate surfactants via the ciliotoxicity model. The results showed that an increase in the alkyl chain length of the surfactant provided reduced toxicity, whereas increased polyoxyethylene chain length contributed to ciliotoxicity. The study suggested that ciliotoxicity was associated with liquid state formation when increasing the polyoxyethylene chain length. Meanwhile, an increase in the alkyl chain length brought about the formation of a gel, which was less toxic than the liquid state.

Table 2. Various therapeutic moiety -loaded proniosomes classified by their therapeutic use for dermal or transdermal action, along with summary of effects on delivery.

Therapeutic use	Drug	Surfactant	Method	Route of delivery	Effect on delivery aspects	Reference
Anti-inflammatory drug	Ketorolac	Span 60 / Tween 20	Coacervation phase separation method	Transdermal	- Proniosomes prepared with Span 60 provided a higher flux across the rabbit skin than those prepared with Tween 20 (7- and 4-fold higher than the control, respectively).	(Alsarra, Bosela, Ahmed, & Mahrous, 2005)
Anti-inflammatory drug	Piroxicam	Span 20 / Span 40 / Span 60 / Span 80	Coacervation phase separation method	Transdermal	- Piroxicam-loaded proniosome gel formulated using Span 60 and lecithin showed the 7-fold higher enhancement in the permeation flux compared to the control (piroxicam carbopol gel). - Anti-inflammatory study showed that the inhibition in carrageenan-induced rat paw inflammation of piroxicam-loaded proniosome gel formulated using Span 60 and lecithin was 4-fold higher than the control.	(Chandra & Sharma, 2008)

Table 2. Continued.

Therapeutic use	Drug	Surfactant	Method	Route of delivery	Effect on delivery aspects	Reference
Anti-inflammatory drug	Ketoprofen	Span 40	Slurry method	Transdermal	- Steady state transdermal flux and permeability coefficients in albino rat skin from proniosome-derived niosomal gel were significantly higher (50.81 μg/cm^2/h and 5.74 x 10^{-3} cm/h, respectively) than those from plain gel (38.12 μg/cm^2/h and 3.81 x 10^{-3} cm/h, respectively).	(Solanki, Parikh, & Parikh, 2009)
Anti-inflammatory drug	Meloxicam	Span 20 / Span 60 / Span 80 / Tween 20 / Tween 60 / Tween 80	Coacervation phase separation method	Transdermal	- The meloxicam-loaded proniosomes provided a significantly enhanced transdermal flux and reduced lag time across the rat skin by approximately 2-fold when compared to the meloxicam standard gel. - The meloxicam proniosome gel provided 65% inhibition of inflammation at 6 h, which was better than the meloxicam standard gel that provided only 29 %inhibition.	(Mahrous, 2010)
Anti-inflammatory drug	Celecoxib	Span 40 / Span 60	Coacervation phase separation method	Transdermal	- Celecoxib-loaded proniosome gel performed approximately 2-fold higher flux across albino rat skin compared to the niosome suspension. - Proniosome gel showed 100% inhibition of paw edema in rats up to 8 h and performed 95% and 92% inhibition after 12 h and 24 h, respectively. In contrast, the standard (carbopol gel) had 100% inhibition up to only 2 h and the percentage of inhibition was decreased to 63% after 24 h.	(Alam, Baboota, Kohli, Ali, & Ahuja, 2010)
Anti-inflammatory drug	Tenoxicam	Span 20 / Span 60 / Span 80 / Tween 20 / Tween 60 / Tween 80	Coacervation phase separation method	Transdermal	- Tenoxicam proniosome gel showed a higher permeation flux (0.11 mg/cm^2/h) compared to the carbopol gel (0.017 mg/cm^2/h) across the rat skin. - The *in-vivo* study in male rats of tenoxicam-loaded proniosomes showed no irritation and significantly higher anti-inflammatory effects (the least area under the plasma concentration-time curve of 49.51) compared to the tenoxicam marketed oral tablets (the least area under the plasma concentration-time curve of 79.75).	(Ammar, Ghorab, El-Nahhas, & Higazy, 2011)
Hormonal therapy and contraceptive	Levonorgestrel	Span 40	Coacervation phase	Transdermal	- The levonorgestrel-loaded proniosomes increased the	(Vora, Khopade, &

Table 2. Continued.

Therapeutic use	Drug	Surfactant	Method	Route of delivery	Effect on delivery aspects	Reference
agent			separation method		uterine mucosal thickness 5-fold and inhibited the corpora lutea formation by 84.81% relative to the control, which indicated the effective effect for contraception.	Jain, 1998)
Hormonal therapy and contraceptive agent	Estradiol	Span 20 / Span 40 / Span 60 / Span 85 / Tween 20 / Tween 60 / Tween 80	Coacervation phase separation method	Transdermal	- Proniosome gel prepared by Span 40 and Span 60 showed a higher flux of estradiol permeated across the rat skin than that of the control group. - The experiment indicated that either the direct transfer of the drug from the vesicles to the skin and the penetration enhancer effect by a non-ionic surfactant might contribute to the mechanism of the proniosomes for enhancing the estradiol permeation through the skin. - The proniosome gel and niosome suspension (diluted proniosome formulation) showed different permeation profiles of estradiol across the skin. The proniosome gel provided a higher permeation flux of estradiol across the skin as compared to the niosome suspension.	(Fang, Yu, Wu, Huang, & Tsai, 2001)
Hormonal therapy and contraceptive agent	Ethinylestradiol and Levonorgestrel	Span 20	Coacervation phase separation method	Transdermal	- The ethinylestradiol and levonorgestrel were released from the proniosomes with an initial fast release phase followed by a sustained release pattern. The percentage cumulative release of the drug in 24 h was found in the range of 74-86%. The formulation containing Span 20, lecithin, and cholesterol at a ratio of 50:150:100 presented the maximum percentage of drug release in 24 h (86.42%). - The increment of cholesterol content in the formulation facilitated the sustained release of ethinylestradiol and levonorgestrel and reduced the initial burst release effect.	(Chauhan, Naved, & Parvez, 2019)
Anti-hypertensive and cardiology drug	Losartan potassium	Span20 / Span 40 / Span 60 / Span 80 / Tween 20 / Tween 40 / Tween 80	Coacervation phase separation method	Transdermal	- The losartan potassium proniosome gel prepared with Span 40 showed the highest flux permeation (0.116 $mg.cm^2/h$) for 24 h across the rat skin, which was 2.6 times higher than the control. - The losartan potassium proniosome gel containing	(Thakur *et al*., 2009)

Table 2. Continued.

Therapeutic use	Drug	Surfactant	Method	Route of delivery	Effect on delivery aspects	Reference
					Span 40 was loaded in hydroxypropyl methylcellulose (HPMC) or carbopol and fabricated as a transdermal patch. The pharmacokinetic study showed a significantly higher extent of absorption of the losartan potassium proniosomal transdermal patch as compared to the oral marketed product by approximately 1.93 times.	
Anti-hypertensive and cardiology drug	Furosemide	Span 40	Coacervation phase separation method	Transdermal	- The transdermal enhancing mechanism of furosemide-loaded proniosomes was explored by the FTIR and DSC techniques. The proniosome gel appeared to disrupt the multi-lamellar lipid bilayers by extracting the lipids, thus resulting in the loosening of the permeable structure for drug penetration. Therefore, after treatment with the proniosomes, the composition and the complex structural arrangement of lipids in the stratum corneum was decreased, subsequently leading to an increase in the stratum corneum permeability.	(Azeem, Ahmad, & Talegaonkar, 2009)
Anti-hypertensive and cardiology drug	Carvedilol	Span 60 / Brij 72[a]/ Brij 78[b]/ Brij 92[c]	Coacervaion phase separation method	Transdermal	- Proniosomes prepared with Brij 72[a] and Span 60 presented better proniosome-forming ability and greater entrapment efficiency than those prepared with Brij 78[b] and Brij 92[c]. - Carvedilol-encapsulated proniosome gel prepared with Span 60 exhibited a higher cumulative amount of drug permeation (37-53 µg/cm^2) at 24 h than those prepared with Brij 72[a] (54-65 µg/cm^2) and the drug solution (~30 µg/cm^2).	(Aboelwafa, El-Setouhy, & Elmeshad, 2010)
Anti-hypertensive and cardiology drug	Atenolol	Span 20 / Span 40 / Span 60 / Span 80	Coacervaion phase separation method	Transdermal	- The atenolol proniosome formulation containing Span 40 and Span 60 showed the maximum percentage of drug release (99.68%). - The relative bioavailability of the atenolol proniosome gel administered to rabbits via the transdermal route presented a 365.38-fold increase from the oral route. The maximum concentration (C_{max}) was reduced, the area under the plasma concentration-time curve)AUC(was increased,	(Ramkanth, Chetty, & Sudhakar, 2014; Ramkanth *et al*., 2018)

Table 2. Continued.

Therapeutic use	Drug	Surfactant	Method	Route of delivery	Effect on delivery aspects	Reference
					and the mean residence time (MRT) was extended	
Corticosteroids	Hydrocortisone	Span 20 / Span 40 / Span 60 / Span 80 / Tween 40 / Tween 60 / Tween 80	Coacervaion phase separation method	Dermal	- The formulations of Span : Span combinations showed a higher entrapment efficiency when compared to Span : Tween combinations. - The *in-vitro* release study indicated that the Span 20 : Span 80 proniosome formulation presented 58.29% drug release, which was extended up to 8 h, whereas the maximum release of the drug from the market cream was 34.7% at 2 h which then decreased over time. - The proniosome hydrocortisone gel showed the prolonged anti-inflammatory action by the inhibition of hind paw inflammation of mice, exceeding the commercial hydrocortisone cream by 4 h.	(Sankar, Praveen, Prasanth, Srinivas, & Ruckmann, 2009)
Antihistamine drug	Chlorpheniramine maleate (CPM)	Span 40	Coacervation phase separation method	Transdermal	- The proniosomes containing Span 40, lecithin, and cholesterol which was prepared by ethanol showed optimum stability, loading efficiency, particle size, and release kinetic over 6 h, which was suitable for the transdermal delivery of CPM.	(Varshosaz, Pardakhty, Mohsen, & Baharanchi, 2005)
Antihistamine drug	Hydroxyzine hydrochloride	Span 40 / Tween 20 / Tween 60	Coacervation phase separation method	Dermal	- Among all formulations, the proniosome gel formulated with Tween 60 : Span 40 and combined with phospholipon 90H provided the highest entrapment efficiency (94.8%) and highest skin deposition in the stratum corneum (88.24%) at the end of 24 h. The presence of phospholipids helped retain the drug molecules within the skin, thus leading to the prolonged presence of the drug and localised action in the skin.	(Rita & Lakshmi, 2012)
Antifungal drug	Griseofulvin	Span 20 / Span 40 / Span 60 / Span 80	Coacervation phase separation method	Transdermal	- The optimised griseofulvin-loaded proniosome formulation showed a 131.5-fold increase in the transdermal flux as compared to the plain drug solution in water.	(Gupta, Ahirwar, Sharma, & Jhade, 2009)
Antifungal drug	Fluconazole	Span 20 / Span 60 / Span 80 /	Coacervation phase separation	Dermal	- The *ex-vivo* skin penetration and retention study showed that the fluconazole-loaded	(Sandeep, Vasavi, & Srinivas,

Table 2. Continued.

Therapeutic use	Drug	Surfactant	Method	Route of delivery	Effect on delivery aspects	Reference
		Tween 20 / Tween 80	method		proniosomes clearly delayed the drug penetration through the skin. The formulation containing Span 60 showed a high amount of drug retention in the skin by 25.97%, which was higher than the control (13.33%).	2014)
		Span 20 / Span 60 / Tween 80	Coacervation phase separation method	Dermal	- The selected fluconazole-loaded proniosome formulation containing a mixture of Span 60 and Tween 80 (1:1) gave a significant prolonged release by 40.5% after 6 h in comparison to the control which released 99.8% within 4 h. - The optimised proniosome formulation had a larger inhibition zone diameter (5.3 cm) which indicated the higher antifungal activity as compared to the control HPMC gel (4.2 cm) and the plain gel (0 cm), respectively.	(El-Enin, Khalifa, Dawaba, & Dawaba, 2019)
Antifungal drug	Clotrimazole	Span 40 / Span 60 / Tween 60 / Tween 80	Coacervation phase separation method	Dermal	- The *ex-vivo* skin permeation and *ex-vivo* drug deposition study through guinea pig skin indicated the sustained release of the drug from the proniosome gel over 24 h. The formulation prepared with Span 60 and cholesterol presented a 2-fold increase in drug deposition in the skin when compared to the conventional cream. - The antifungal activity, revealed as the diameter of the inhibition zone, of the proniosome gel was 35.1 mm, which was larger than that of the market formulation (29.3 mm).	(Pankaj, Rini, & Dandagi, 2013)
Antifungal drug	Itraconazole	Span 60	Slurry method	Transdermal	- Itraconazole proniosome-loaded 5% methyl cellulose gel presented a higher drug permeation through rat skin than other gel bases. - The percentages of the relative bioavailability for the itraconazole proniosome gel in comparison to the marketed capsule and solution (Sporanox®) were found to be 189.91% and 143.75%, respectively, indicating the higher bioavailability of the	(Samy, Ramadan, Abu El-Enin, Mortagi, & Abd-Alhaseeb, 2018)

Table 2. Continued.

Therapeutic use	Drug	Surfactant	Method	Route of delivery	Effect on delivery aspects	Reference
					- itraconazole proniosome gel compared to the marketed capsule and solution. - The itraconazole proniosome gel presented better antifungal activity in the form of a larger zone of inhibition (3.2 cm) as compared to the marketed capsule (Sporanox®) (2.8 cm) and itraconazole suspension (2.5 cm).	
Antihyperlipidemic drug	Atorvastatin	Span 60	Coacervation phase separation method	Transdermal	- The optimised proniosomes showed 99.72% drug release within 24 h which was slow and in a controlled manner as compared to the control. - The pharmacokinetics study in rats by transdermal application indicated that the C_{max} of the atorvastatin proniosome gel was significantly reduced (8.4 ng/ml) compared to the atorvastatin suspension (10.5 ng/ml). The AUC of the atorvastatin proniosome gel was increased to 117 ng h/ml while it was 85 ng h/ml in the atorvastatin suspension. Moreover, the half-life ($t_{1/2}$) of the atorvastatin proniosome gel was extended 2-fold (7 h) compared to the atorvastatin suspension (3.5 h).	(Soujanya & Prakash, 2018a)
Antihyperlipidemic drug	Lovastatin	Tween 80	Coacervation phase separation method	Transdermal	- The optimised proniosomes showed 99.49% drug release within 24 h which was slow and in a controlled manner as compared to the control. - The pharmacokinetics study in rats by transdermal application indicated that the C_{max} of the lovastatin proniosome gel was significantly reduced (7.5 ng/ml) compared to the lovastatin suspension (9.4 ng/ml). The AUC of the lovastatin proniosome gel was increased to 145 ng h/ml while it was 105 ng h/ml in the lovastatin suspension. Additionally, the $t_{1/2}$ of the lovastatin proniosome gel was extended to 6.3 h from 4.3 h in the lovastatin suspension.	(Soujanya & Prakash, 2018b)
Antidiabetic drug	Metformin hydrochloride	Span 40 / Span 60	Coacervation phase separation method	Transdermal	- In comparison with other formulations, the metformin hydrochloride-loaded proniosome gel consisting of Span 60 : cholesterol : lecithin	(Loona, Gupta, & Khan, 2012)

Table 2. Continued.

Therapeutic use	Drug	Surfactant	Method	Route of delivery	Effect on delivery aspects	Reference
					(9:2:9) formulation provided the maximum entrapment efficiency (76.8%) and the lowest percentage of drug release after 24 h (75.9%), which indicated the prolonged release action over 24 h.	
Antidiabetic drug	Glimepiride	Span 20 / Span 60 / Tween 20 / Tween 60	Coacervation phase separation method	Transdermal	- The glimepiride-loaded proniosome gel presented a higher permeation flux (36.54 µg/cm^2/h) across the rabbit skin as compared to the HPMC niosome gel (29.67 µg/cm^2/h) and HPMC gel (25.13 µg/cm^2/h). - The *in-vivo* hypoglycemic activity study in diabetic wistar rats showed that the hypoglycemic activity was extended to 24 h by the transdermal administration of the glimepiride–loaded proniosome gel compared to the oral administration of the glimepiride suspension, which terminated after 6 h.	(Abdallah, Sabry, & Hasan, 2016)
Dietary supplement and cosmetics	Vinpocetine	Span 20 / Span 80 / Tween 20 / Tween 80 / SE L-1695[d] / SE M-1695[e] / SE P-1670[f] / SE S-370[g] / SE S-970[h] / SE S-1670[i]	Coacervation phase separation method	Transdermal	- The SE L-1695[d] proniosome formulation exhibited a 4-fold increase in permeation flux across the mouse skin as compared to the control. - One patch containing the same drug loading as one commercial oral tablet was able to preserve the plasma concentration over the minimum effective concentration for 48 h and would be able to replace 6 commercial tablets.	(El-Laithy, Shoukry, & Mahran, 2011)
Dietary supplement and cosmetics	Curcumin	Span 60 / Span 80 / Tween 20	Coacervation phase separation method (Ether injection method)	Transdermal	- The optimised formulation of Span 80: cholesterol (1:4) showed the prolonged *in-vitro* drug release over a period of 24 h. - The result for the anti-inflammatory and anti-arthritic activity of the curcumin-loaded proniosomes was similar to the standard indomethacin but not as efficient as the commercial products.	(Kumar & Rai, 2011b, 2012)
Dietary supplement and cosmetics	Tretinoin	Span 40 / Span 60	Slurry method	Dermal	- The tretinoin-loaded proniosomes incorporated in the carbopol gel showed a higher propensity to decrease the open and closed comedones, papules and total	(Rahman *et al*., 2015)

Table 2. Continued.

Therapeutic use	Drug	Surfactant	Method	Route of delivery	Effect on delivery aspects	Reference
					number of acne lesions in acne patients when compared to the marketed product.	

Note: [a] Brij 72 is polyoxyethylene (2) stearyl ether; [b] Brij 78 is polyoxyethylene (20) stearyl ether; [c] Brij 92 is polyethylene glycol oleyl ether; [d] SE L-1695 is sucrose laurate (HLB=16); [e] SE M-1695 is sucrose myristate (HLB=16); [f] SE P-1670 is sucrose palmitate (HLB=16); [g] SE S-370 is sucrose stearate (HLB =3); [h] SE S-970 is sucrose stearate (HLB =9); [i] SE S-1670 is sucrose stearate (HLB =16).

10. Conclusions

Proniosomes are promising drug carriers that can be hydrated to yield niosomal dispersions. Proniosomes provide greater physical and chemical stability and can overcome the stability problems of niosomes and liposomes, such as fusion, aggregation, and leakage of drugs during storage. They have the ability to entrap both hydrophilic and lipophilic drugs and allow cost-effective scale-up. Proniosomes in dry powder form can be processed to convenient forms, such as beads, granules, capsules, or tablets. Proniosome gels are also attractive as carriers to deliver drugs through transdermal/topical routes, due to their advantages including non-toxicity, penetration enhancing effects, and capacity to modify drug release properties. Several therapeutic active ingredients have been studied and proniosome systems have been developed for many purposes. Proniosomes obviously represent a drug delivery technology that can be exploited for efficiency and good permeability in dermal and transdermal delivery.

Acknowledgements

This research project is supported by Mahidol University, Bangkok, Thailand.

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