

REVIEW

Open Access



Recent advances of non-ionic surfactant-based nano-vesicles (niosomes and proniosomes): a brief review of these in enhancing transdermal delivery of drug

Durga Bhavani G^{1*}  and Veera Lakshmi P²

Abstract

Background: Hepatic first-pass metabolism and poor therapeutic efficiency at targeted region are the endemic problems of new drug molecules. Thus, comprehensive research has been carried out on the novel vesicular drug delivery systems in nanotechnology from the last few years. These nano-carrier systems have developed to overcome the limitations that are associated with hepatic first-pass metabolism in conventional oral dosage forms and the barrier properties of the lipid bilayer in stratum corneum via transdermal drug delivery for improving the bioavailability of various drugs.

Main body: In recent years, several targeted vesicular drug delivery carriers are developing like liposomes, niosomes, proniosomes, transferosomes, ethosomes, and electrosomes. Among them, niosomes and proniosomes are to be better carriers to increase therapeutic efficiency and bioavailability by reducing the side effects and acting as a promising approach for transdermal drug delivery. Both are non-ionic surfactant-based vesicles and are amphiphilic. This article concisely reviews the possible mechanisms within niosomes and proniosomes to enhance transdermal drug delivery, types, composition, preparation techniques, characterizations, and its applications.

Conclusion: As per the researches done in the formulation of various nano-carrier systems through transdermal approach for the enhancement of bioavailability, it can be stated that the hepatic first pass metabolism can be reduced as well as therapeutic efficiency can be increased by many folds compared to their oral marketed formulations.

Keywords: Niosomes, Proniosomes, Possible mechanisms of skin penetration, Methods of preparation, Characterization and its applications

Background

The phenomenon of targeting drug delivery systems is to deliver the drug in the body in such a manner that it should show its action to the targeted desired site to achieve the therapeutic response, i.e., where its action should be needed by limiting undesirable interaction to non-targeted tissues. Paul Ehrlich introduced this idea in 1909, and he called this strategy “magic bullets” [1, 2].

In the drug delivery system, although the oral administration route is beneficial but limited due to the hepatic first-pass metabolism that increases undesirable side effects, it reduces the therapeutic efficiency and bioavailability of many drugs in various treatments of diseases [3, 4]. Thereby, transdermal drug delivery system offers an attractive, a non-invasive, and better alternative method to reduce the number of doses, frequency of administration, systemic toxicity, hepatic first-pass metabolism, gastric irritation, unwanted side effects associated with oral, control drug level in plasma for a sustained period for locally and systematically that result enhancing bioavailability, and better patient compliance [5, 6].

* Correspondence: bhavanidurga246@gmail.com

¹Jawaharlal Nehru Technological University, School of pharmaceutical Sciences and Technologies, Department of Pharmaceutics, Kakinada, Andhra Pradesh 533003, India

Full list of author information is available at the end of the article

Nevertheless, the lipid bilayer of skin that is stratum corneum acts as a very tough diffusion barrier, limiting the permeation of active drug moieties. Novel approaches like nanotechnology have developed in the field of science, which has introduced various targeted novel vesicular drug carrier systems like liposomes, niosomes, proniosomes, ethosomes, and electrosomes. Among these, niosomes and proniosomes have distinct advantages over the other vesicles by acting as drug-containing reservoirs [7, 8]. Liposomes were not preferred as these were composed of concentric phospholipids that make chemically unstable vesicles due to oxidative degradation and rancidification [9].

Main text

Niosomes are the microscopic lamellar structures in an emerging drug delivery system, composed of non-ionic alkyl or polyglycerol etheric surfactant and cholesterol in an aqueous medium. Handjani-vila et al. introduced the class of niosomes [10]. These are amphiphilic, biocompatible, biodegradable, non-toxic materials to encapsulate the medication in vesicles that improve the bioavailability of the drug, therapeutic efficiency, drug penetration through the skin, releases the drug in a sustained and controlled manner, and used to target the desired site by adjusting the composition that helps to reduce the side effects. However, the major drawback is physical instability during storage that causes aggregation, fusion, sedimentation, and leakage of the entrapped drug. This lead to the development of a revolutionary technique of provesicular system called “proniosomes” [11, 12].

Proniosomes are the niosome hybrid of liquid crystalline compact or dry formulated carrier particles coated with non-ionic surface-active agents, converted to niosomal dispersion immediately by hydrating with hot water on gentle agitation before use. These versatile vesicular carriers exhibit a more potential promising approach for transdermal drug delivery and act as vehicles or permeation enhancers via stratum corneum. These are preferred and well documented than other vesicles as it shows more excellent physical and chemical stability, non-toxic, biodegradable, biocompatible, skin permeation ability, prolonged drug release, enhanced bioavailability, and reducing side effects and high reflux. Most of the research innovators agreed that effective drug delivery is achieved through direct contact of these vesicles to the skin [13, 14].

Possible Mechanisms of action of niosomes and proniosomes for transdermal drug delivery

An important requirement for transdermal delivery is that the drug carried by a vehicle should be able to reach the skin surface at an adequate rate and in sufficient

amounts. A wide range of applications and several mechanisms have been reported because of their ability to enhance the percutaneous drug delivery to the deeper layer of skin. In general, a permeant applied to the skin has three possible routes across the epidermis. The transcellular route, a lipid domain associated with the proteins inside corneocytes, the intercellular route, and the appendageal route, through hair follicles, via associated sebaceous glands, and sweat ducts. Based on the drug nature, the mechanism of drug transport may be varied [7, 15, 16].

Mechanisms for transdermal enhancement of hydrophilic drugs include (i) increasing drug thermodynamic activity—the encapsulated drug vesicles get adsorbed and fused on to the surface of the skin. Then, a thermodynamic activity gradient is developed, which enhances the diffusion pressure for drug permeation at the surface that acts as a driving force for drug penetration across stratum corneum (sc) [17–19]; (ii) modification of surface electrical charge of ionic drugs; (iii) solubilizing of sebum by vesicles to facilitate follicular delivery; and (iv) pore pathway of large water-soluble molecules loaded in niosomes.

Mechanisms for transdermal enhancement of hydrophobic drugs include (i) disruption of lipid bilayer of the stratum corneum (SC)—structural modification of stratum corneum, i.e., the densely packed lipid bilayer, helps to fill up the extracellular spaces by a disruption to enhance the permeation rate; (ii) enhancement of transdermal permeation through nano-sizing; (iii) changing drug partition into skin layers; (iv) hydrating skin and the dilation of the SC intercellular channels—niosomes cause an alteration in the barrier property of stratum corneum, which enhances sc hydration by reducing trans-epidermal water loss, leading to loosening the tightly packed structure and lyses of the membrane by lysozyme and releasing the entrapped drug into the system [20–26]; and (v) changing the permeation pathway of lipophilic permeants to follicular delivery [27]. The non-ionic surfactants play a crucial role as a penetration enhancer that enters into the intercellular lipids through endocytosis [28, 29]. The possible mechanisms of action to enhance skin penetration are as shown in Fig. 1.

Structure of niosome

It is a bilayered spherical structure composed of non-ionic surfactant and cholesterol, i.e., as shown in Fig. 2. In this, the non-ionic surfactant is present in such a way that hydrophobic end faces inwards (toward the lipophilic phase). In contrast, hydrophilic end faces outwards (toward aqueous phase), resulting in the closed lipid bilayer that surrounds solutes in the aqueous phase, which appears like the outer and inner surface of the

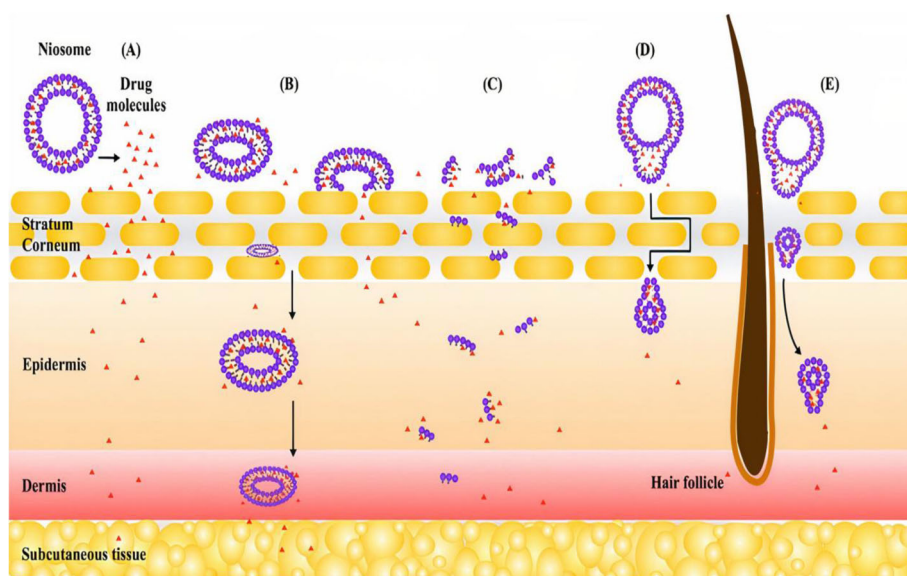


Fig. 1 Possible mechanisms of action of niosomes and proniosomes for skin penetration in topical and transdermal drug delivery. **a** Release of drug molecules by niosomes. **b** Niosomes adsorption and fusion with stratum corneum. **c** Penetration of niosomes through intact sc. **d** Components of niosomes act as penetration enhancer and increase absorption of drug. **e** Penetration of niosomes through hair follicles or pilosebaceous units [16]

hydrophilic area, that sandwiched lipophilic area in between them [31, 32].

Composition of niosome

Two components are essential to form the vesicle of the niosome.

A. Cholesterol

It is a steroid derivative that helps to form a proper shape and rigid structure to niosome [33].

B. Non-ionic surfactant

The hydrophilic-lipophilic balance (HLB) value of a surfactant is essential in the formation of niosomes. The

range of HLB should be between 4 and 8 [34, 35] to produce stable optimum vesicles with high drug compatibility. Various types of non-ionic surfactants with examples are listed in Table 1. In addition to these, charge inducers are also added because they cause repulsions on the surface of vesicles that provide higher zeta potential. Thus, it helps to prevent fusion and enhance vesicle stability [36, 37].

Types of niosomes

Niosomes are categorized into three groups, based upon the size of a vesicle, i.e., as shown in Table 2 and represented in Fig. 3.

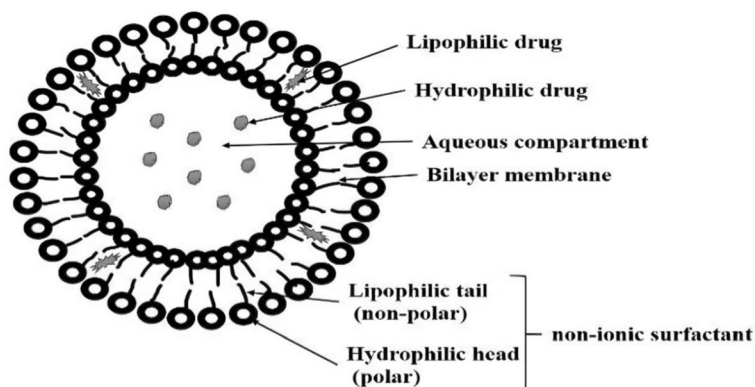


Fig. 2 Schematic representation of structure of niosome [30]

Table 1 Types of non-ionic surfactants

Non-ionic surfactants	Examples [1]
Ethers	Brij, decylglucoside, octyl glucoside, lauryl glucoside
Esters	Spans, glyceryl laurate, polysorbates
Fatty alcohols	Cetyl alcohol, cetostearyl alcohol, stearyl alcohol
Block copolymers	Poloxamers

Advantages of niosomes

1. Niosomes have an amphiphilic infrastructure, which provides a wide range of solubility for drug molecules [2].
2. It is the dispersion containing water as a vehicle that offers more patient compliance than oily preparations [10].
3. It enhances the skin penetration of medicament and improves the oral bioavailability of poorly soluble drugs [39].
4. These can be taken via oral, parenteral, topical, and transdermal routes of applications [40].
5. Niosomes are safe as they composed of biocompatible, biodegradable, and non-toxic materials [41].
6. These vesicle formulation characteristics are variable and controllable by altering the composition, dimension, lamellarity, surface load, and concentration [42].
7. This vesicle can act as a depot, and drug release from the closed bilayer structure may be controlled to the target site [43].
8. Due to the chemical stability of their structural composition, handling and storage conditions do not require special conditions.
9. These are osmotically active and stable and have longer shelf-life.
10. It protects the drug from enzymatic degradation [44].
11. Highly economical for large-scale production.

Disadvantages of niosomes

1. Due to the dispersion form of niosomes, there may be a chance to sediment, accumulate, fuse, or leakage the entrapped drug during storage [45].

Table 2 Types of niosomes

S.no.	Type	Size [12]
a.	Small unilamellar vesicle	0.025–0.05 μm
b.	Large unilamellar vesicle	$\geq 0.05 \mu\text{m}$
c.	Multi lamellar vesicle	$\geq 0.10 \mu\text{m}$

2. Some of the formulation techniques are time-consuming and require special equipment.
3. During the process of hydration, there may be a chance of incomplete hydration of surfactants [46].

Factors governing vesicle formation

(a) Drug

The physicochemical properties of encapsulated drugs can influence the rigid bilayer structure, vesicle size, and charge on the surface of niosome. By interacting with the solute and surfactant head group, the entrapped drug may enhance the charge and mutual repulsions that result in the large size of the vesicle [47].

(b) Type of surfactant

Generally, ether types of surfactants are more favorable than ester forms, as these are quickly degraded and became unstable in vivo. The structure of the surfactant is as shown in Fig. 4.

i. Hydrophilic-lipophilic balance (HLB)

It indicates the solubility of the surfactant, which is a dimensionless parameter [49]. The lower the HLB value indicates the more lipophilic nature of surfactant and vice-versa. It also influences the entrapment efficiency of the drug molecule in niosomes.

ii. Critical packing parameter

It influences the geometry of vesicles. Based on the surfactant's critical packing parameter (CPP) value, it is possible to predict the shape of the nanostructure [50, 51]. It depends upon the symmetry of surfactant and can be calculated by using the following equation:

$$\text{CPP} = v/lc \times a_0$$

where v is the hydrophobic group volume, lc is the critical hydrophobic group length, and a_0 is the area of hydrophilic head group.

Based on the CPP value, the state and structure of vesicles are varied and is as shown in Fig. 5.

(c) Membrane composition

Niosomes can be stabilized through the addition of various additives to the mixture of surfactant and drug. Additives like cholesterol influence the permeability of vesicle [53]. If the membrane has more cholesterol content that results in a more rigid vesicle structure and helps to reduce the leakage of the drug, it improves entrapment efficiency.

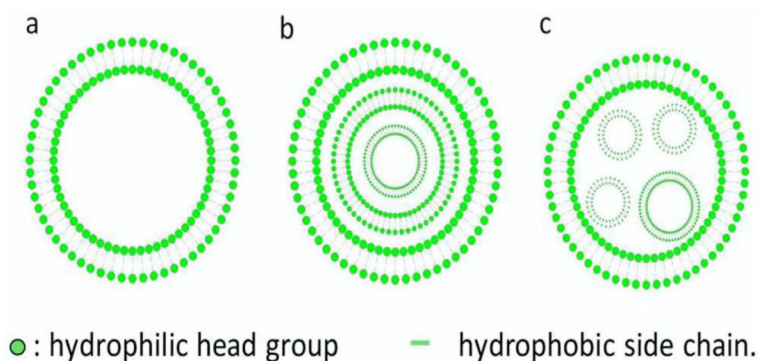


Fig. 3 Different types of niosomes [38]

(d) Method of preparation

The size of the vesicle is varied depending on the preparation method. Thus, it influences the entrapment efficiency and release of drugs from the vesicle.

(e) Temperature of hydration

It influences the shape and size of the niosome. The temperature of the system should be above the gel to liquid phase transitional temperature for ideal conditions. Along with these, the time of hydration and hydration medium volume are also critical parameters because improper hydration results in fragile niosomes or create leakage of the drug [54].

(f) Resistance to osmotic stress

It influences the diameter of vesicles. The addition of hypertonic salt solution results decreases in the diameter of the vesicle, whereas hypotonic salt solution causes slight swelling.

(g) Charge

The size, stability, and volume within niosomes are altered by charge inducing agents. The interlamellar distance between successive bilayer increases because of the presence of a charge in a

multilamellar vesicle structure that contributes to the higher total volume [55].

Preparation methods of niosomes

Preparation methods will affect the number of bilayers, size distribution, dimensions, and entrapment efficiency [56, 57].

General procedure

Handjani-Vila method

A mixed equivalent amount of cholesterol and surfactant (lipid mixture) in an aqueous phase containing active substance, agitated for a few minutes to get homogeneous lamella phase. Then, homogenize at a controlled temperature by using ultra-centrifugation or employing ultra-sonicator that resulted in the formation of niosomes [58]. Baillie AJ et al. [59] have reported the preparation and properties of niosomes-non-ionic surfactant vesicles by using this method.

A. Preparation of small unilamellar vesicles

i. Sonication method

It is the conventional method to produce small uniform size niosomes. This process includes

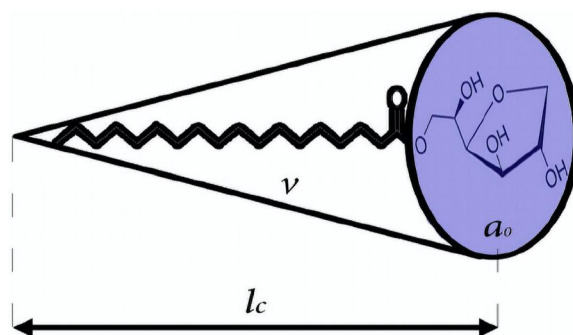


Fig. 4 Schematic representation of structure of surfactant [48]
























	State	CPP		Structure	Symbol	Texture
<div style="display: flex; flex-direction: column; align-items: center;"> <div style="display: flex; justify-content: space-around; width: 100%;"> <div style="text-align: center;"> Hydrophilic ↑ HLB ↓ Lipophilic </div> <div style="text-align: center;"> Positive ↑ Curvature ↓ Negative </div> </div> </div>	Micelle	 $v/al \leq 1/3$		Sphere	L_1	—
		 $1/3 < v/al \leq 1/2$		Cylinder	L_1	—
	Liquid Crystal	 $v/al \leq 1/3$		Discontinuous Cubic	I_1	—
		 $1/3 < v/al \leq 1/2$		Hexagonal	H_1	
		 $1/2 < v/al \leq 1$		Bicontinuous Cubic	V_1	—
		 $v/al \approx 1$		Lamellar	L_α	
		 $1 \leq v/al$		Rev. Bicontinuous Cubic	V_2	—
		 $1 < v/al$		Rev. Hexagonal	H_2	
		 $1 < v/al$		Rev. Discontinuous Cubic	I_2	—
	Rev. Micelle	 $1 < v/al$		Sphere	L_2	—

Fig. 5 Self-assembly structures formed in surfactant systems, and their relationship between the structure and three parameters, CPP, HLB and interfacial curvature [52]

mixing an aliquot of drug solution with a lipid mixture of surfactant and cholesterol and subjected to sonication by using titanium probe at a temperature of 60 °C for 3 min to get niosomes. Pando D et al. [60] have successfully reported the preparation and characterization of niosomes containing resveratrol by using this method.

ii. Micro fluidization method

This method involves the submerged jet principle (Fig. 6). The two fluidized streams interact at ultra-high velocities, in precisely defined microchannels within the interaction chamber. The impingement of thin liquid film along a joint front is arranged; thereby, the energy supplied to the system remains within the area of formation of niosomes. That resulted in a smaller uniform size, reproducible niosomes. It is reported that Obeid MA et al. [61] successfully prepared non-ionic surfactant vesicles using microfluidics device NanoAssemble for the purpose of delivering therapeutic siRNA into cancer cells (Fig. 7).

B. Preparation of large unilamellar vesicles

i. Ether injection method

The initial step in this preparation is to dissolve surfactant in diethyl ether and inject it into an aqueous phase containing a drug, which was at 60 °C through 14 gauge needles. Subsequently, ether was vaporized and resulted in single layer vesicles with a diameter ranging from 50 to 1000 nm. Here, the drawback is that it is difficult to remove the small amount of ether, i.e., still present in the vesicle [62, 63]. Singh CH et al. [64] has successfully formulated, characterized, and performed in vitro evaluation of niosomes containing nimesulide.

ii. Reverse phase evaporation method

Weighed surfactant and cholesterol in a 1:1 ratio and dissolved in chloroform and ether mixture (Fig. 8). To this mixture, aqueous phase containing drug was added and followed by sonication at a temperature of 4–5 °C; a small quantity of phosphate buffer saline

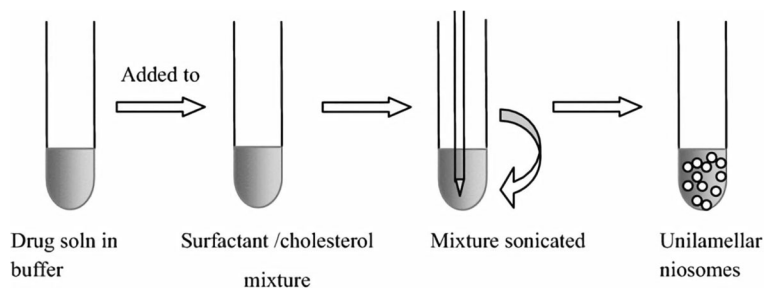


Fig. 6 Schematic diagram of the preparation of niosomes via sonication method [36]

was added and continued to sonicate. Then the organic solvent is removed by applying it to low pressure at 40 °C after that remaining suspension is diluted with phosphate buffer saline. The final product of the niosomes was obtained by heating the mixture at 60 °C for 10 min [65]. Zarei M et al. [66] have successfully loaded niosomes with Paclitaxel via this method.

C. Preparation of multilamellar vesicles

- i. Thin film hydration technique (hand shaking method)
In a round bottom flask, the mixture of cholesterol and surfactant was dissolved in a volatile organic solvent (diethyl ether, chloroform, or methanol) (Fig. 9). Then, remove the solvent by using a rotary evaporator at room temperature (20 °C) that leaves a thin film of the solid mixture on the flask's walls. This dried film is rehydrated with the aqueous phase by gentle agitation at 0–60 °C resulting in the formation of niosomes [68]. Chandraprakash et al. [69] entrapped methotrexate in niosomes using lipophilic surfactants like span 40, span 60 and span 80,

cholesterol, and di-cetyl phosphate in ratio of 47.5:47.5:5. It was reported that the tissue distribution of methotrexate was improved after entrapping into niosomes.

- ii. Transmembrane pH gradient (inside acidic) cycle of drug absorption (remote charge)

In a round bottom flask, the mixture of cholesterol and surfactant was dissolved in chloroform (Fig. 10). Then remove the organic solvent by using a rotary evaporator at room temperature (20 °C) that left a thin film of the solid mixture on the walls of the flask, which rehydrates with 300 mM citric acid (pH 4.0). Further, subjected to 3 successive freeze-thaw cycles and sonicated. To this, adding the aqueous drug solution and vortexes increased the pH 7.0–7.2 by adding disodium phosphate (1 M) and subjected to heating for 10 min at 60 °C to obtain niosome [70]. Bartelds et al. [71] studied the niosomes of varying composition and did a comparative study of niosomes with liposomes. In their study, they found that freeze and thaw cycle shrinks the niosomes prepared using unsaturated surfactants. They also found that the entrapment efficiency of niosomes was reduced.

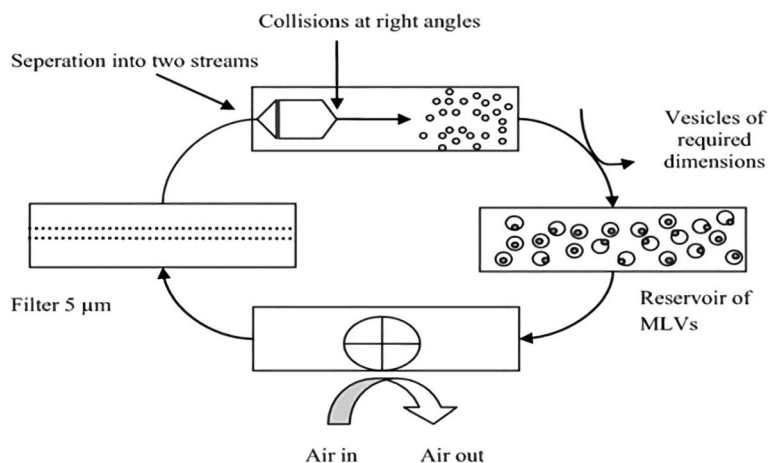


Fig. 7 Schematic diagram of the preparation of niosomes via micro fluidization method [2]

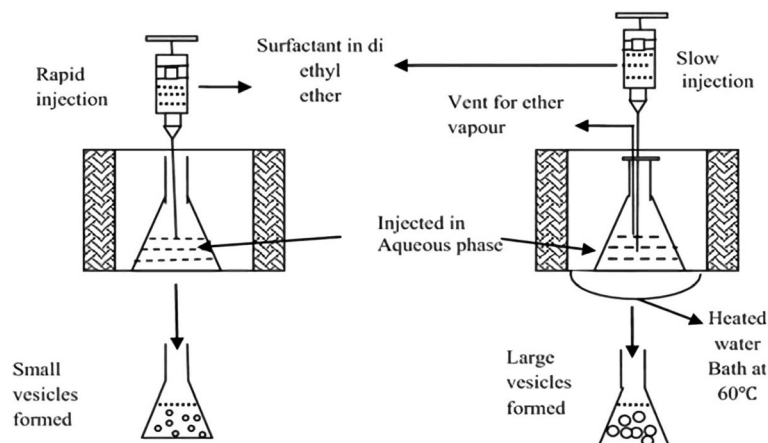


Fig. 8 Schematic diagram of the preparation of niosomes via ether injection method [2]

D. Miscellaneous methods

i. Multiple membrane extrusion method

It is a good method to produce small size niosomes (Fig. 11). In this, the mixture of surfactant, cholesterol, diacetyl phosphate, and chloroform is evaporated, leaving a thin film and rehydrated with the aqueous drug solution. The resultant dispersion extruded through a polycarbonate membrane, then placed in a series of up to 8 passages to obtain niosomes. Rogerson AC et al. [72] studied the distribution of doxorubicin in mice following administration in niosomes.

ii. Lipid injection method

The mixture of surfactant and lipids melted and injected into a hot aqueous drug solution to get niosomes (Fig. 12). The inclusion of drugs in lipids by melting is an alternative method. Kremer J et al.

[73] have prepared vesicles of variable diameter by a modified injection method.

iii. Emulsion method

It forms niosomes by using oil in water emulsion, which was prepared by adding an organic solution of surfactant and cholesterol to the aqueous drug solution. Yoshioka et al. [74] formulated a range of vesicle-in water-in-oil (v/w/o) emulsion from niosomes made from Spans (Span 20, Span 40, Span 60, Span 80) dispersed in an oil (octane, hexadecane, isopropyl myristate). They reported that the release of carboxyfluorescein is slower than vesicle suspensions and w/o emulsion; the release was affected by the HLB value of the surfactant, nature of oil, and temperature of dialysis media. This system has potential for use in drug delivery or as a vaccine vehicle.

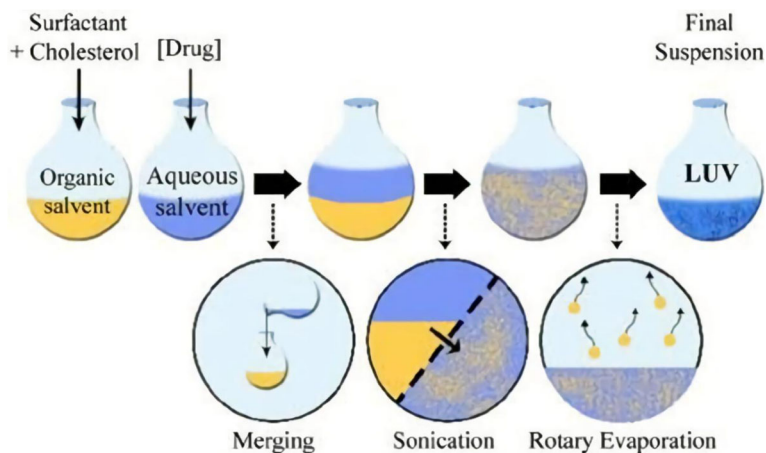


Fig. 9 Schematic diagram of the preparation of niosomes via reverse phase evaporation method [67]

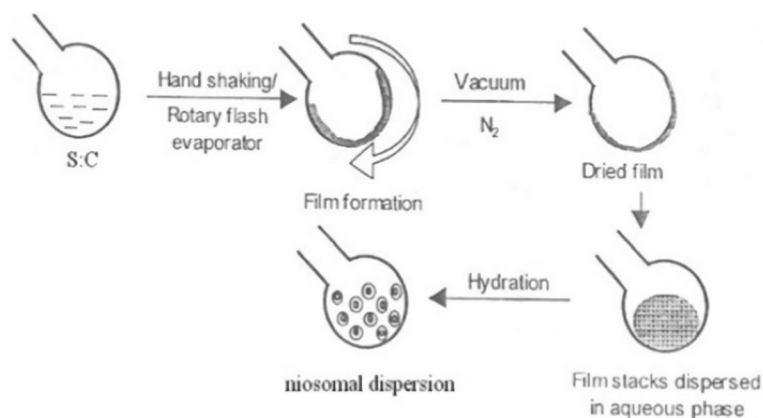


Fig. 10 Schematic diagram of the preparation of niosomes via thin film hydration technique (hand shaking method) [2]

iv. The “bubble” method

It is a novel technology to get niosomes in one step without adding an organic solvent (Fig. 13). This method contains a “bubbling unit” having round-bottomed flask with three necks, i.e., positioned in a water bath. Water-cooled reflux, thermometer, and nitrogen gas suppliers are positioned in first, second, and third necks, respectively. In this, surfactant and cholesterol are mixed in the buffer and then homogenized and “bubbled” at 70 °C in a “bubbling unit” to obtain niosomes. Talsma H et al. [75] have reported the one-step preparation of liposomes and nonionic surfactant vesicles without the use of organic solvents.

Formulation of niosomes from proniosomes

Nowadays, these provesicular drug carrier systems are more beneficial than conventional niosomes (Fig. 14). These are converted into niosomes by naturally

hydrating it with the hot aqueous medium, before use or by hydration of skin itself after application.

Types of proniosomes

This exists as two forms.

1. Dry granular proniosomes

These are dry powder in nature; based upon the carrier that is used in the preparation, and it again involves sorbitol and maltodextrin-based proniosomes [32].

2. Liquid crystalline proniosomes

These are gel form of proniosomes that mainly used for transdermal drug delivery systems [77] (Table 3).

Advantages of proniosomes

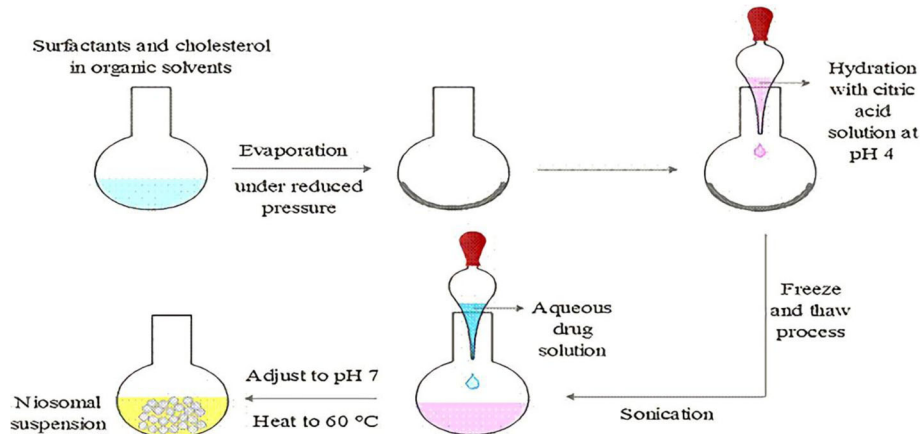


Fig. 11 Schematic diagram of the preparation of niosomes via Trans membrane pH gradient (inside acidic) drug uptake process (remote loading) [15]

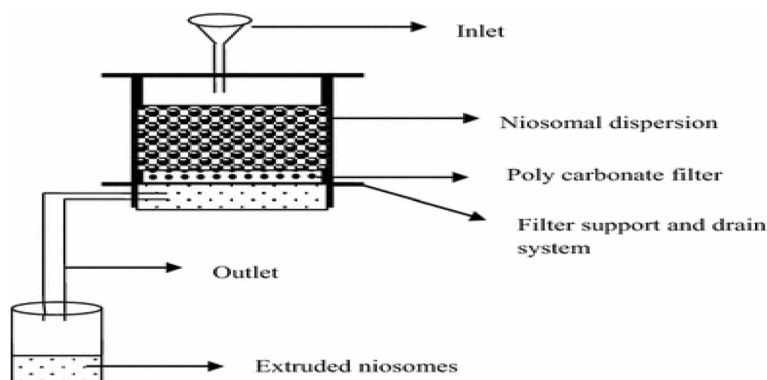


Fig. 12 Schematic diagram of the preparation of niosomes via multiple membrane extrusion method [36]

1. Avoid physical stability problems like fusion, sedimentation, and drug leakage during storage.
2. Prevent the hydrolysis of embedded drugs that inhibit the dispersion's durability.
3. Proniosomes does not show any problems during sterilization and shipping process.
4. Biocompatible, biodegradable, and non-immunogenic.
5. Simple handling and storage conditions [78].

Methods of preparation of proniosomes

These are prepared by three methods, as shown in Fig. 15.

I. Slurry method

Cholesterol and surfactant were mixed in a suitable solvent and transferred into a round-bottomed flask containing the drug and carrier mixture. Add an excess amount of solvent if the surfactant is not loaded correctly, then the solvent was evaporated at 600 mmHg pressure at 50–60 °C in a rotary evaporator under vacuum, resulting in a free-flowing powder of proniosomes, mixed with a suitable gelling agent to get the proniosomal gel [79–82]. Madni et al. [83] formulated the proniosomes by quick slurry method using maltodextrin (carrier), Span 60 (non-ionic surfactant), and cholesterol (stabilizer). They

reported that proniosomes have been shown to be promising candidates for topical delivery of pentazocine.

Advantages

- a. It protects the drug and surfactant from oxidation and hydrolysis.
- b. Surfactant coating is thinner due to the high surface area that makes the rehydration process more efficient.

Disadvantages

- a. As the preparation utilizes specialized equipment using vacuum and nitrogen gas, that makes the process time-consuming.

II. Slow spray coating method

Weighed the required quantity of carrier material into a round bottom flask and kept it in a rotary evaporator. Then surfactant and cholesterol are mixed and sprayed on to the carrier and evacuate under 65–70 °C for 20 min in a water bath. Continue the evaporation process till to get

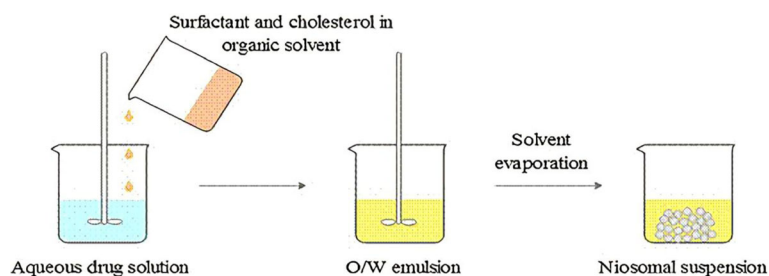
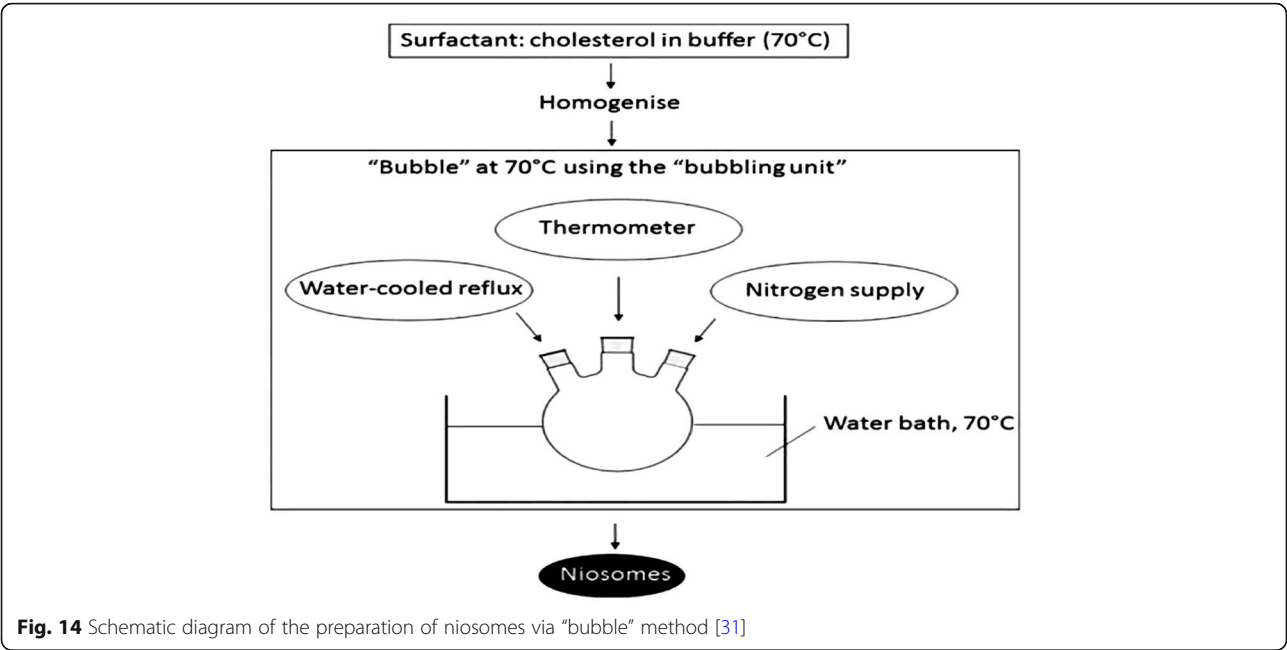


Fig. 13 Schematic diagram of preparation of the niosomes via emulsion method [15]



free-flowing proniosomal powder [84–88]. Ravaghi et al. [89] have prepared and characterized the proniosomal powder of natural canthaxanthin using this method.

Advantages

- a. It is a simple method.

Disadvantages

- a. If the coating to surfactant solution was applied too quickly, that results in degradation and sample would become slurry.
- b. The encapsulation efficiency of a drug may be affected by the carrier [67].

drug, and a small quantity of organic solvent in a full mouth glass tube, subjected to heating at 60 °C for a few minutes to dissolve surfactant completely. Close it with a lid to prevent the loss of solvent. Then, hydrate it with the aqueous phase and continue the heating for a few minutes till it cleared to get a clear solution, and then it is cooled to room temperature to get gel form. Niosomes are formed by hydrating the gel with a little amount of aqueous medium [74, 90–92]. Vora B et al. [93] have prepared proniosome-based transdermal delivery of levonorgestrel for effective contraception.

Advantages

- a. Specialized equipment is not needed.
- b. Easy process and time-saving method.
- c. Adopted for the preparation of gel [38].

Characterization of vesicles

- 1. Bilayer formation and number of lamellae

III. Coacervation phase separation method

In this, proniosomal gel is formed by mixing the weighed quantities of surfactant, cholesterol, lecithin,

X-cross formation is used to characterize the bilayer formation. Electron microscopy, small-angle X-ray

Table 3 Materials used for the preparation of proniosomes

S.no.	Materials/ingredients	Property
1.	Non-ionic surfactants (spans, tweens)	Emulsifier, wetting agent, solubilizer, permeation enhancer
2.	Cholesterol	Vesicle stabilizer
3.	Lecithin	Permeation enhancer
4.	Carrier	Increase flexibility
5.	Organic solvents (ethanol, methanol)	Effect vesicle size, solubilizer [76]

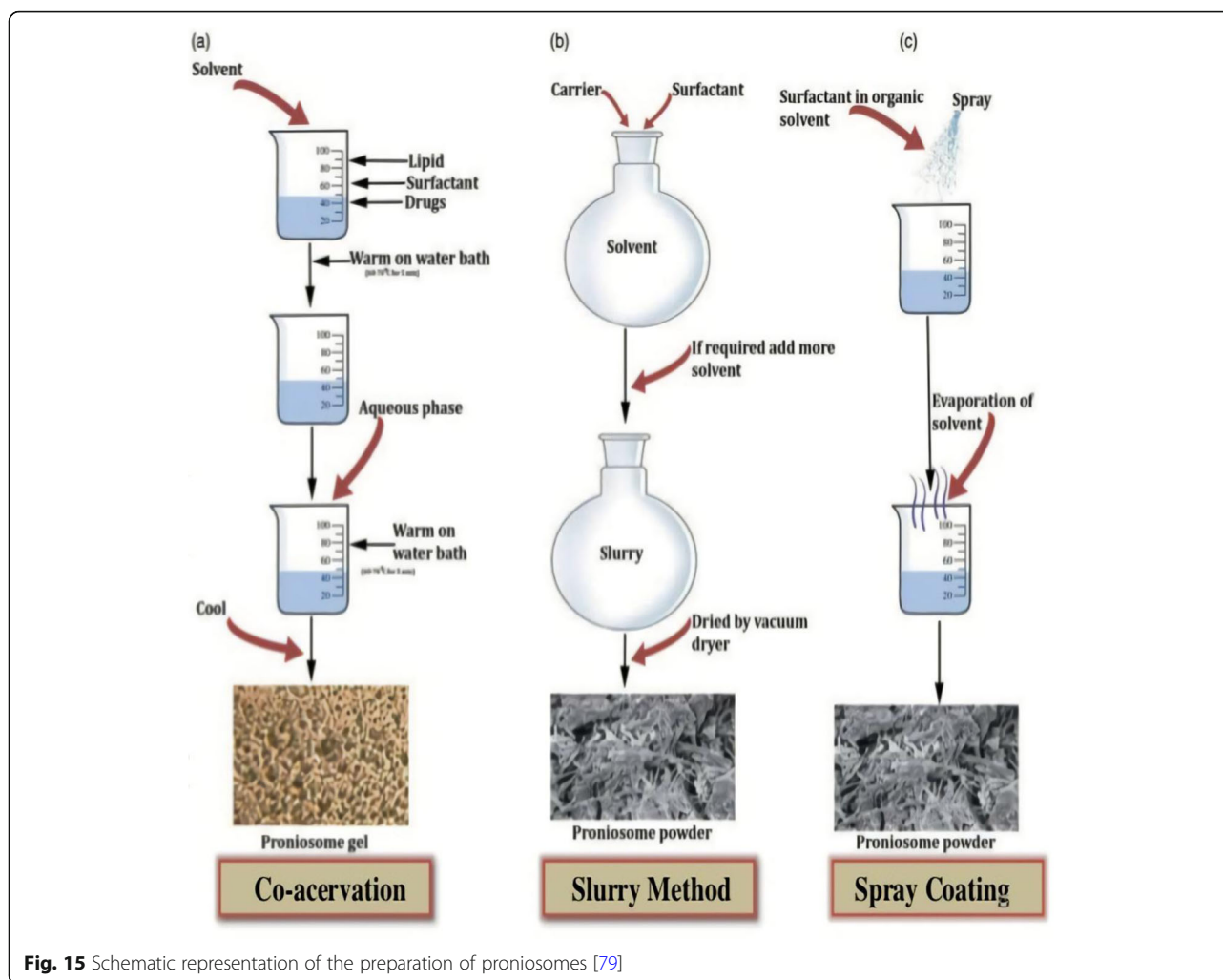


Fig. 15 Schematic representation of the preparation of proniosomes [79]

scattering, and NMR spectroscopy are used to characterize the number of lamellae [94].

2. Membrane rigidity and homogeneity

Probe fluorescence by using the function of temperature used to determine the membrane rigidity. Differential scanning calorimetric (DSC), P-NMR, FTIR, and fluorescence resonance energy transfer (FRET) are used to determine the membrane homogeneity [16, 95, 96].

3. Vesicle size and morphology

Light microscopy is used to determine the shape of the vesicle and its size distribution, whereas the coulter counter method determines the niosomal (less than 1 μm) distribution volume in dispersion. Differential light scattering techniques are used to know the size of the vesicles of sub-micron [97]. Electron microscopic analysis such as transmission electron

microscopy (TEM) and freeze-fracture techniques analyze the number of bilayers but is not used to determine the size of niosomes. Scanning electron microscopy (SEM), atomic force microscopy, and cryo-TEM are used to give information regarding the shape and surface of niosomes like roundness, smoothness, and aggregates [98]. Further, a photon correlation spectroscopy or particle size distribution analyzer is used to determine the mean size and polydispersity index.

4. Vesicle charge

Zeta potential is used to determine the charge of niosomes. In general, charged niosomes are more stable against aggregation, fusion than the uncharged [99]. Micro electrophoresis, dynamic light scattering, and pH-sensitive fluorophores are the alternative methods to determine the charge of the vesicle.

5. pH

It determined by using the pH meter [32].

6. Rate of hydration (spontaneity)

Neubauer's chamber is used to determine the number of niosomes formed after hydrating the proniosomes for 15 min [2, 5, 11].

7. Angle of repose

For the dry powder form of proniosomes, the angle of repose is determined by the funnel method. Fix the funnel in a specific position such that the funnel's 13-mm outlet orifice should be 5 cm above from the bottom surface. Pour the powder from the funnel to form a cone shape, thereby determining the angle of repose by measuring the base diameter and cone height [13].

8. Drug content

It is determined by weighing the equivalent amount of drugs from preparation, is added to the organic solvent, and stirs it for a specific time. Then filter the solution with suitable dilutions and measure the absorbance at a specific wavelength by using UV-Spectroscopy [100]. Calculate the drug content from the following equation:

$$\text{Drug content (\%)} = \frac{\text{actual drug content}}{\text{theoretical drug content}} \times 100$$

9. Entrapment efficiency and drug loading

The untrapped drug in niosome formulation can be separated by using either a dialysis method or gel filtration or centrifugation method. In the centrifugation method, a specific amount of niosomal dispersion is subjected to cold centrifuge (4 °C) at a specific speed (rpm) for a particular time. Then remove the supernatant liquid from Eppendorf tubes. Resuspend the settled product and again subjected to centrifuge, then remove the untrapped drug with no void volume by washing it twice, and an assay of free drug determined by measuring the absorbance at a specific wavelength by using UV-spectroscopy [101]. Calculate the entrapment efficiency and drug loading from the following equations:

$$\begin{aligned} \text{Entrapment efficiency (\%)} \\ = \frac{\text{Total entrapped drug} - \text{unentrapped drug}}{\text{Total entrapped drug}} \times 100 \end{aligned}$$

$$\begin{aligned} \text{Drug loading (\%)} \\ = \frac{\text{Amount of drug in niosomes}}{\text{amount of niosomes recovered}} \times 100 \end{aligned}$$

10. In vitro drug release

It is characterized by the following two methods [102, 103].

a. Dialysis method

In this, the dialysis membrane or sac is soaked in the hot aqueous medium before experimenting with opening the pore of the membrane. Then the dialysis bag is filled with dispersion of niosomes and tied both ends, then placed on the beaker containing a specific volume of buffer on a magnetic stirrer at a specific speed and 37 °C temperature. Aliquots of niosomes containing drug samples were withdrawn at certain time intervals and replaced the same volume of fresh medium to maintain the sink conditions. Check the absorbance at a specific wavelength by using UV-spectroscopy.

b. Franz diffusion cell

It consists of a donor and receptor compartment. Niosomal dispersion is placed over the donor, and the receptor filled with buffer. In between these compartments, a cellophane membrane is placed, and this whole assembly is kept on a magnetic stirrer with a certain speed (rpm) at 37 °C. Aliquots of drug samples were withdrawn at certain time intervals and replaced the same volume of fresh medium to maintain the sink conditions. Check the absorbance at a specific wavelength by using UV-Spectroscopy.

11. Drug release kinetics and drug analysis

In vitro, the drug release data is fitted into various kinetic equations to understand the mechanism of drug release by determining the correlation coefficient and "n" value.

- Zero-order, as cumulative % drug release vs. time
- First-order, as log cumulative % drug retained vs. time
- Higuchi's model, as cumulative % drug release vs. square root of time
- Peppas's model, as log cumulative % drug release vs. log time and determine the "n" value from slope [52]

12. In vivo studies

It is carried out on male albino rats of weight 150–200 g. After the administration of niosomal preparation, aliquots of blood samples were withdrawn and subjected to centrifuge, and HPLC or UV spectroscopy analyzes drug content. El-Nabarawi MA et al. [104] have successfully prepared Natamycin niosomes as a promising

Table 4 Summary of recent niosomal and proniosomal developed formulations for transdermal delivery

Topical/TDDS	Drug	Therapeutic category	Reference
Niosomes	Aceclofenac	NSAID	[107]
	Salidroside	Anti-depressant	[108]
	Capsaicin	Pain reliever	[114]
Niosomal gel	Meloxicam	NSAID	[115]
	Lopinavir	Anti-retro viral drug	[116]
	Simvastatin	Lipid lowering agent	[117]
Proniosomes	Nisoldipine	Anti-hypertensive	[118]
	Nifedipine	Anti-hypertensive	[16]
	Vinpocetine	Cerebro-vascular and cerebral degenerative diseases	[6]
Proniosomal gel	Tenoxicam	NSAID	[119]
	Fluboprofen	NSAID	[120]
	Vinpocetine	Cerebro-vascular and cerebral degenerative diseases	[6]
Proniosomal gel and patch	Levonorgestrel	Contraceptive agent	[6]
	Estradiol	Female hormone	[6]
	Ketoloroc	NSAID	[6]
	Fruzemide	Diuretic	[6]
	Captopril	Antihypertensive	[6]
	Chlorpheniramine maleate	Anti-histamine	[6]

ocular nanosized delivery system with ketorolac tromethamine for dual effects for treatment of candida rabbit keratitis.

13. Stability studies

According to the ICH guidelines of accelerated stability studies, the niosome dispersion placed at refrigerator ($4 \pm 2^\circ\text{C}$), room temperature (25° or $37 \pm 2^\circ\text{C}$) and elevated temperature ($40 \pm 2^\circ\text{C}$ and $60 \pm 5\% \text{ RH}$) for 3 months. Check the entrapment efficiency, in vitro drug release, and morphological characters at 0, 1, 2, and 3 months intervals. Observe if there are any variation or stability problems.

Applications of niosomes

These are potentially applicable to many pharmacological agents to show their actions against various diseases [105–108].

Table 5 Comparison of liposomes and niosomes/proniosomes [42, 46, 47]

Liposomes	Niosomes/ proniosomes	Reference
1. More expensive	1. Less expensive	[123]
2. Require special methods of storage and handling purpose	2. Does not require any special conditions	[123]
3. Phospholipids may be neutral or charged, makes the preparation unstable	3. Non-ionic surfactants are uncharged, makes the preparation more stable	[107]
4. Less shelf-life	4. Long shelf-life	[107]
5. Physical and chemical instability	5. Highly stable	[107]

A. Leishmaniasis

It is a type of parasitic disease to the liver and spleen cells in which the infecting organism resides. These are used for the treatment of diseases in the organs of the reticuloendothelial system in which the infecting organism resides. Pardakhty et al. [109] reported that positively charged niosomes entrapped with autoclaved *Leishmania major* against cutaneous leishmaniasis has a moderate effect and it successfully delayed the development of lesions in the BALB/c mice.

B. Carrier for hemoglobin

Niosomes used as hemoglobin carriers. Dispersion of niosomes reveals an overlapping visible spectrum of free hemoglobin. Compared to non-encapsulated hemoglobin, the dissociation curve can be modified as these vesicles are permeable to oxygen and hemoglobin. Patil S et al. [110] have studied the surface-modified mesoporous ceramics as delivery vehicle for hemoglobin.

C. Delivery of peptide drugs

The oral delivery of 9-desglycinamide and 8-arginine vasopressin in an in vitro intestinal loop model was investigated, and stability of peptide significantly increased was reported by Yoshida et al [111].

D. Immunological applications

The nature of the immune response caused by antigens was studied using niosomes. Brewer and Alexander [112] have reported niosomes as potent adjuvant in

Table 6 Products available in market

Brand	Product name [2]
Orlane-lipcolor and lipstick	Lip gloss
Lancôme	Flash retouch brush on concealer

terms of immunological selectivity, low toxicity, and stability.

E. Targeting to bioactive agents

i. To reticulo-endothelial system

The reticulo-endothelial system (RES) cells take the vesicle ideally. The absorption of niosome by the cell is also achieved through the circulating serum factors known as opsonins, which makes them apparent. Nevertheless, this localized medicine build-up was used for the treatment of tumors that are likely to metastases the liver and spleen for a parasitic liver infection.

ii. To the organs other than RES

These carriers help to guide antibodies to specific locations in the body. Immunoglobulins seem to quickly bind on the lipid surface, providing a natural means for the drug carriers targeting. Most cells can identify and bind different carbohydrate determinants, which can be used in the framework of direct actions. Arora S et al. [113] have studied the unique vesicular drug carriers.

F. Transdermal delivery of drugs through niosomes and proniosomes

The major drawback of transdermal drug delivery is the slow penetration through the skin. Transdermal drug delivery system of niosomes and proniosomes has led to increasing the penetration rate thereby enhancing therapeutic efficiency and bioavailability of the drug (Table 4).

G. Other applications

i. Sustained release

Azmin et al. [121] suggested the role of liver as a depot for methotrexate after niosomes are taken up by the liver cells. The niosomes containing a substance with low therapeutic indices and low water solubility can be released continuously because those can be retained by niosomal encapsulation in the circulation.

ii. Localized drug action

It enhances the effectiveness of the drug's ability and reduces its toxic systemic effects. Conacher M and Alexander J [122] have studied the niosomes as immunological adjuvants. Its approach is to deliver localized drug action through niosomes. These vesicles make the drug confined at the site of administration because of their size and low penetrability through the epithelium and connective tissues.

Comparison of liposomes and niosomes /proniosomes

Table 5 shows the comparison of liposomes and niosomes /proniosomes.

Marketed products

Table 6 shows the products available in the market.

Conclusion

The transdermal drug delivery system was found to be an effective way to overcome the problems associated with conventional oral dosage forms such as poor bioavailability, frequency of high dosing, and untargeted drug action. But the stratum corneum acts as a tough barrier that reduces the drug permeability followed by the bioavailability of hydrophilic drugs and large molecules. Further investigations in recent years have led to the development of a new versatile non-ionic surfactant-based vesicular approach for efficient drug delivery through the skin such as niosomes and proniosomes. These vesicles have explored with a wide range of applications in the delivery of anti-inflammatory (Ammonium glycyrrhizinate [124]), anti-cancer (Vincristine [125]), anti-viral (Tenofovir [126]), etc., by reducing side effects, enhancing penetration of drugs through skin and bioavailability. This review explains brief information regarding their structure, composition, advantages, disadvantages, their role as percutaneous permeation enhancer, and their recent applications in transdermal drug delivery. They have a promising approach to deliver the drug in a controlled and sustained manner. These do not require any special handling and storage conditions. Further exploration and research need to be developed on the niosomal and proniosomal preparations, which help to be available the products commercially.

Abbreviations

SC: Stratum corneum; HLB: Hydrophilic-lipophilic balance; CPP: Critical packing parameter; nm: nanometre; μ m: Micrometer; cm: Centimetre; gm: Grams; °C: Degree centigrade; RH: Relative humidity; RES: Reticulo-endothelial system; rpm: Revolutions per minute; NMR: Nuclear magnetic resonance; FTIR: Fourier transforms infrared

Acknowledgement

We express our sincere thanks to Dr. U.V. Ratna kumari, In-charge to School of Pharmaceutical Sciences and Technologies in Jawaharlal Nehru Technological University-Kakinada.

Authors' contributions

DB complied and designed the final manuscript data. She collected the basic information by literature survey and formatted the blinded manuscript as review of non-ionic surfactant based vesicles. VL checked the initially manuscript format and grammatically corrected the blinded manuscript. DB contributed in the designing and final editing of collected manuscript data. She also checked for the plagiarism of the manuscript and edited the final manuscript accordingly. All authors have read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Data here is literature and images/graphs included in this review article that are available upon request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Jawaharlal Nehru Technological University, School of pharmaceutical Sciences and Technologies, Department of Pharmaceutics, Kakinada, Andhra Pradesh 533003, India. ²School of Pharmaceutical Sciences and Technologies, Jawaharlal Nehru Technological University, Kakinada 533003, India.

Received: 12 June 2020 Accepted: 21 September 2020

Published online: 25 November 2020

References

- Kaur D, Kumar S (2018) Niosomes: present scenario and future aspects. *Journal of Drug Delivery and Therapeutics*. Sep 6 8(5):35–43
- Madhav NV, Saini A (2011) Niosomes: a novel drug delivery system. *International journal of research in pharmacy and chemistry*. 1(3):498–511
- Wilson V, Krishnakumar K, Dineshkumar B (2017) Proniosomal gel: transdermal drug delivery: a review. *Mar, Vol*. 8(1)
- Yadav K, Yadav D, Saroha K, Nanda S, Mathur P, Syan N (2010) Proniosomal Gel: A provesicular approach for transdermal drug delivery. *Der Pharmacia Lettre*. 2(4):189–198
- Patel NN, Vikran KR, Gupta A, Gupta A (2013) Proniosomes for improved transdermal drug delivery—a review. *The Pharma, a Journal of Pharmacy Research*.
- Ramesh YV, Jawahar N, Jakki SL (2013) Proniosomes: a novel nano vesicular transdermal drug delivery. *Journal of Pharmaceutical Sciences and Research*. Aug 1; 5(8):153.
- Mittal S, Chaudhary A, Chaudhary A, Kumar A (2020) Proniosomes: the effective and efficient drug-carrier system. *Therapeutic Delivery*. Feb 11(2): 125–137
- Lakshmi radhika k (2017) Proniosomal gel, a novel approach for drug delivery. A review. *Indo American Journal of pharmaceutical research*. (03).
- Bachhav AA (2016) Proniosome: A novel non-ionic provesicules as potential drug carrier. *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm*. Sep 10; 10(03).
- Jaydeep DY, Priyanka RK, Kumar AV, Gurubas TS (2011) Niosomes: a review. *J Pharm Res*. 4:632
- Bhardwaj P, Tripathi P, Gupta R, Pandey S (2020) Niosomes: a review on niosomal research in the last decade. *Journal of Drug Delivery Science and Technology*. Apr 1; 56:101581.
- Sudheer P, Kaushik K (2015) Review on niosomes—a novel approach for drug targeting. *Journal of Pharmaceutical Research*. Mar 1 14(1):20–25
- Rahimpour Y, Hamishehkar H (2012) Niosomes as carrier in dermal drug delivery. *Recent Advances in Novel Drug Carrier Systems*. Oct 31 1(1): 141–164
- Yasam VR, Jakki SL, Natarajan J, Kuppusamy G (2014) A review on novel vesicular drug delivery: proniosomes. *Drug delivery*. Jun 1 21(4):243–249
- Mishra A, Kapoor A, Bhargava S (2011) Proniosomal gel as a carrier for improved transdermal drug-delivery. *Asian J Pharm Clin Res*. 2231:4423
- Chen S, Hanning S, Falconer J, Locke M, Wen J (2019) Recent advances in non-ionic surfactant vesicles (niosomes): Fabrication, characterization, pharmaceutical and cosmetic applications. *European Journal of Pharmaceutics and Biopharmaceutics*. Nov 1; 144:18–39.
- Javadzadeh Y, Hamishehkar H (2011) Enhancing percutaneous delivery of methotrexate using different types of surfactants. *Colloids and Surfaces B: Biointerfaces*. Feb 1 82(2):422–426
- Fang JY, Yu SY, Wu PC, Huang YB, Tsai YH (2001) In vitro skin permeation of estradiol from various proniosome formulations. *International journal of pharmaceutics*. Mar 14 215(1-2):91–99
- Singh S, Parashar P, Kanoujia J, Singh I, Saha S, Saraf SA (2017) Transdermal potential and anti-gout efficacy of Febuxostat from niosomal gel. *Journal of drug delivery science and technology*. Jun 1; 39:348–61.
- Junyaprasert VB, Singhsa P, Jintapattanakit A (2013) Influence of chemical penetration enhancers on skin permeability of ellagic acid-loaded niosomes. *asian journal of pharmaceutical sciences*. Apr 1 8(2):110–117
- Gupta PN, Mishra V, Rawat A, Dubey P, Mahor S, Jain S, Chatterji DP, Vyas SP (2005) Non-invasive vaccine delivery in transfersomes, niosomes and liposomes: a comparative study. *International journal of pharmaceutics*. Apr 11 293(1-2):73–82
- Choi MJ, Maibach HI (2005) Liposomes and niosomes as topical drug delivery systems. *Skin pharmacology and physiology*. 18(5):209–219
- Sambhakar S, Paliwal S, Sharma S, Singh B (2017) Formulation of risperidone loaded proniosomes for effective transdermal delivery: an in-vitro and in-vivo study. *Bulletin of faculty of pharmacy, Cairo University*. Dec 1 55(2):239–247
- Maheshwari C, Pandey RS, Chaurasiya A, Kumar A, Selvam DT, Prasad GB, Dixit VK (2011) Non-ionic surfactant vesicles mediated transcutaneous immunization against hepatitis B. *International immunopharmacology*. Oct 1 11(10):1516–1522
- Kassem AA, Abd El-Alim SH, Asfour MH (2017) Enhancement of 8-methoxypsoralen topical delivery via nanosized niosomal vesicles: Formulation development, in vitro and in vivo evaluation of skin deposition. *International journal of pharmaceutics*. Jan 30 517(1-2):256–268
- Fang JY, Hong CT, Chiu WT, Wang YY (2001) Effect of liposomes and niosomes on skin permeation of enoxacin. *International journal of pharmaceutics*. May 21 219(1-2):61–72
- Shaker DS, Ishak RA, Ghoneim A, Elhuoni MA (2019) Nanoemulsion: a review on mechanisms for the transdermal delivery of hydrophobic and hydrophilic drugs. *Scientia Pharmaceutica*. Sep; 87(3):17.
- Maghraby GM, Williams AC, Barry BW (2006) Can drug-bearing liposomes penetrate intact skin? *Journal of Pharmacy and Pharmacology*. Apr 58(4):415–429
- Tavano L, Gentile L, Rossi CO, Muzzalupo R (2013) Novel gel-niosomes formulations as multicomponent systems for transdermal drug delivery. *Colloids and Surfaces B: Biointerfaces*. Oct 1; 110:281–8.
- Katrolia A, Chauhan SB, Shukla VK (2019) Formulation and evaluation of Metformin Hydrochloride-loaded Curcumin-Lycopene Niosomes. *SN Applied Sciences*. Dec 1; 1(12):1703.
- Yeo PL, Lim CL, Chye SM, Ling AP, Koh RY (2018) Niosomes: a review of their structure, properties, methods of preparation, and medical applications. *Asian Biomedicine*. Mar 21 11(4):301–314
- Makeshwar KB, Wasankar SR (2013) Niosome: a novel drug delivery system. *Asian journal of pharmaceutical research*. 3(1):16–20
- Lohumi A (2012) A novel drug delivery system: niosomes review. *Journal of drug delivery and therapeutics*. 2012 Sep 15; 2(5).
- Gharbavi M, Amani J, Kheiri-Manjili H, Danafar H, Sharafi A (2018) Niosome: a promising nanocarrier for natural drug delivery through blood-brain barrier. *Advances in Pharmacological and Pharmaceutical Sciences*. (Jan 1)
- Ag Selec D, Selec M, Walter JG, Stahl F, Scheper T (2016) Niosomes as nanoparticulate drug carriers: fundamentals and recent applications. *Journal of nanomaterials*. (Jun 16)
- Sankhyan A, Pawar P (2012) Recent trends in niosome as vesicular drug delivery system. *Journal of Applied Pharmaceutical Science*. 2(6):20–32
- Khan MI, Madni A, Peltonen L (2015) Development and in-vitro characterization of sorbitan monolaurate and poloxamer 184 based niosomes for oral delivery of diacerein. *European Journal of Pharmaceutical Sciences*. Dec 1; 95:88–95.
- Ge X, Wei M, He S, Yuan WE (2019) Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. *Pharmaceutics*. Feb; 11(2):55.

39. Kalra N, Jeyabalan G, Singh G, Choudhary S (2016) Non-ionic surfactant vesicles and their therapeutics potentials. Vol 3(2):193–201
40. Muzzalupo R, Tavano L (2015) Niosomal drug delivery for transdermal targeting: recent advances. *Research and reports in transdermal drug delivery*. 4:23.
41. Kumari R, Verma K, Verma A, Yadav GK, Maurya SD (2014) Proniosomes: a key to improved drug delivery. *Journal of Drug Delivery and Therapeutics*. Jun 24:56–65
42. Azeem A, Anwer MK, Talegaonkar S (2009) Niosomes in sustained and targeted drug delivery: some recent advances. *Journal of drug targeting*. Nov 1 17(9):671–689
43. Jothy MA, Shanmuganathan S (2015) An overview on niosome as carrier in dermal drug delivery. *Journal of pharmaceutical sciences and research*. Nov 1; 7(11):923.
44. Shirsand SB, Keshavshetti GG (2019) Recent advances in niosomal drug delivery—a review. May – June *RJLBPCS* 5(3) Page No.516.
45. Arunachalam A, Jegannath S, Yamini K (2012 Jan 10) Tharangini K (2012) Niosomes: a novel drug delivery system. *International journal of novel trends in pharmaceutical sciences*. 2(1):25–31
46. Sanklecha VM, Pande WV, Pawar SS, Pagaro B, Jadhav AC (2018) Review on niosomes. *Austin pharmacology and pharmaceuticals*. 3(2):1–7
47. Usman MR, Ghuge PR, Jain BV (2017) Niosomes: a novel trend of drug delivery. *European Journal of Biomedical*. 4(7):436–442
48. Saraswathi TS, Mothilal M, Jaganathan MK (2019) Niosomes as an emerging formulation tool for drug delivery—a review. *Int J App Pharm*. 11(2):7–15
49. Dwivedi C, Sahu R, Tiwari S, Satapathy T, Roy A (2014) Role of liposome in novel drug delivery system. *Journal of Drug Delivery and Therapeutics*, Mar 14 4(2):116–129
50. Rai A, Code QR (2017) Niosomes: an approach to current drug delivery—a review. *International Journal of Advances in Pharmaceutics*. 6:41–48
51. Jain SC, Gowda DV, Gupta NV, Kulkarni PK (2017) A brief review on niosomes. *Journal of pharmacy research*. May 11(5):450–458
52. Yamashita Y (2018) Recent dispersion technology using liquid crystal. *Liquid Crystals: Recent Advancements in Fundamental and Device Technologies*. Feb 28:243.
53. Rastogi B, Nagaich U, Jain D (2014) Development and characterization of non-ionic surfactant vesicles for ophthalmic drug delivery of diclofenac potassium. *Journal of Drug Delivery and Therapeutics*, Jun 23:1–6
54. Biswal S, Murthy PN, Sahu J, Sahoo P, Amir F (2008) Vesicles of non-ionic surfactants (niosomes) and drug delivery potential, *International Journal Of Pharmaceutical Sciences And Nanotechnology*. Apr 1(1):1–8
55. Hunter CA, Dolan TF, Coombs GH, Baillie AJ (1988) Vesicular systems (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. *Journal of pharmacy and pharmacology*. Mar 40(3):161–165
56. Khindri S, Aggarwal G (2015) Role of niosomes and proniosomes for enhancing bioavailability of drugs. *Journal of Drug Delivery and Therapeutics*. Jan 13 5(1):28–33
57. AdlinJinoNesalin J (2015) Niosome as a novel drug delivery system-review. *International Research Journal of Pharmaceutical and Applied Sciences*. Jun 30 5(3):1–7
58. Arora R (2016) Advances in niosome as a drug carrier: a review. *Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm*. Sep 9; 1(1).
59. Baillie AJ, Florence AT, Hume LR, Muirhead GT, Rogerson A (1985) The preparation and properties of niosomes—non-ionic surfactant vesicles. *Journal of pharmacy and pharmacology*. Dec 37(12):863–868
60. Pando D, Gutiérrez G, Coca J, Pazos C (2013) Preparation and characterization of niosomes containing resveratrol. *Journal of Food Engineering*. Jul 1 117(2):227–234
61. Obeid MA, Elburi A, Young LC, Mullen AB, Tate RJ, Ferro VA (2017) Formulation of Nonionic Surfactant Vesicles (NISV) prepared by microfluidics for therapeutic delivery of siRNA into cancer cells. *Molecular pharmaceutics*. Jul 3 14(7):2450–2458
62. Mayer LD, Bally MB, Hope MJ, Cullis PR (1985) Uptake of antineoplastic agents into large unilamellar vesicles in response to a membrane potential. *Biochimica et Biophysica Acta (BBA)-Biomembranes*. Jun 27 816(2):294–302
63. Marianecci C, Di Marzio L, Rinaldi F, Cella C, Paolino D, Alhauque F, Esposito S, Carafa M (2014) Niosomes from 80s to present: the state of the art. *Advances in colloid and interface science*. Mar 1; 205:187–206.
64. Singh CH, Jain C, Kumar BN (2011) Formulation, characterization, stability and invitro evaluation of nimesulide niosomes. *Pharmacophore*. 3(168):e185
65. Mujoriya RZ, Dhamande K, Bodla RB (2011) Niosomal drug delivery system—a review. *Int j appl pharm*. May 28 3(3):7–10
66. Zarei M, Norouzian D, Honarvar B, Mohammadi M, Shamabadi HE, Akbarzadeh A (2013) Paclitaxel loaded niosome nanoparticle formulation prepared via reverse phase evaporation method: an in vitro evaluation. *Pakistan journal of biological sciences: PJBs*. Mar 15; 16(6):295.
67. Moghassemi S, Hadjizadeh A (2014) Nano-niosomes as nanoscale drug delivery systems: an illustrated review. *Journal of controlled release*. Jul 10; 185:22–36.
68. Navya M (2014) Niosomes as novel vesicular drug delivery system—a review. *Asian Journal of Research in Biological and Pharmaceutical Sciences*. 2:62–68
69. Chandraprakash K, Udupa N, Umadevi P, Pillai G (1993) Effect of macrophage activation on plasma disposition of niosomal 3H-Methotrexate in sarcoma-180 bearing mice. *Journal of drug targeting*. Jan 1 1(2):143–145
70. Sharma A, Rathor P, Bhandari SS, Kabra PM (2013) Liposomes: a novel drug delivery system. *Asian Journal of Pharmaceutical Research and Development*. Sep 1:108–123
71. Bartelds R, Nematollahi MH, Pols T, Stuart MC, Pardakhty A, Asadikaram G, Poolman B (2018) Niosomes, an alternative for liposomal delivery. *PLoS One*. Apr 12; 13(4):e0194179.
72. Rogerson AC, Cummings J, Willmott N, Florence AT (1988) The distribution of doxorubicin in mice following administration in niosomes. *Journal of pharmacy and pharmacology*. May 40(5):337–342
73. Kremer J, Van der Esker MW, Pathmamanoharan C, Wiersema PH (1977) Vesicles of variable diameter prepared by a modified injection method. *Biochemistry*. Aug 16(17):3932–3935
74. Yoshioka T, Sternberg B, Florence AT (1994) Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60 and 80) and a sorbitan triester (Span 85). *International journal of pharmaceutics*. Apr 25 105(1):1–6
75. Talsma H, Van Steenberg MJ, Borchert JC, Crommelin DJ (1994) A novel technique for the one-step preparation of liposomes and nonionic surfactant vesicles without the use of organic solvents. *Liposome formation in a continuous gas stream: The 'Bubble' method*. *Journal of pharmaceutical Sciences*. Mar 83(3):276–280
76. Nirosha M, Chandrashekar KB (2016) Proniosomal gel—an effective approach for topical and transdermal drug delivery. *International journal of research in pharmaceutical sciences*. Apr 20 7(2):179–183
77. Vashist S, Kaushik J, Sunil BK (2015) A Review Article: Proniosomes. *PharmaTutor*. Jul 1 3(7):25–30
78. Varsha VR, Savitha SK (2019) Proniosomes: as a potential drug delivery system. *Journal of Pharmaceutical Sciences and Research*. Jul 1 11(7):2594–2597
79. Ahmad MZ, Mohammed AA, Mokhtar Ibrahim M (2017) Technology overview and drug delivery application of proniosomes. *Pharmaceutical development and technology*. Apr 3 22(3):302–311
80. Vasistha P, Ram A (2013) Non-ionic provesicular drug carrier: an overview. *Asian J Pharm Clin Res*. 6(1):38–42
81. Radha GV, Rani TS, Sarvani B (2013). A review on proniosomal drug delivery system for targeted drug action. *Journal of basic and clinical pharmacy*. Mar; 4(2):42.
82. Pandit PG, Parakh DR, Patil MP (2015) Proniosomal gel for improved transdermal drug delivery: an overview. Vol 4, Issue 8, 560–586.
83. Madni A, Rahim MA, Mahmood MA, Jabar A, Rehman M, Shah H, Khan A, Tahir N, Shah A (2018) Enhancement of dissolution and skin permeability of pentazocine by proniosomes and niosomal gel. *AAPS PharmSciTech*. May 1 19(4):1544–1553
84. Sankar V, Ruckmani K, Durga S, Jailani S (2010) Proniosomes as drug carriers. *Pak J Pharm Sci*. Jan 1 23(1):103–107
85. Kakar R, Rao R, Goswami A, Nanda S, Saroha K (2010) Proniosomes: an emerging vesicular system in drug delivery and cosmetics. *Der Pharmacia Lettre*. 2(4):227–239
86. Cong CY (2019) Emerging trends of nanovesicles drug delivery system in nanotechnology: PRONIOSOMES. Jun 18.
87. Blazek-Welsh AI, Rhodes DG (2001a) Maltodextrin-based proniosomes. *Aaps Pharmsci*. Mar 1; 3(1):1.
88. Blazek-Welsh AI, Rhodes DG (2001b) *Pharm. Res*. 8, 656–661.
89. Ravaghi M, Sinico C, Razavi SH, Mousavi SM, Pini E, Fadda AM (2017). Proniosomal powders of natural canthaxanthin: preparation and characterization. *Food chemistry*. Apr 1; 220:233–41.
90. Gupta A, Prajapati SK, Balamurugan M, Singh M, Bhatia D (2007) *Tropical J. Pharm Res*. 6(2):687–693
91. Solanki AB, Parikh JR, Parikh RH (2007) Formulation and optimization of piroxicam proniosomes by 3-factor, 3-level Box-Behnken design. *Aaps Pharmscitech*. Oct 1; 8(4):43.

92. AD B. Standish MM, Watkins JC (1965) *J. Mol. Biol.* 13(2387):252.
93. Vora B, Khopade AJ, Jain NK (1998) Proniosome based transdermal delivery of levonorgestrel for effective contraception. *Journal of controlled release.* Jul 31 54(2):149–165
94. Srikanth K, Nappinnai M, Gupta VR (2010) Proniosomes: a novel drug carrier system. *Research Journal of Pharmacy and Technology.* 3(3):709–711
95. Mahale NB, Thakkar PD, Mali RG, Walunj DR, Chaudhari SR (2012) Niosomes: novel sustained release nonionic stable vesicular systems—an overview. *Advances in colloid and interface science.* Nov 15; 183:46–54.
96. Hu C, Rhodes DG (1999) Proniosomes: a novel drug carrier preparation. *International journal of pharmaceutics.* Aug 5 185(1):23–35
97. Breimer DD, Speiser R (1985) *Topics in pharmaceutical sciences.* Elsevier Science Publishers, New York, USA. 291
98. Handjani-Vila RM, Ribier A, Rondot B, Vanlerberghe G (1979) Dispersions of lamellar phases of non-ionic lipids in cosmetic products. *International journal of cosmetic Science.* Oct; 1(5):303.
99. Uchegbu IF, Vyas SP (1979) Non-ionic surfactant based vesicles (niosomes) in drug delivery. *International journal of pharmaceutics.* Oct 15 172(1-2):33–70
100. Allen TM (1998) *Liposomal drug formulations.* Drugs. Nov 1 56(5):747–756
101. Buckton G (1995) *Harwood Interfacial phenomena in drug delivery and targeting academic publishers.* Switzerland. 154–5
102. Shahiwala A, Misra A (2002) Studies in topical application of niosomally entrapped nimesulide. *Journal of pharmacy and pharmaceutical sciences.* Sep 1 5(3):220–225
103. Reddy DN, Udupa N (1993) Formulation and evaluation of oral and transdermal preparations of flurbiprofen and piroxicam incorporated with different carriers. *Drug development and industrial pharmacy.* Jan 1 19(7): 843–852
104. El-Nabarawi MA, Abd El Rehem RT, Teaima M, Abary M, El-Mofty HM, Khafagy MM, Lotfy NM, Salah M (2019) Natamycin niosomes as a promising ocular nanosized delivery system with ketorolac tromethamine for dual effects for treatment of candida rabbit keratitis; in vitro/in vivo and histopathological studies. *Drug development and industrial pharmacy.* Jun 3 45(6):922–936
105. Debnath A, Kumar A (2015) Structural and functional significance of niosome and proniosome in drug delivery system. *Int J Pharm and Eng.* 3(3):621–637
106. Kumar A, Pal JL, Jaiswal A, Singh V (2011) Review on niosomes as novel drug delivery system. *International research journal of pharmacy.* 2(5):61–65
107. Nasr M, Mansour S, Mortada ND, Elshamy AA (2008) Vesicular aceclofenac systems: a comparative study between liposomes and niosomes. *Journal of microencapsulation.* Oct 1 25(7):499–512
108. Zhang Y, Zhang K, Wu Z, Guo T, Ye B, Lu M, Zhao J, Zhu C, Feng N (2015) Evaluation of transdermal salidroside delivery using niosomes via in vitro cellular uptake. *International journal of pharmaceutics.* Jan 15 478(1):138–146
109. Pardakhty A, Shakibaie M, Daneshvar H, Khamesipour A, Mohammadi-Khorsand T, Forootanfar H (2012) Preparation and evaluation of niosomes containing autoclaved *Leishmania major*: a preliminary study. *Journal of microencapsulation.* May 1 29(3):219–224
110. Patil S, Pancholi SS, Agrawal S, Agrawal GP (2004) Surface-modified mesoporous ceramics as delivery vehicle for haemoglobin. *Drug delivery.* Jan 1 11(3):193–199
111. Yoshida H, Lehr CM, Kok W, Junginger HE, Verhoef JC, Bouwstra JA (1992) Niosomes for oral delivery of peptide drugs. *Journal of controlled release.* Jul 1 21(1-3):145–153
112. Brewer JM, Alexander J (1992) The adjuvant activity of non-ionic surfactant vesicles (niosomes) on the BALB/c humoral response to bovine serum albumin. *Immunology.* Apr; 75(4):570.
113. Arora S, PRASHAR B, HITESH HD, CHANDEL A, THAKUR V (2012) Niosomes: the unique vesicular drug carriers. *Journal of Drug Delivery and Therapeutics.* Jan 25; 2(1).
114. Tavano L, Alfano P, Muzzalupo R, de Cindio B (2011) Niosomes vs microemulsions: new carriers for topical delivery of capsaicin. *Colloids and surfaces B: Biointerfaces.* Oct 15 87(2):333–339
115. El-Menshaweh SF, Hussein AK (2013) Formulation and evaluation of meloxicam niosomes as vesicular carriers for enhanced skin delivery. *Pharmaceutical Development and Technology.* Aug 1 18(4):779–786
116. Alsarra IA, Bosela AA, Ahmed SM, Mahrous GM (2005) Proniosomes as a drug carrier for transdermal delivery of ketorolac. *European journal of pharmaceutics and biopharmaceutics.* Apr 1 59(3):485–490
117. Zidan AS, Hosny KM, Ahmed OA, Fahmy UA (2016) Assessment of simvastatin niosomes for pediatric transdermal drug delivery. *Drug delivery.* Jun 12 23(5):1536–1549
118. El Maghraby GM, Ahmed AA, Osman MA (2015) Penetration enhancers in proniosomes as a new strategy for enhanced transdermal drug delivery. *Saudi Pharmaceutical Journal.* Jan 1 23(1):67–74
119. Ammar HO, Ghorab M, El-Nahhas SA, Higazy IM (2011) Proniosomes as a carrier system for transdermal delivery of tenoxicam. *International journal of pharmaceutics.* Feb 28 405(1-2):142–152
120. Zidan AS, Mokhtar M (2011) Multivariate optimization of formulation variables influencing flurbiprofen proniosomes characteristics. *Journal of pharmaceutical sciences.* Jun 1 100(6):2212–2221
121. Azmin MN, Florence AT, Handjani-Vila RM, Stuart JF, Vanlerberghe G, Whittaker JS (1985) The effect of non-ionic surfactant vesicle (niosome) entrapment on the absorption and distribution of methotrexate in mice. *Journal of Pharmacy and Pharmacology.* Apr 37(4):237–242
122. Conacher M, Alexanderand J, Brewer JM, Conacher M, and Alexander J (2000) Niosomes as immunological adjuvants. In "Synthetic Surfactant Vesicles" (Ed. I.F. Uchegbu) International Publishers Distributors Ltd. Singapore, 185–205.
123. Rezvani M, Hesari J, Peighambaroust SH, Manconi M, Hamishehkar H, Escibano-Ferrer E (2019). Potential application of nanovesicles (niosomes and liposomes) for fortification of functional beverages with Isoleucine-Proline-Proline: A comparative study with central composite design approach. *Food chemistry.* Sep 30; 293:368–77.
124. Paolino D, Muzzalupo R, Ricciardi A, Celia C, Picci N, Fresta M (2007) In vitro and in vivo evaluation of Bola-surfactant containing niosomes for transdermal delivery. *Biomedical microdevices.* Aug 1 9(4):421–433
125. Parthasarathi G, Udupa N, Umadevi PI, Pillai G (1994) Niosome encapsulated of vincristine sulfate: improved anticancer activity with reduced toxicity in mice. *Journal of drug targeting.* Jan 1 2(2):173–182
126. Zidan AS, Rahman Z, Khan MA (2011) Product and process understanding of a novel pediatric anti-HIV tenofovir niosomes with a high-pressure homogenizer. *European Journal of Pharmaceutical Sciences.* Sep 18 44(1-2): 93–102

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen[®] journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)