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Recent advances in non-ionic surfactant vesicles (niosomes): Fabrication, characterization, pharmaceutical and cosmetic applications

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ABSTRACT

Development of nanocarriers for drug delivery has received considerable attention due to their potential in achieving targeted delivery to the diseased site while sparing the surrounding healthy tissue. Safe and efficient drug delivery has always been a challenge in medicine. During the last decade, a large amount of interest has been drawn on the fabrication of surfactant-based vesicles to improve drug delivery. Niosomes are self-assembled vesicular nano-carriers formed by hydration of non-ionic surfactant, cholesterol or other amphiphilic molecules that serve as a versatile drug delivery system with a variety of applications ranging from dermal delivery to brain-targeted delivery. A large number of research articles have been published reporting their fabrication methods and applications in pharmaceutical and cosmetic fields. Niosomes have the same advantages as liposomes, such as the ability to incorporate both hydrophilic and lipophilic compounds. Besides, niosomes can be fabricated with simple methods, require less production cost and are stable over an extended period, thus overcoming the major drawbacks of liposomes. This review provides a comprehensive summary of niosomal research to date, it provides a detailed overview of the formulation components, types of niosomes, effects of components on the formation of niosomes, fabrication and purification methods, physical characterization techniques of niosomes, recent applications in pharmaceutical field such as in oral, ocular, topical, pulmonary, parental and transmucosal drug delivery, and cosmetic applications. Finally, limitations and the future outlook for this delivery system have also been discussed.

1. Introduction

Conventional drug delivery systems face some significant challenges, such as unfavorable pharmacokinetics and distribution, which can lead to unwanted side effects [1]. Drug degradation in blood circulation by the reticuloendothelial system and insufficient drug uptake at the target site can reduce drug efficacy [2]. Nanocarriers have been extensively investigated in the past decades to overcome the challenges associated with conventional drug delivery systems, due to the following advantages: (a) facilitate targeted drug delivery to the diseased site; (b) enhance absorption as surface area increases and hence increase bioavailability; (c) improve pharmacokinetics and biodistribution of therapeutic agents; (d) increase retention in biological systems and prolong the efficacy of drugs [2,3]. Numerous papers have been published regarding the development of different types of nanocarriers, such as polymeric nanoparticles, solid lipid nanoparticles, liposomes, micelles, dendrimers, carbon tubules, mesoporous silica and quantum dots. However, only a few of them have demonstrated significant clinical potential [2,4]. The ultimate goals for designing an effective nano drug delivery system include formulation with biocompatible and biodegradable materials; achieving target delivery of therapeutics to the pathological site without affecting the surrounding healthy tissue or organs; no premature or burst release; ability to load a significant amount of drug in order to achieve the desired therapeutic effect; controlled release of drug over an extended period to reduce dose frequency and improve patient compliance [1]. Among the different drug delivery systems, niosomal delivery systems can achieve majority of the goals listed above.

Niosomes are formed by self-assembly of non-ionic surfactants. They are structurally similar to liposomes and were developed as an alternative delivery system to liposomes, as niosomes can overcome the problems associated with large-scale production, sterilization and

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physical stability [5,6]. Also, the raw materials for niosomes are relatively cheaper and more readily available than phospholipids used for liposomes. Niosomes can be prepared as unilamellar or multilamellar vesicles following similar preparation methods as liposomes [7,8]. They were first reported by researchers from L'Oréal (Clichy, France) for cosmetic applications in the 1970s and 1980s. Since then, niosomes have been extensively investigated for multiple applications in different fields including pharmaceutical, cosmetic and food sciences, leading to a large number of publications and patents [2]. Niosomes can enhance drug delivery across the skin barrier – stratum corneum (SC) [9,10]. Some mechanisms have been proposed to explain their penetration-enhancing effects [2]. Topical vaccine delivery using niosomes as carriers have been reported in the literature, where the antigen remains intact in the aqueous core while the niosomal components enhance penetration across the skin and initiate an immunological response. Niosomes are also studied for the ocular delivery of therapeutics due to their low toxicity and penetration enhancing effects [11–13]. In anti-cancer research, niosomes can achieve targeted delivery of anti-cancer agents and decrease toxicity to reduce side effects associated with these drugs [4,14]. Proniosomes are of particular interest in the pulmonary delivery of aerosol drugs through nebulization devices, where drug loaded proniosomes can be deposited into the deep lung and achieve a better therapeutic response [15–17].

This up-to-date review of niosome drug delivery systems covers the elemental composition of niosomes, recent advances of new materials, functionalized ligands for targeted delivery, fabrication methods and different types of niosomes. Characterization studies, applications in various fields including pharmaceutical and cosmetic and comments on limitations and future directions of the niosomal system are also presented.

2. Types of niosomes

Various kinds of niosomes have been reported in the literature. These are classified into different groups according to their size or number of lamellar layers. Based on the size, there are small unilamellar vesicles (SUV) and large unilamellar vesicles. Based on the number of bilayers, there are multilamellar vesicles (MLV) and small unilamellar vesicles (SUV) [2]. The size of niosomes is also a crucial factor that affects the choice of administration route. Submicron size vesicles are suitable for intravenous or transdermal applications, whereas those up to 10 μm are often used for intraperitoneal, intramuscular, nasal and oral administration [18]. Small unilamellar vesicles (SUVs) are produced from multilamellar vesicles by methods such as sonication, extrusion under high pressure and high shear homogenization. The size of SUVs is around 10 to 100 nm (Fig. 1A). They are thermodynamically less stable compared with other types of niosomes and have poor drug loading capacity for hydrophilic drugs as well as a higher tendency to form aggregates [2,3]. Large unilamellar vesicles (LUVs) comprise a single bilayer surrounding the aqueous core and are around 0.1–1 μm in diameter (Fig. 1B). LUV niosomes have a large aqueous compartment, can be used for encapsulation of hydrophilic drug molecules [2]. Multilamellar vesicles (MLV) comprises several bilayers surrounding the aqueous lipid compartments separately. The diameter of these vesicles ranges from 0.5 μm to 10 μm (Fig. 1C). MLVs can be easily prepared without complex techniques and are more stable compared to the other two types of niosomes under normal storage conditions. Also, they are favorable in the loading of lipophilic drugs due to the presence of multiple bilayer membranes [2,3].

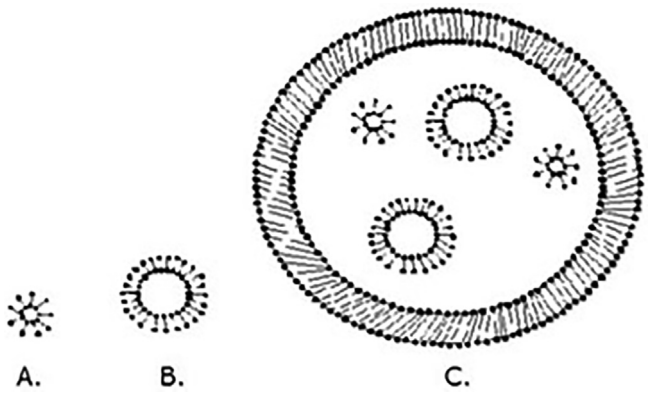

Fig. 1. (A) Small unilamellar (SUV) (10 to 100 nm), (B) large unilamellar (LUV) (0.1 to 1 μm) and (C) multilamellar vesicles (MLV) (0.5 μm to 10 μm).

2.1. Types of specialized niosomes

2.1.1. Proniosomes

Proniosomes are produced by coating a thin layer of non-ionic surfactant on a water-soluble carrier [2,11,19]. To make proniosomes, the water-soluble carriers need to be non-toxic, safe, free-flowing and have good water solubility to allow easy hydration. Maltodextrin, sorbitol, mannitol, glucose monohydrate, lactose monohydrate, and sucrose stearate have been used to prepare proniosomes [2,19]. Proniosomes present in a dry powder form and have several advantages over the conventional niosomes such as better stability, less likely to form aggregates as well as reduced drug leakage [3]. Proniosomes can be prepared by various methods such as slurry method, slow spray coating method and coacervation phase separation method. They exist in two forms, depending on the method of preparation, which are dry granular proniosomes and liquid crystalline proniosomes [17,18,20–22].

2.1.2. Elastic niosomes

Elastic niosomes are flexible niosomes, which can pass through pores that are smaller than their size without destroying their structure. The components of these vesicles are surfactants, cholesterol, water, and ethanol (Fig. 2B). They are commonly used in topical or transdermal drug delivery owing to their ability to pass through small pores and therefore improve penetration through the skin barrier. Manosroi and colleagues prepared elastic niosomes for transdermal delivery of diclofenac diethylammonium; the deformability index was around 14 times higher than conventional niosomes [23]. Another study carried out by the same group of researchers found that elastic niosomes prepared by addition of sodium cholate improved transdermal delivery of papain for scar treatment [24].

2.1.3. Discomes

Discomes are large disc-like niosomes. In a previous work by Uchegbu and co-workers, discomes were prepared using hexadecyl diglycerol ether, cholesterol and dicetyl phosphate by mechanical agitation and sonication [25]. In the study, they found the size of discomes were large (11–60 μm) and further increased in size after sonication. Discomes are also thermoresponsive; their structure becomes less organized when the temperature increases above 37 °C. Abdelkader et al. investigated discomes for ocular delivery of naltrexone for the treatment of diabetic keratopathy [26].

2.1.4. Bola niosomes

Bola niosomes are made of bola surfactants. This particular type of surfactants was found in the membrane of archaebacteria in the early 1980s. They have two hydrophilic heads that are connected by one or two lipophilic linkers. Zakharova (2010) has shown that bola surfactants have a strong assembling ability, which was demonstrated by their much higher surface tension and lower critical micelle concentration than the conventional surfactants; further research revealed their tolerability both *in vitro* and *in vivo* [27].

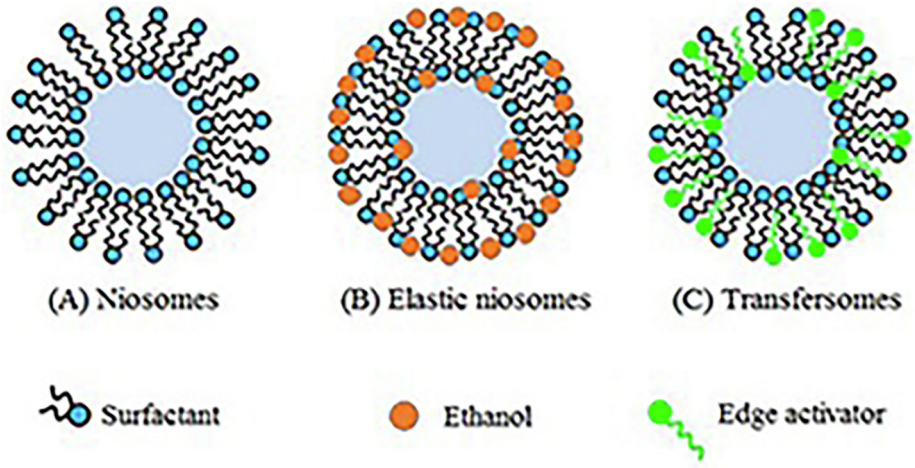

Fig. 2. Schematic representation of the different types of surfactant based vesicular delivery systems. (A) Niosomes (B) elastic niosomes and (C) transfersomes.

2.1.5. Transfersomes

Transfersomes are novel deformable vesicular carrier systems primarily composed of phospholipids, which self-assemble into a lipid bilayer in an aqueous environment and close to form a vesicle. A lipid bilayer softening component is added to increase lipid bilayer flexibility and permeability. This is known as an edge activator. An edge activator usually consists of a single chain surfactant of non-ionic nature that causes destabilization of the lipid bilayer, thereby increasing its fluidity and elasticity (Fig. 2C). Transfersomes comprise both hydrophobic and hydrophilic moieties and as a result can accommodate drug molecules with a wide range of solubilities. They can act as a carrier for low as well as high molecular weight drugs [28].

2.1.6. Aspasomes

Ascorbyl palmitate has been explored as bilayer forming material; it forms vesicles with cholesterol, ascorbyl palmitate and a negatively charged lipid (dicetyl phosphate). Aspasomes are prepared by film hydration method followed by sonication. They have been studied for the transdermal delivery of active ingredients, and it was found that aspasomes can enhance transdermal penetration across the skin barrier. Gopinath and co-workers developed azidothymidine (AZT) loaded aspasomes for topical application. Transdermal permeation of AZT loaded in aspasomes was much higher than AZT solution and ascorbyl palmitate aqueous dispersion. Although no study was conducted to determine the mechanism by which aspasome is enhancing the permeation of AZT, it is speculated that due to its lipophilicity it partitions into lipids of the skin and by its amphiphilic character alters the intercellular space and thus improve permeation. This study also revealed that the antioxidant potency of ascorbyl moiety is retained after converting ascorbyl palmitate been converted into vesicles, aspasomes rendered much better antioxidant activity compared with ascorbic acid. The antioxidant property and skin permeation enhancing property indicate a promising future for aspasome as a transdermal drug delivery system [29].

3. Formulation components and their effects

The components for niosomes include surfactants (generally non-ionic surfactants), cholesterol and charge inducing agents [3,30,31]. Understanding the physicochemical properties of these formulation components as well as their effects on niosomes is essential for preparing niosomes with desired properties [32,33]. Formulation components such as surfactants, cholesterol, charge inducing agents, the effect of hydrophilic-lipophilic balance (HLB) value, liquid gel transition temperature will be discussed in the following sections [2,3].

3.1. Surfactants

Surfactants are amphiphilic molecules, which comprise a lipophilic tail and a hydrophilic head. They are classified according to the charges on their hydrophilic head groups, which are cationic, anionic, amphoteric and non-ionic (Fig. 3) [1]. The tail group of surfactants can be alkanes, fluorocarbons, aromatics or other non-polar groups. Non-ionic surfactants are the major components of niosomes due to their low toxicity and biocompatibility compared with the other types of surfactants. A variety of non-ionic surfactants have been commonly used in the preparation of niosomes. For example, derivatives of alkyl ethers, alkyl esters, and sorbitan fatty acid esters [1–3,34].

Alkyl esters include sorbitan fatty acid esters (Span) (Fig. 4) and polyoxyethylene sorbitan fatty acid esters (Tween), these surfactants are non-toxic and non-irritating. Tween surfactants are derived from a reaction between polyoxyethylene and sorbitan fatty acid esters. They have higher HLB values compared with surfactants in the Span family [2]. Brij surfactants are an example of alkyl ethers. Among the members of the Brij family is Brij 30 (Polyoxyethylene(4)lauryl ether) with a phase transition temperature less than 10 °C and able to form large unilamellar vesicles with high drug loading [35].

Sucrose esters (SEs) are another group of non-ionic surfactants, they have a sugar substituent, sucrose, as the polar head group and fatty acids as non-polar groups [36]. As sucrose contains eight hydroxyl groups, compounds ranging from sucrose monoesters to octaesters can be produced. These esters contain different fatty acids (stearic, palmitic, myristic and lauric acid) in different ratios [37]. The type of fatty acid and the degree of esterification determine the hydrophilic lipophilic balance (HLB) value and the melting point of these materials. They have HLB values from 1 to 16, because of this variety, they are applied

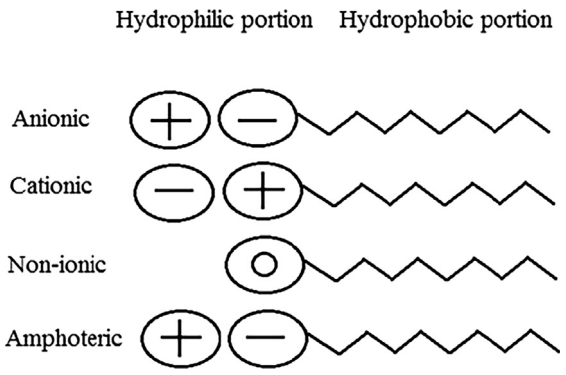

Fig. 3. The different types of surfactants.

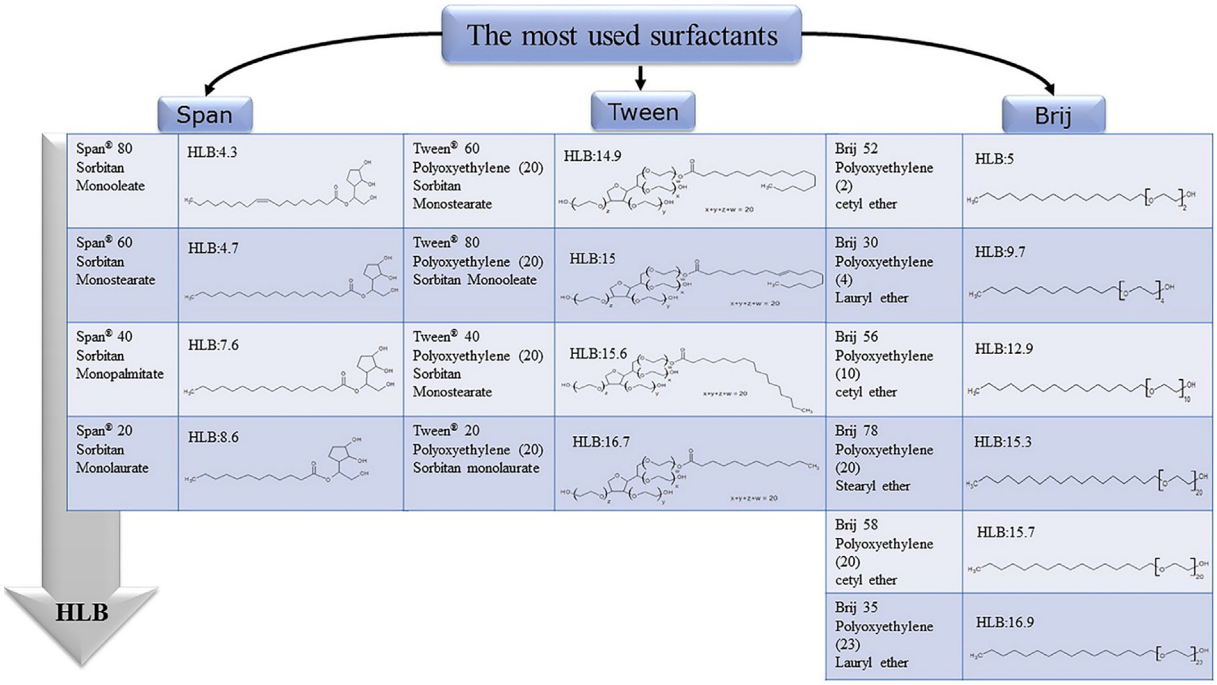

Fig. 4. The most used surfactants.

in many areas of pharmaceutical and cosmetical technology as emulsifiers, solubilizing agents, lubricants, penetration enhancers and pore forming agents [38,39]. SEs have low toxicity, they are biocompatible, are less hemolytic and irritating than other surfactants, and finally, they have excellent biodegradability [40]. SEs have drawn a worldwide interest as permeation enhancers of reduced irritation potentials; they are approved by Food and Agriculture Organization (FAO), World Health Organization (WHO), in Japan, USA and Europe, as food additives owing to their high safety and excellent properties. Sucrose stearate and sucrose palmitate are approved as inactive ingredients by the Food and Drug Administration (FDA) and listed in the Inactive Ingredients Database for oral dosage forms and sucrose distearate and sucrose polyesters are listed for administration by topical route [39]. Most applications of SEs are found in transdermal drug delivery while they are also studied for oral administration of antigens and sucrose stearate-based proniosomes have been investigated for pulmonary delivery of cromolyn sodium [20].

Bola and Gemini surfactants are the newer generations of surfactants that have been synthesized to produce niosomes with optimal properties [2]. Gemini surfactants have a low critical micelle concentration and are non-toxic, non-irritating and non-hemolytic [2,10,41]. Bola surfactants are of higher solubility and higher critical micelle concentration [1]. Another new type of surfactant is tyloxapol, which is composed of ethylene oxide and formaldehyde and forms niosomes in water. It is a non-ionic biological surfactant of alkyl aryl polyether alcohol type that has been used in ophthalmic preparations and as a mucolytic agent for pulmonary diseases [2].

3.2. Additive agents

Various additives have been used for niosome membrane among which the most common and important of these agents is cholesterol (Fig. 5) [25]. Cholesterol interacts with surfactant by forming a hydrogen bond between its hydroxyl groups and the alkyl chain of surfactant molecules. It increases the transition temperature of vesicles and hence can improve stability by altering the fluidity of chains in bilayers. When present in sufficient concentration, it abolishes the gel to liquid phase transition endotherm of surfactant bilayers [12,42–46].

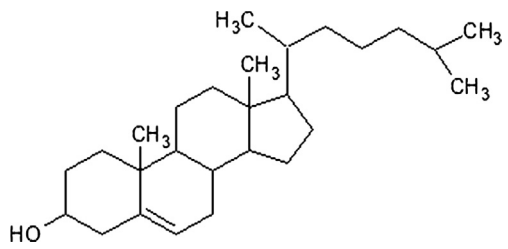

Fig. 5. Chemical structure of cholesterol.

Cholesterol also improves EE due to its membrane stabilizing effect, as it distributes between the bilayer, occupying otherwise void space and decreasing membrane fluidity, thus enhancing stability [3,5,47–49]. On the other hand, increasing cholesterol above a certain point may inhibit the formation of the regular linear structure of the vesicular membrane, as it competes with the drug molecules for space and excludes them [44,50].

Cholesterol influences other properties such as membrane rigidity, permeability, and ease of hydration [51–53]. The fluidity of the niosomal membrane is one of the critical factors governing the release of drug molecules. The difference in release behavior is due to the variation in cholesterol content in different niosomes. The amount of cholesterol required in a particular formulation is dependent on the HLB value of the surfactants; when the value is greater than 6; cholesterol must be used to form niosomes. For Span niosomes, Span 60 and 80 can form niosomes requiring little or no addition of cholesterol due to their low HLB values. Tween 60, with a higher HLB, needs more cholesterol to maintain membrane rigidity [8].

Drug loading capacity can be influenced by cholesterol, the addition of cholesterols delays drug release by abolishing gel to liquid phase transition and improving drug loading of hydrophilic drugs [20]. On the other hand, for lipophilic drugs, decreasing the concentration of cholesterol in the formulation lead to an increase in EE as cholesterol disrupts the regular linear structure of the niosomal membrane, which does not allow more entrapment for lipophilic drugs [54–56].

Charge inducing agents also play an essential role in stabilizing bilayer membranes by imparting either a negative charge or positive

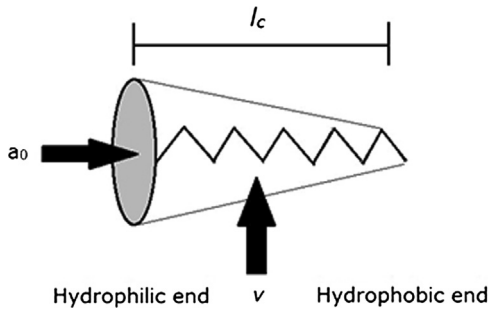

Fig. 6. Schematic structure of a single-chain surfactant, *V* is the hydrophobic group volume, *l*c is the hydrophobic group length, and a_0 is the area of the hydrophilic head group.

charge to the surface of the niosomes, preventing aggregation by electrostatic repulsion [57]. Negatively charged ionic compounds such as dicetyl phosphate (DCP) and positively charged compounds like stearyl amine (STR) or stearyl pyridinium chloride are commonly used charge inducing agents in the preparation of niosomes. Generally, these charged molecules are added to the formulation in an amount of 2.5–5 mol% [17,25,58,59]. However, increasing amount of the charge inducing agents beyond the limit will prevent the formation of niosomes [3].

3.3. Critical packing parameter

Nonionic surfactants are composed of both polar and non-polar parts. The formation of bilayer vesicles instead of micelles depends on the HLB of the surfactant, chemical structure of surfactants and the critical packing parameter (CPP) (Fig. 6) [2]. CPP can be expressed by the following equation:

$$\mathrm{CPP} = V/a_0 l_c$$

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

From the CPP value, the type of micellar structure formed can be ascertained. A CPP of less than 0.5 suggests the formation of spherical micelles, whereas a CPP between 0.5 and 1 suggests the formation of bilayer micelles. A CPP of greater than 1 suggests the formation of inverted micelles. A comparison between Tween surfactants confirmed the influence of the surface area of the polar head. Tween 21 and 20 have the same alkyl chain but different hydrophilic head groups, which influences the HLB value, the former being HLB 13.3 and the latter being HLB 16.7 [3].

3.4. Hydrophilic-lipophilic balance (HLB)

HLB is an empirical expression for the relationship of the hydrophilic and the hydrophobic groups of surfactants [2]. Surfactants with a higher HLB value are more water-soluble than surfactants with a lower HLB [8,42–44]. HLB value affects the size of the niosomes as well as EE of the active ingredient [35,60,61]. It has been reported that surfactants with an HLB value between 4 and 8 can form niosomes, whereas surfactants with an HLB value of 6 or higher require the addition of cholesterol to form niosomes. Surfactants with an HLB outside of this range do not form niosomes [62,63].

3.5. Gel liquid transition temperature (Tc)

Gel liquid transition temperature (Tc) of the surfactants is an essential factor that influences the formation of niosomes. It affects EE, membrane fluidity, membrane permeability, and stability. Tc and the length of the alkyl chain of non-ionic surfactants are correlated with each other. Shorter alkyl chains have a lower Tc, which leads to the formation of “leaky” niosomes. Surfactants with a higher Tc are more likely to be in an ordered gel form, reducing bilayer leaking compared with surfactants that have a lower phase transition temperature [19,43]. Tc is dependent on the degree of the unsaturated alkyl chain. Lack of saturation in the alkyl chain lowers Tc and increases chain fluidity and membrane permeability. Studies have shown that niosomes formed by surfactants with lower Tc are more flexible than those formed with a higher Tc. The temperature of the hydration medium should be higher than the Tc of the surfactant, as this affects the formation of niosomes and could induce modifications in the bilayer [64–66].

4. Methods of preparation

There are multiple methods for preparing niosomes. These include the thin film hydration (hand shaking) method, ether injection method, reverse phase evaporation method, trans-membrane pH gradient drug uptake process, emulsion method, lipid injection method, micelle solution and enzyme method, bubble method, microfludization method, the formation of niosomes from proniosomes and supercritical reverse phase evaporation method. Some new methods have been developed in the past decade; for example, the supercritical reverse phase evaporation method was described by Manosroi and colleagues using supercritical carbon dioxide fluid [60]. Another microfluidization method was introduced recently, which is rapid and provides controlled mixing of surfactant cholesterol solution and an aqueous solution in microchannels [3]. Also, proniosome methods have been proposed to overcome physical instability issues. Niosomes obtained as a dry powder

Table 1
Advantages and disadvantages of niosome preparation methods.

Preparation method	Advantages	Disadvantages	References
Thin film hydration (hand shaking) method	An easy technique for laboratory researches	Involves the use of organic solvents	[3,67,68]
Ether injection method	An easy technique for laboratory researches	Cannot be used for heat labile drugs	[3,46]
Reverse phase evaporation method	High drug EE	Involves the use of organic solvents	[69]
Trans-membrane pH gradient drug uptake process	High drug EE	Involves the use of organic solvents	[70]
Emulsion method	An easy technique for laboratory research	Involves the use of organic solvents	[2]
Lipid injection method	No organic solvents involved	Cannot be used for heat labile drugs	[2]
Niosome prepared using micelle solution and enzymes	No organic solvents involved	The active ingredient may be degraded by enzymatic degradation	[1]
Bubble method	No organic solvents involved	Cannot be used for heat labile drugs	[71]
Micro fluidization	No organic solvents involved	Cannot be used for heat labile drugs	[2]
Formation of niosomes from proniosomes	No organic solvents involved Better physical stability	Complex process Complete drug entrapment may not be possible during hydration	[2,20,21]
Supercritical reverse phase evaporation method	No organic solvents involved	Special equipment required for this method	[72]

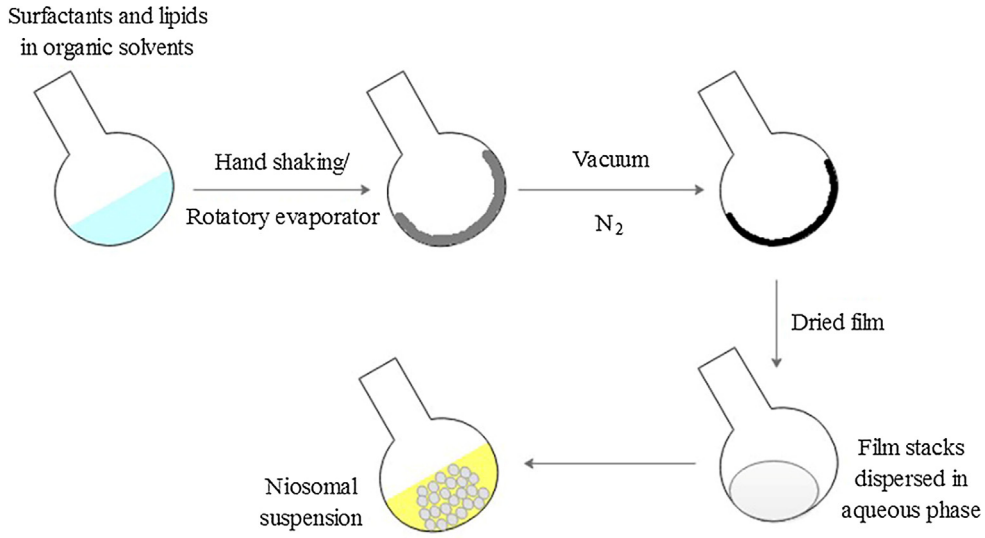

Fig. 7. Schematic diagram of the preparation of niosomes using thin film hydration (hand shaking) method.

provide easy unit dosing and can also be applied in pulmonary delivery [61]. The advantages and disadvantages of the different preparation methods are summarised in Table 1. Niosomes prepared by different method yield difference sizes of vesicles. The methods of preparation are detailed below.

4.1. Thin film hydration (hand shaking) method

The thin film hydration method is a simple technique (Fig. 7); however, it requires the use of organic solvents to dissolve surfactant and cholesterol. Surfactants and cholesterol are dissolved in a round-bottomed flask followed by evaporation of the organic solvent to form a thin film on the bottom of the flask. Addition of aqueous medium swells the film from the wall of the round bottom flask at a temperature above the transition temperature of the surfactant for a specified period with constant mild agitation to produce multilamellar vesicles, which are then treated to produce unilamellar vesicles [2,3,67,68].

4.2. Ether injection method

In this method, surfactant and drug are dissolved in diethyl ether and injected slowly to an aqueous phase, then heated above the boiling point of the organic solvent (Fig. 8). This method produces LUVs and can be further treated to reduce the size [3,46].

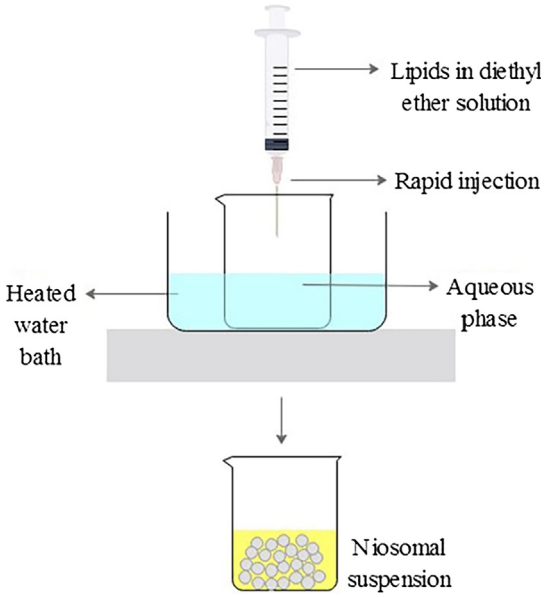

Fig. 8. Schematic diagram of the preparation of niosomes via ether injection method.

4.3. Reverse phase evaporation method

In this method, surfactants are dissolved in an organic solution of ether and chloroform, followed by addition of an aqueous drug solution (Fig. 9). The two immiscible phases are then homogenized, and organic solvents are removed under reduced pressure to form a niosome suspension. This method is considered ideal for preparation of hydroxychloroquine niosomes, due to high EE, large particles size with a small variation [73]. The reverse phase method has been reported to encapsulate large hydrophilic macromolecules with relatively higher EE than other methods [69].

4.4. Trans-membrane pH gradient drug uptake process

In this method, surfactants and cholesterol are dissolved in an organic solvent. This solution is then evaporated under reduced pressure to obtain a thin film on the wall of the round bottom flask (Fig. 10). Hydration of this film is carried out with a citric acid solution at pH 4 by vortex mixing. The resultant vesicles then undergo a freeze and thaw process for three cycles and sonication. An aqueous drug solution is then added and vortexed. The pH of this solution is adjusted to 7 and heated at 60 °C to produce multilamellar vesicles [70].

4.5. Emulsion method

With the emulsion method, surfactant and cholesterol are dissolved in organic solvent and then added to an aqueous drug solution to form an oil in water emulsion (Fig. 11). The organic solvent is then evaporated to obtain niosomal suspension in an aqueous medium [2].

4.6. Lipid injection method

This method does not require the use of organic solvents. Surfactant and cholesterol are melted and then injected into a highly agitated heated aqueous phase containing dissolved drug molecules to form a niosomal suspension (Fig. 12) [2].

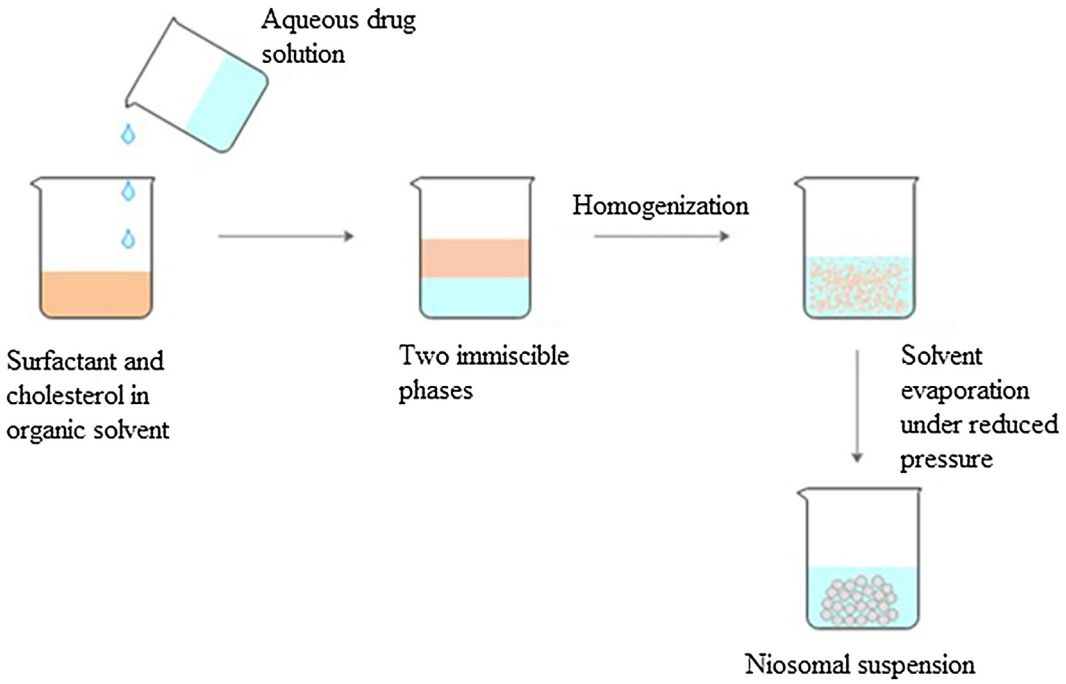

Fig. 9. Schematic diagram of the preparation of niosomes via the reverse phase evaporation method.

4.7. Niosomes prepared using micelle solution and enzymes

Niosomes can be prepared with a mixed micellar solution by the use of enzymes. For example, esterases break the ester links of polyethylene stearyl derivatives leading to the formation of breakdown products such as cholesterol and polyoxyethylene, which can form multilamellar niosomes with the addition of dicetyl phosphate and other lipids (Fig. 13) [1].

4.8. The bubble method

The bubble method is a single step technique that does not require the use of organic solvents. Surfactants and cholesterol are added to a buffer solution at 70 °C, the dispersion is mixed for fifteen seconds with a high shear homogenizer, and nitrogen gas is passed through this solution leading to the formation LUVs (Fig. 14) [71].

4.9. Microfluidization

This newly developed method produces smaller unilamellar vesicles

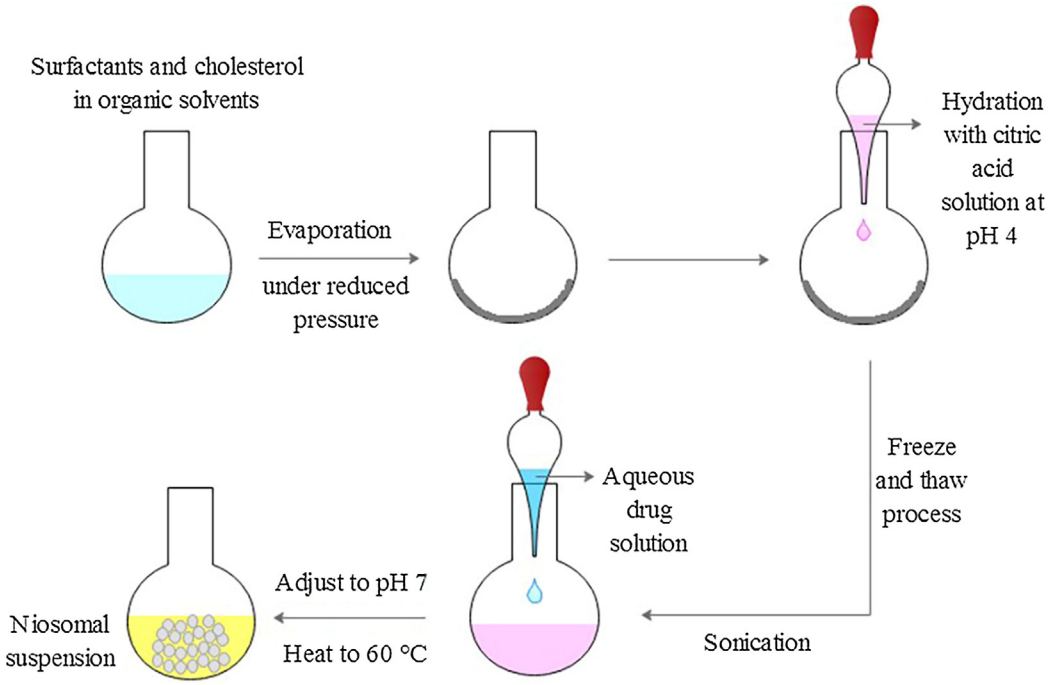

Fig. 10. Schematic diagram of the preparation of niosomes via the trans-membrane pH gradient drug uptake process.

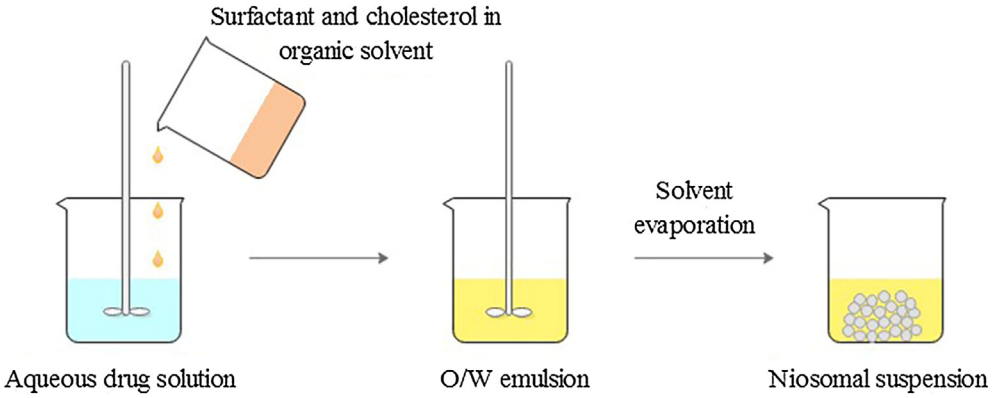

Fig. 11. Schematic diagram of the preparation of niosomes using the emulsion method.

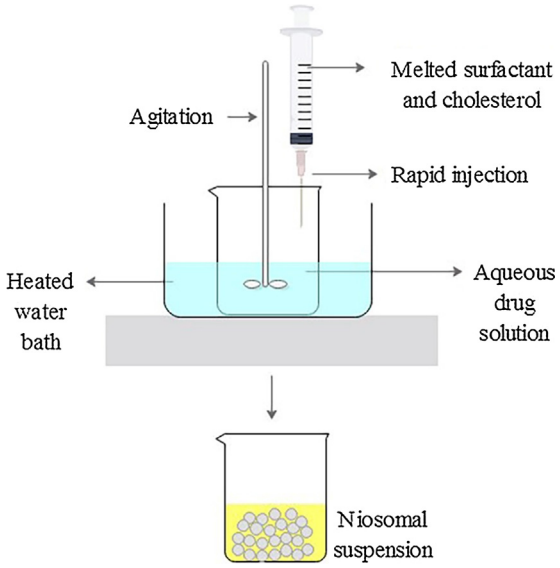

Fig. 12. Schematic diagram of the preparation of niosomes via lipid injection method.

with narrow size distribution. A solution of surfactants and drug is pumped through an interaction chamber under pressure at a rate of 100 ml/min. The solution is then passed through a cooling loop to remove the heat produced during microfluidization to form niosomes (Fig. 15) [2].

4.10. Proniosomal method

Proniosomes are produced by coating a water-soluble carrier material with non-ionic surfactants, such as water-soluble materials including sucrose stearate, maltodextrin or mannitol. The water-soluble carriers are covered by a thin layer of surfactant and are rehydrated under agitation in hot aqueous media to form a niosomal suspension. Proniosomes are obtained as a dry powder, thus eliminating the physical instability issue of niosomes, such as aggregation, fusion, and leaking. Proniosomes made from this method are stable during storage and transport; the dry powder also allows easy unit dosing for patients [2,20,21].

Proniosomes can also be obtained using the coacervation phase separation method (Fig. 16). A mixture of surfactant, cholesterol, drug and phosphatidylcholine are dissolved in absolute ethanol in a wide mouth glass tube. The open end of this tube is covered with a lid and warmed in a water bath at 70 °C for 5 min. An aqueous phase is then added and warmed on a water bath until a clear solution is observed. The mixture is allowed to cool down at room temperature until the dispersion is converted into a proniosomal gel [12].

4.11. Supercritical reverse phase evaporation method

This method involves supercritical fluid as described by Manosroi and colleagues [60]. It does not require the use of organic solvent, which can be difficult to remove and toxic. This method can also be easily scaled up to produce a large number of niosomes. However, large unilamellar niosomes are obtained with a size between 100 and 500 nm. Sonication or extrusion method can be combined with this method to produce smaller niosomes [2,72].

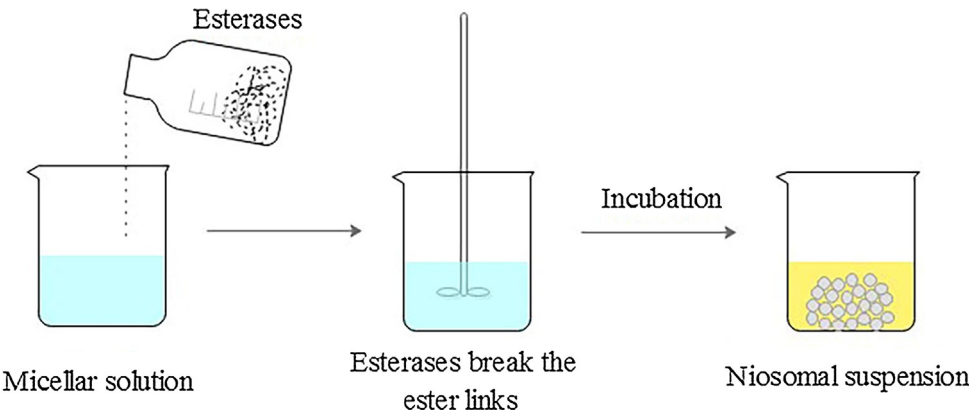

Fig. 13. Schematic diagram of the preparation of niosomes using micellar solution and enzymes.

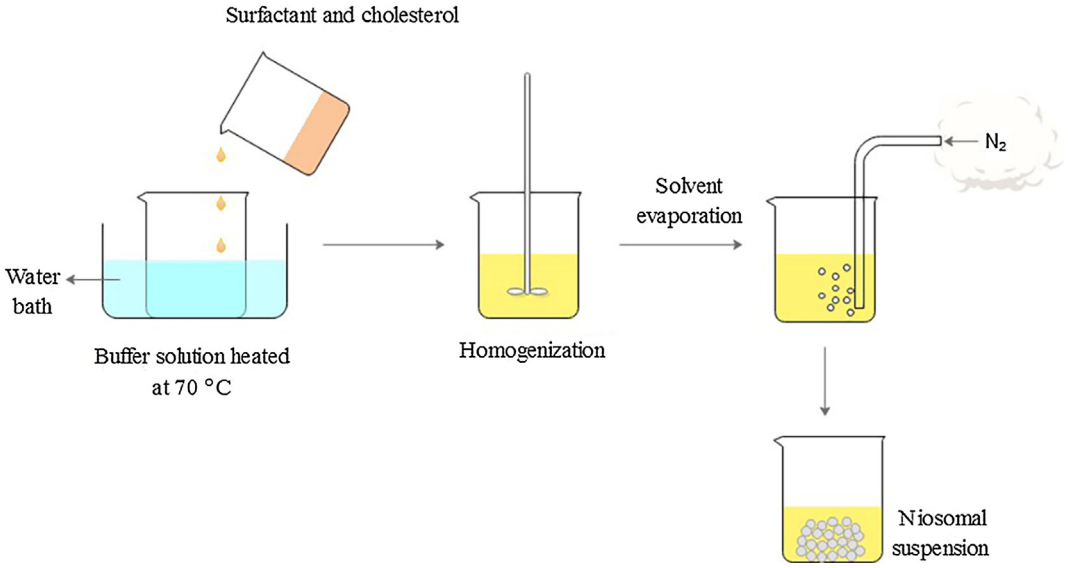

Fig. 14. Schematic diagram of the preparation of niosomes via the bubble method.

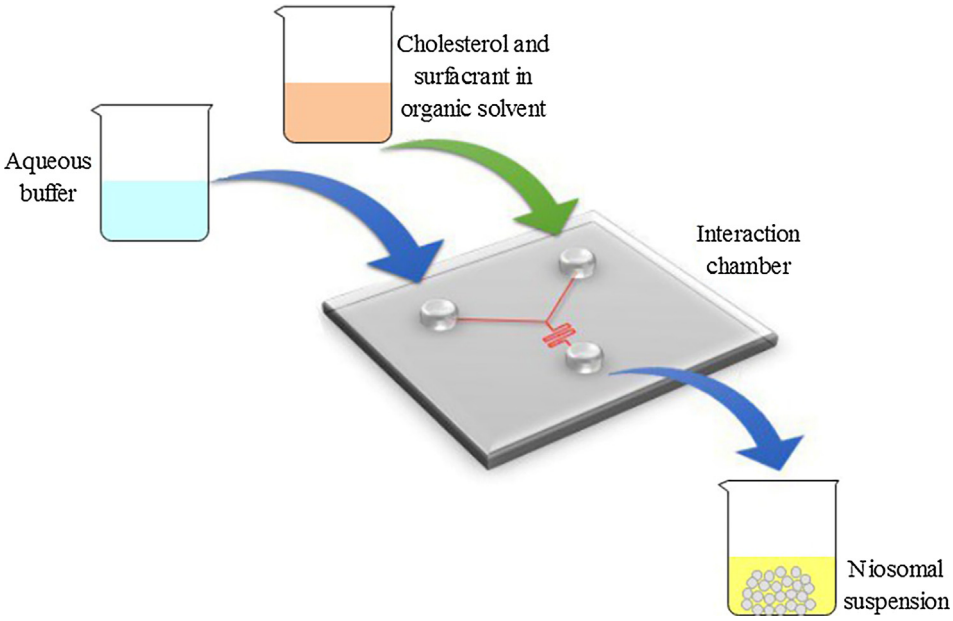

Fig. 15. Schematic diagram of the preparation of niosomes using the microfludization method.

5. Niosome purification

Purification of niosomes is an essential step, as complete encapsulation of drug molecules in niosomes is seldom possible regardless of optimization of the drug loading processes. The free drug must be removed to prevent the burst release of niosomes when applied in *in vitro* and *in vivo* experiments [67]. Purification methods used to remove unentrapped drug molecules include dialysis, gel filtration, and centrifugation. The dialysis method is based on the diffusion of the solute through a semi-permeable membrane, which is frequently used by researchers to remove free drug. Niosomes are filled into a dialysis bag and then dialyzed against a saline solution. The concentration of the drug in the saline solution is determined by spectrophotometry [2]. Purification of niosomes from the unencapsulated drug can be carried out by gel filtration chromatography on Sephadex G75, G50 or G25, which allows efficient separation of free drug molecules [2,72]. Centrifugation and ultracentrifugation have also been used to purify niosomes. These methods can be applied to a variety of solutes and more than 90% recovery can be achieved without dilution of niosome preparation [62,74,75].

6. Characterization studies

The characterization of niosomes includes parameters such as size, distribution, zeta potential, morphology, EE, and *in vitro* release behavior. These are studied to determine the quality of the niosomes in formulation development and their applications in future clinical studies. These parameters have a direct impact on stability and *in vivo* performance [2,3]. They are summarized in Table 2 and discussed in more detail below.

6.1. Niosome particle size and size distribution

Particle size is a fundamental parameter in the characterization of niosomes as it provides information on physical properties and stability of the formulation [3]. The size of niosomes can be measured by

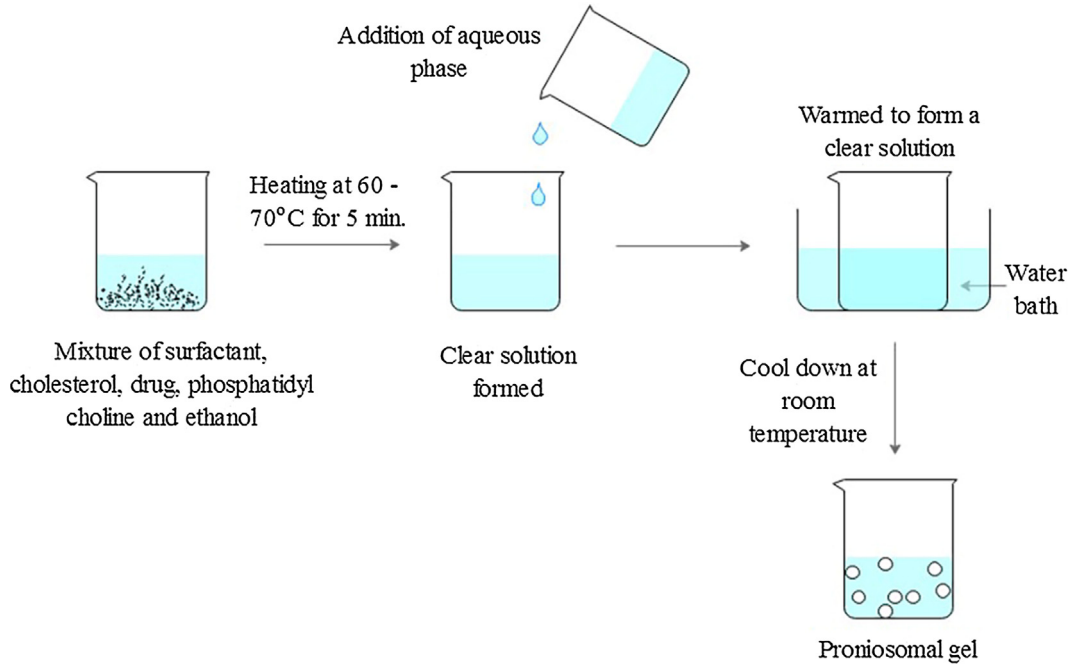

Fig. 16. Schematic diagram of the preparation of proniosomes via coacervation phase separation method.

techniques such as dynamic light scattering (DLS) and microscopy. DLS is also known as photon correlation spectroscopy [2]. This method is rapid and non-destructive, and only a small amount of sample is required. It can be used to measure particles in the size range of 3–3000 nm. This technique is based on the principle of random Brownian motion of small particles dispersed in a medium. A laser generated by the equipment irradiates the niosome suspension and the niosomes scatter light. This is detected at either a fixed or variable scattering angle, with the intensity of the fluctuations in scattered light from the collision of particles arising from random Brownian motion as a function of time. Smaller particles produce higher intensity fluctuations due to their higher diffusion coefficient, whereas larger particles move relatively slowly and cause a lower intensity of fluctuations. The polydispersity index (PDI) is an indication of the distribution of niosome size, with PDI value of less than 0.5 indicating a monodispersed sample. The limitation of DLS is that it does not provide any information on the shape of the niosomes [1]. Electronic microscopic techniques are also used to determine the size of niosomes, DLS and microscopic techniques are sometimes used in combination to produce more reliable results [3].

6.2. Morphology

Microscopic techniques are used to study the morphology of niosomes. Electronic microscopic methods including transmission electronic microscopy (TEM), negative-staining transmission electronic microscopy (NS-TEM) and freeze-fracture transmission electronic microscopy (FF-TEM) are used preferentially for liquid state samples, whereas scanning electron microscopy (SEM) is used for solid samples. Atomic force microscopy (AFM) and scanning tunneling microscopy (STM) were used by Binnig's group in 1982 for characterization of micro- and nano-scale structures. STM is useful in determining the bilayer thickness of liposomes and niosomes due to its analytical ability in the vertical axis [2,23,76].

6.3. Zeta potential

The zeta potential, which is also known as surface charge, provides essential information in determining the physical stability of niosomes. The surface potential can be measured by laser Doppler anemometry and the magnitude of zeta potential provides an indication of the degree of electrostatic repulsion between two adjacent particles. Niosomes with a zeta potential higher than +30 mV or lower than −30 mV are considered to have acceptable stability [3,77,78].

6.4. Bilayer characterization

Niosomes are either present in a single layer (unilamellar) or multiple layers (multilamellar) [3]. The number of lamellae can be determined by small angle X-ray scattering (SAXS), nuclear magnetic resonance spectroscopy (NMR) and AFM. The SAXS can be coupled with

Table 2
Characterization techniques for niosomes.

Parameters	Applied techniques or methods	Reference
Particle size and distribution	Dynamic light scattering, Scanning electron microscopy (for solid samples), Transmission electronic microscopy (for liquid samples)	[3]
Morphology	Transmission electronic microscopy, Negative-staining transmission electronic microscopy, Freeze-fracture transmission electronic microscopy, Atomic force microscopy, Scanning electron microscopy, Cryo-scanning electron microscopy	[2,23,76]
Zeta potential	Laser doppler anemometry	[45,77,78]
Bilayer characterization	Fluorescence polarization	[60]
Vesicle stability	Dynamic light scattering, Microscopic techniques	[20,49,55,67,79]
EE	UV-spectrometer, High performance liquid chromatography and Fluorescence	[80–82]
In vitro release	Dialysis, Franz diffusion cells	[22,25,34,76,78,83–85]

Table 3
Examples of niosomes that have been investigated for oral drug delivery.

Drug	Surfactant	Method of Preparation	Reference
Celecoxib	Span 60	Proniosome derived niosome method	[15]
Diacerein	Sorbitan monolaurate and poloxamer 184	Thin film hydration	[57]
Ganciclovir	Span 40 and 60	Reverse phase evaporation	[93]
Methotrexate	Tween 80	Thin film hydration	[48]
Paclitaxel	Span 40	Thin film hydration	[61]
Plasmid DNA for Hepatitis B	Span 60	Reverse phase evaporation	[69]
Tetanus toxoid	Span 60 and ween 20	Reverse phase evaporation	[94]
Tramadol	Tween 80, Tween 40, Span 80 and 40	Proniosome derived niosome method	[92]
Valsartan	Span 60	Proniosome derived niosome method	[90]

energy-dispersive X-ray diffraction (EDXD) to characterize the thickness of niosomal bilayer. The fluidity of the niosomal membrane allows membrane deformation without changing bilayer integrity and can be measured by the mobility of the fluorescent probe as a function of time and temperature. Microviscosity of niosomal membranes can be determined by fluorescent polarization to study the packing structure of the lipid bilayer [60].

6.5. Niosome stability

Stability of the vesicular system is an issue and concerns not only physical and chemical but also biological stability. This fundamental parameter is used to determine the potential *in vivo* and *in vitro* application of the niosomes [64]. Stability is generally determined by monitoring particle size and zeta potential over time, with variations in these two parameters indicating possible instability. Stability is often determined over three months in different conditions, such as 4 °C, 25 °C, 40 °C at 75% relative humidity, to assess the effect of temperature on stability [20,49,55,67,79].

6.6. Entrapment efficiency (EE)

EE is described as the number of drug molecules that have been successfully entrapped within the vesicles and in this case the niosomes, and can be expressed by the following equation:

$$EE = (\text{Amount of drug entrapped} \div \text{Total amount of drug added}) \times 100\%$$

The amount of drug entrapped refers to the actual amount of drug molecules been successfully enclosed in the vesicles and the total amount of drug refers to the amount of drug used in preparation [2]. The free drug molecules need to be separated from the entrapped drug by methods such as dialysis, filtration or centrifugation [86,87]. The EE can be determined by spectrophotometry, or by gel electrophoresis followed by UV densitometry for genetic materials [88]. Moreover, this parameter can also be determined using a fluorescence marker such as calcein to evaluate the number of marker molecules entrapped [80–82].

6.7. In vitro drug release

In vitro release behavior of the niosomes is a fundamental parameter, which can be affected by many factors such as drug concentration, hydration volume, and nature of the membrane. The release of drug molecules from niosomes is generally studied using a dialysis membrane. This is where purified niosomal suspension without free drug is filled into a dialysis bag, then tied at both ends and placed in a beaker of phosphate buffered saline (PBS) at a constant temperature at 37 °C and under magnetic agitation. Samples are taken at predetermined time intervals and replaced with the same amount of fresh medium. These samples are then analyzed using appropriate assays to determine the concentration of drug released over time [34,76,78]. Franz diffusion cells have also been used to study the release behavior of niosomes. This is where the dialysis membrane is placed between the donor and receptor compartment of the apparatus; the niosomal suspension is filled into the donor compartment. The receptor compartment contains PBS at pH 7.4 and the whole system is maintained at 37 °C. Samples are collected from the receptor compartment at defined time intervals and replaced with the same amount of release medium [22,25,83–85].

7. Applications of niosomes in drug delivery

Applications of niosomes can be found in areas such as drug delivery and cosmetics, they are suitable for the delivery of many pharmaceuticals and have been studied for various routes of administration including oral, topical, transdermal, ocular, intravenous, pulmonary and transmucosal; the design of the formulation is influenced by the route of administration of the niosomal formulation [32,56,57,69,84,89].

7.1. Oral delivery

Oral delivery is widely regarded as the most accessible and convenient route of drug administration, especially when repeated administration is required. However, there are several challenges to consider when formulating oral drugs, such as the acidic environment of the stomach, enzymatic degradation in the gastrointestinal tract, first pass metabolism, poor absorption and variable drug bioavailability. Niosomes have been explored to overcome these challenges by improving absorption and bioavailability [3,61,90]. Examples of niosomes that have been developed for oral delivery are outlined in Table 3.

The first application of niosomes in oral delivery was reported in 1985 by Azmin et al., who found that the niosomal formulation significantly improved the bioavailability of methotrexate [91]. Niosomes modified with polysaccharide o-palmitoyl mannan have also been studied for oral genetic immunization of hepatitis B [69]. Niosomes have been investigated for oral delivery of lipophilic drugs such as diacerein, which has limited bioavailability due to low solubility and belongs to Class II of the Biopharmaceutical Classification System (BCS). Researchers investigated sorbitan monolaurate and Poloxamer 184 based niosomes for oral delivery of diacerein and found improved *in vitro* dissolution profiles of the niosomal formulations compared with diacerein aqueous suspension [57]. Paclitaxel (PCT) is an anticancer drug used to treat several types of cancers including ovarian, breast, lung, cervical and pancreatic cancer. Bayindir and co-workers have successfully encapsulated this drug in various niosomal formulations. Niosomes composed of Span 40, cholesterol and DCP showed a high EE and better stability of PCT against gastric enzymatic degradation than other formulations prepared with Span 20, 60, Tween 20, 60 and Brij 76, 78, 72. PCT released from niosomes by a diffusion-controlled mechanism and the resulting sustained release could be beneficial for reducing the adverse effects associated with PCT [61]. Tramadol HCl encapsulated niosomes have been investigated for extending the analgesic effect following oral administration. Tramadol has poor bioavailability due to first pass metabolism, with only 68% of the administered dose reaching the blood circulation following a single oral dose, and patients often

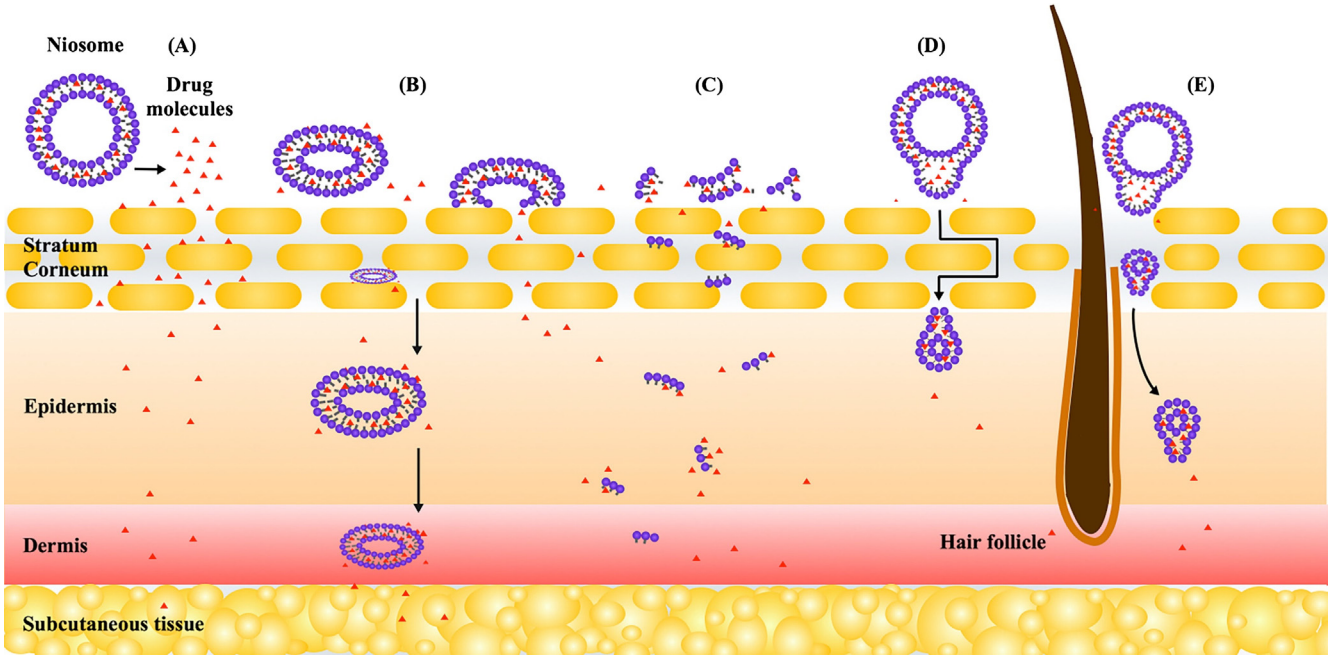

Fig. 17. Possible mechanisms of action of niosomes for dermal and transdermal drug delivery, (A) drug molecules released by a niosome; (B) adsorption of niosome and fusion with the SC; (C) intact niosome/elastic penetration through intact SC; (D) components of niosomes act as penetration enhancer to enhance drug absorption; (E) niosome penetration through hair follicles or pilosebaceous units (not to scale) (modified from El Maghraby et al., 2006 [101]).

experience adverse side effects such as sedation. In order to improve bioavailability and reduce side effects, an oral dosage form was developed using niosomes. Proniosome gel and solution were prepared with Span and Tween surfactants, then niosomes were formed by mixing the heated phosphate buffered saline to the gels or solution of tramadol proniosomes. Oral administration of tramadol loaded niosomes to mice showed extended analgesic effects compared to tramadol solution [92].

7.2. Topical and transdermal delivery

Topical drug delivery has several advantages, such as localized drug release at the site of action and reduced side effects by minimizing systemic absorption [9,10]. In transdermal drug delivery, the active ingredients are delivered across the skin for systemic circulation, which has several advantages compared with other routes of administration. Transdermal delivery has higher bioavailability as first-pass hepatic metabolism can be avoided, is non-invasive as no needle is required, avoids acidic and enzymatic degradation in the gastrointestinal tract and eliminates potential drug-food interaction. However, use of the transdermal route is limited due to the poor penetration rate of drug molecules, with the primary barrier for drug absorption across the skin being the stratum corneum (SC) [95,96]. Low molecular weight ($\leq$500 Da), lipophilicity, and effectiveness at low dosage are the ideal characteristics of the drugs for transdermal delivery [40]. However, many drugs do not possess ideal physicochemical properties; only a minimal number of drugs have been successfully formulated into transdermal preparations. Topical applications of niosomes have been widely reported due to their ability to enhance cutaneous drug delivery to the epidermis and dermis layer [24,76,97–100]. Several mechanisms have been proposed to explain their penetration-enhancing effects. Firstly, adsorption and fusion of drug-loaded vesicles onto the surface of the skin leads to a high thermodynamic activity gradient of the drug at the surface of vesicles and SC, which acts as a driving force for the penetration of drugs across the SC [55,58,101–104]. Secondly, disruption of the densely packed lipids that fill extracellular spaces of the SC, enhance the permeability of drugs through structural modification of SC. Thirdly, the non-ionic surfactants play a crucial role in improving penetration by acting as penetration enhancers. Wherein vesicle bilayers enter the SC with subsequent modification of the intercellular lipids, which increases overall membrane fluidity [50,55,58,84,102,103,105–110]. Lastly, niosomes cause an alteration in the SC properties through a reduction in the *trans*-epidermal water loss, thus leading to an increase in SC hydration with the loosening of its closely packed cellular structure [55,102].

An important research contributes to the evaluation of niosomes as permeation enhancers for transdermal delivery was made in 2011. It aimed to evaluate if the increased hydrophilic drug permeation across the skin, which is always observed with vesicular systems, is dependent on the structural organization of niosomes, that are used to transport the active molecule, or it is only dependent on the dual nature of surfactant. The study was designed to examine the real role of surfactant molecule and the influence of its structural organization on the *ex vivo* permeation of a hydrophilic drug. The percutaneous permeation profiles of sulfadiazine sodium salt were obtained, according to the following experimental conditions: a drug-loaded niosome formulation, drug solubilized in a sub-micellar solution of surfactants, a drug aqueous solution after skin pretreatment with empty niosomes, a drug aqueous solution after skin pretreatment with the sub-micellar solution of surfactants. The results showed that the permeation of sulfadiazine was not increased after pretreatment with sub-micellar solutions of surfactants or direct treatment with a sub-micellar solution of surfactant containing the drug respect to the control. Only the direct treatment of the skin with loaded niosomes gave a relevant increase of the percutaneous permeation of the drug, confirming their role as permeation enhancers. It has been reported that the intercellular lipid barrier in the SC would be dramatically changed to be more permeable by treatment with non-ionic surfactants in the form of niosomes that act as penetration enhancers [85]. The possible mechanisms of action of niosomes to enhance skin penetration are shown in Fig. 17.

Moreover, topical application of niosomes is limited by its liquid nature of the preparation; when applied they may leak from the application site. This challenge is overcome by incorporation gelling agents to niosomal dispersion, thereby forming a niosomal gel. Niosomal gels can provide a reservoir of drugs in SC for the sustained release, which leads to high accumulation of drugs in the dermis and

epidermis. The gel can also promote the penetration of drug across the SC owing to the occlusion effects from the gel formation which can enhance skin hydration and subsequently increase the absorption and penetration of drug across the skin [24,40]. The most recent development in vesicle design for transdermal delivery is the use of elastic vesicles, which differ from conventional niosomes by their characteristic fluid membrane with high elasticity. This feature enables them to squeeze themselves through the intercellular regions of the SC under the influence of transdermal water gradient upon application on the skin surface [24,105]. Ethanol used in the preparation of elastic niosomes is known as an efficient permeation enhancer, it can interact with the polar head group region of the lipid molecules, resulting in the reduction of the melting point of the SC lipid, thereby increasing lipid fluidity, and cell membrane permeability [10]. Penetration can also be due to the adhesion of the vesicle to the skin surface followed by the destabilization and finally the fusion with the SC lipid matrix. Studies have demonstrated that elastic vesicles were often localized and accumulated in the channel like regions which are located within the intercellular lipid lamellae of the skin surface [24]. Manosroi and co-workers developed novel elastic niosomes entrapped with the non-steroidal anti-inflammatory drug, diclofenac diethylammonium for topical application. Various formulation composing of dipalmitoylphosphatidylcholine, Tween 61, or Span 60 mixed with different molar ratios of cholesterol and ethanol at 0%–25% (v/v) were prepared. Elastic Tween 61 niosomes were selected due to their better stability. The deformability index values for elastic niosomes were significantly higher than for the conventional empty or loaded niosomes, indicating the higher flexibility of the elastic vesicles, especially when entrapped with the drug. Gels containing elastic niosomes demonstrated enhanced transdermal absorption through rat skin by exhibiting higher fluxes of diclofenac in the SC, viable epidermis and dermis and receiver chamber compared to commercial emulgel containing an equivalent amount of drug. Diclofenac entrapped in the elastic niosomes and incorporated in the gel also demonstrated good anti-inflammatory effect in the rat ear edema assay [23].

Drugs with different physicochemical properties have been investigated for topical and transdermal delivery include diacerein [53], itraconazole [111], tretinoin [112], salidroside [102] and finasteride are listed in Table 4 [113]. An exciting area in dermal drug delivery is a topical vaccine, niosomes have been studied in this area for delivery of antigens. The topical vaccine has the advantages of safety and flexibility. The skin acts as a barrier to protect from foreign invaders; there are specialized cells of the immune system throughout the layers of the skin, e.g., Langerhans cells, dendritic cells, and epidermotropic lymphocytes. Hepatitis B infection remains a significant worldwide health problem. Vyas and co-workers investigated niosomes for a non-invasive topical genetic vaccine against hepatitis B virus [69,114]. DNA encoding hepatitis B surface antigen (HBsAg) were loaded in niosomes composed of Span 85 and cholesterol. The immune-stimulating activity was determined by measuring hepatitis B surface antigen titer and cytokine levels following topical application of antigen-loaded niosomes in Balb/c mice. Results were compared with naked DNA and liposome encapsulated DNA applied topically, naked DNA and pure recombinant HBsAg administered intramuscularly. Topical niosomes elicited a similar serum antibody titer and endogenous cytokine levels when compared to intramuscularly injected recombinant antigens [105,114]. Gupta et al. also studied the topical delivery of tetanus toxoid for non-invasive immunization using transfersomes, niosomes, and liposomes. The *in vivo* study found that transfersomes elicited a higher immune response in comparison to niosomes and liposomes due to its elastic bilayer, which allows transfersomes to deform and pass through the minute pores present in the skin [105,114]. Niosomes have been studied to deliver antioxidant enzyme catalase (CAT) for wound healing. Researchers used biocompatible non-ionic sugar ester surfactants to deliver enzyme catalases. The mean diameter of the resulting niosomes was around 222–275 nm and the catalytic activity of enzymes was improved after encapsulation by a factor of 1.7-fold. Further, the niosomes were able to preserve the catalytic activity for 180 days when stored at 4 °C. The *in vivo* studies showed a significant improvement of the prepared CAT niosomes on wound healing [37]. A hybrid system of moxifloxacin-loaded niosomes incorporated into chitosan gel was studied for preventing burn infection by Sohrabi et al. The optimized niosomal formulation showed 74% EE and approximately 50% of the drug released in 8 h. The gel embedded niosomes showed pseudoplastic flow behavior and more sustained release compared with niosomes. Both of the formulations were found efficiency against common skin bacteria, while the hybrid formulation was more superior against *Staphylococcus aureus* [115].

7.3. Ocular delivery

Conventional ocular drug delivery preparations such as eye drops, ointments, and suspensions are unable to achieve high bioavailability due to physiological barriers in the eyes, such as the barrier properties of retinal pigment epithelium and the endothelium lining the inner side of the retinal blood vessels. Also, a significant amount of the dose is usually washed away into the nasolacrimal ducts [56]. Studies have shown that niosomes can overcome some of these barriers and may be suitable carriers for ocular delivery. Firstly, the nano-sized niosomes can resist drainage by reflex tearing and blinking. Secondly, niosomes are better retained on the eye surface compared to other carriers [12]. Zeng and co-workers have investigated hyaluronic acid (HA) coated niosomes. HA is a linear polymer composed of long chains of repeating disaccharide units of N-acetyl glucosamine and glucuronic acid has attracted more attention in ocular delivery as it is a natural component of the vitreous body and aqueous humor of the eye. The mucoadhesive property of HA facilitates ocular contact time of the formulation and hence improves drug absorption and bioavailability. This study demonstrated that HA-coated niosomes were able to prolong pre-corneal retention, increase aqueous humor pharmacokinetics and bioavailability of tacrolimus [11]. Chitosan-coated niosomes were studied by Zubairu and his team for trans-corneal delivery of gatifloxacin. Niosomes were prepared with Span 60 by the solvent injection method and coated with different concentrations of chitosan. Permeation studies showed that the chitosan coated niosomes increased transcorneal permeation of gatifloxacin by more than two-fold when compared with the drug solution. The uncoated niosomes showed longer retention, which was further enhanced in coated niosomes [77]. Abdelkader and co-workers investigated niosomes and discomes for delivery of naltrexone hydrochloride. They evaluated spreading, rheological properties and their ability to prevent autoxidation of naltrexone hydrochloride in aqueous solutions. The prepared niosomes showed better wetting and spreading abilities than aqueous drug solutions. Niosomes were also significantly more viscous than the aqueous drug solution. The lipid content, size, and composition of niosomes are the main factors affecting the viscosity of niosomal dispersions. The stability of naltrexone hydrochloride was evaluated by exposing it to artificial daylight illumination; the niosomal dispersion was able to protect the extensive degradation of naltrexone from photo-induced oxidation compared with free naltrexone solution [26]. Recently, proniosome-derived niosomes were developed for topical ocular delivery of tacrolimus; these niosomes were prepared with poloxamer 188, lecithin and cholesterol. Proniosomes were reconstituted to form niosomes with ethanol and a small amount of water before use. *In vitro* permeation studies were performed on freshly excised rabbit cornea, and it was determined that the cumulative permeation amount of tacrolimus from niosomes and the drug retention in the cornea was significantly increased compared with the commercial ointment. An *In vivo* ocular irritation test in rat eyes showed no irritation and good biocompatibility with the cornea. *In vivo* anti-allograft rejection assessment was performed in a rat corneal xenotransplantation model. The results showed that treatment with 0.1% tacrolimus loaded niosomes delayed the occurrence of corneal

Table 4
Examples of niosomes that have been investigated for dermal and transdermal delivery.

Drug	Surfactant	Method of preparation	Reference
Acetazolamide	Span 60	Thin film hydration	[76]
Antioxidant enzyme catalase	Sugar ester surfactants	Thin film hydration	[37]
Artemisone	Span 60	Thin film hydration	[83]
Capsaicin	Span 60	Thin film hydration	[62]
Diacerein	Span 60	Thin film hydration	[53]
Diclofenac diethylammonium	Tween 61 and Span 60	Thin film hydration	[23]
Ellagic acid	Span 60 and Tween 60	Reverse phase evaporation	[107]
Ellagic acid	Span 60 and Tween 60	Reverse phase evaporation	[116]
Enoxacin	Span 40 and Span 60	A combination of ethanol injection and freeze drying	[58]
Estradiol	Span 40, 60 and 85	Proniosome derived niosome method (coacervation phase separation)	[103]
Febuxostat	Tween 20 and Span 60	Thin film hydration	[104]
Finasteride	Brij 52, 72, 97 and Span 40	Thin film hydration	[113]
Gallidermin	Tween 61	Freeze dried	[40]
Hydroxychloroquine	Pluronic 27, Brij 98, Tween 20, 40, 65 and 80, Span 20, 40, 60 and 80	Reverse phase evaporation	[73]
Itraconazole	Span 40 and Span 60	Thin film hydration	[111]
Lacidipine	Span 60	Thin film hydration	[74]
Methotrexate	Span 60	Thin film hydration	[96]
Minoxidil	Brij 52, 76 and Span 20, 40, 60 and 80	Thin film hydration	[35]
Moxifloxacin	Span 20 and 60, Tween 20, 40, 60 and 80	Thin film hydration	[115]
N-terminal Tat-GFP fusion protein	Tween 61	Freeze dried liposome method	[97]
Papain	Tween 61	Thin film hydration	[117]
Plasmid DNA (Hepatitis B)	Span 85	Reverse phase evaporation	[114]
Propolis	Span 60	Ethanol injection method	[49]
Resveratrol	Span 80	Thin film hydration and ether injection	[75]
Resveratrol	Gelot 64	Thin film hydration and ethanol injection	[95]
Risperidone	Tween 20, 60 and 80, Span 20, 40, 60, 80	Proniosome derived niosome method (coacervation phase separation)	[108]
Roxithromycin	Span 60	Thin film hydration	[22]
Salidroside	Span 40	Thin film hydration	[102]
Sulfadiazine sodium	Pluronic L64 and P105	Modified lipid film method	[85]
Sumatriptan succinate	Brij 72, Eumulgin B2, Span 60 and 80	Thin film hydration	[45]
Tenoxicam	Span 80 and 60, Tween 20 and 60	Proniosome derived niosome method (coacervation phase separation)	[110]
Tramadol	Span 20, 40, 60 and 80, Tween 20, 40, 60 and 80	Proniosome derived niosome method (coacervation phase separation)	[98]
Tretinoin	Brij 30, Span 40 and 60	Thin film hydration	[79]
Tretinoin	Pluol Oleique CC	Thin film hydration	[112]
Tretinoin	Alkyl polyglucoside	Thin film hydration	[99]
Ursolic acid	Span 60	Thin film hydration	[50]
Vitamin E	Tween 80 and Span 20	Emulsion evaporation	[100]
8-methoxypsoralen	Span 40 and 60	Thin film hydration	[55]
Sulfasalazine, propranolol, tyrosol	Pluronic L64, sodium bis(2-ethylhexyl) sulfosuccinate)	Thin film hydration	[106]

allograft rejection and significantly prolonged the median survival time of corneal allograft to approximately of fourteen days as compared with those treated with 1% cyclosporine eye drops, plain niosomes or untreated. The investigated niosomes showed a potential for ocular delivery of tacrolimus [12].

Cationic lipids have been used with non-ionic surfactants to fabricate cationic niosomes for gene delivery, as cationic lipids form complexes by electrostatic interactions upon the addition of negatively charged genetic materials. Cationic lipids are considered as “helper” lipids and have a marked influence on both the physio-chemical and biological properties of niosome gene carriers. Mashal et al. investigated the retinal gene delivery enhancement by lycopene incorporated into cationic niosomes based on *N*-[1-(2,3-dioleoyloxy) propyl]-*N*,*N*,*N*-trimethylammonium chloride (DOTMA) and Tween 60. Niosomes were prepared by the reverse phase evaporation method and characterized for size, zeta potential, PDI and capacity to condense, release and protect the DNA against enzymatic degradation. The results showed the incorporation of a natural lipid – lycopene to the niosome formulation significantly increased transfection efficiency in human retinal pigment epithelial cells without compromising cell viability. *In vivo* administration to the rat retina showed the niosomes were able to transfect the outer segment of the retina and indicated their potential application in retinal gene delivery [56]. Table 5 lists the uses of niosomes in ocular delivery.

Table 5
Examples of niosomes that have been investigated for ocular delivery.

Drug	Surfactant	Method of preparation	Reference
Gatifloxacin	Span 60	Solvent injection method	[77]
Naltrexone	Span 60	Reverse phase evaporation	[117]
Plasmid pCMS-EGFP	Tween 80	Emulsification and thin film hydration	[13]
Plasmid pCMS-EGFP	DOTMA and Tween 60	Reverse phase evaporation	[56]
Plasmid pCMS-EGFP	Tween 80	Solvent emulsification evaporation	[118]
Tacrolimus	Poloxamer 188 and lecithin	Proniosome derived niosome method	[11]

7.4. Pulmonary delivery

Pulmonary drug delivery is preferred over the oral route when treating diseases such as lung infection, inflammatory diseases of the respiratory tract, or lung cancer, as drugs are directly administered to the site of action for either local or systemic treatment. The lung contains the equivalent of approximately 2400 km of airways and 700 million alveoli, with an estimated surface area of around 50 to 75 square meters [18,119]. This large surface area is ideal for drug absorption, and drug delivery devices such as inhalers and nebulizers have

Table 6
Examples of niosomes that have been investigated for pulmonary delivery.

Drug	Surfactant	Method of preparation	Reference
Amphotericin B	Tween 80	–	[119]
Beclomethasone dipropionate	Span 60	Thin film hydration and Proniosome derived niosome method	[18]
Ciprofloxacin	Span 60 and Tween 60	Thin film hydration	[121]
Glucocorticoid	Tween 20	Thin film hydration	[120]

been used for decades to treat various lung diseases. However, there are some limitations, such as the low efficiency of the inhalation systems and uneven drug loading per inhalation from the inhaler. Various drugs have been studied for pulmonary delivery including steroids, anti-tuberculosis drugs, antifungal drugs and antibacterial drugs [18,119–121]. Table 6 lists the application of niosomes in pulmonary delivery. Proniosomes have been investigated for pulmonary delivery of beclomethasone dipropionate. This technique allows the preparation of drug in a powder form, which forms niosomes by hydration before administration to patients [18]. Amphotericin B-loaded niosomes have been studied both *in vitro* and *in vivo* for treating leishmania and aspergillosis. Researchers found a significant reduction in fungal lung burden in a rat model of invasive pulmonary aspergillosis and significant suppression of *Leishmania donovani* liver parasite. These results indicate that amphotericin B loaded niosomal formulations enhanced pulmonary delivery while reducing toxicity by minimizing systemic exposure [119].

7.5. Parenteral delivery

The parenteral route is the most common and efficient way to administer drugs with poor bioavailability and narrow therapeutic index [2]. Parenteral administration has additional advantages, such as a reduction in fluctuation of the steady-state plasma drug level, and maximum utilization of medicine. On the other hand, drawbacks include reduced potential for dosage adjustments, retrieval of the drug is difficult in case of toxicity, and injections can lead to low patient compliance due to needle phobia [69]. Some progress has been made using nanocarriers, which are capable of achieving targeted drug delivery and sustained release, to overcome the problems associated with conventional parenteral delivery formulations [3]. Niosomal formulations have been reported for parenteral delivery of a variety of drugs (Table 7). Mukherjee and colleagues compared liposomes and niosomes for parenteral delivery of acyclovir. This study aimed to determine whether drug-loaded nanocarriers could achieve sustained release to reduce dose-related systemic toxicity. The results indicated that niosomes are better carriers for acyclovir as they showed better stability and achieved sustained release when compared to liposomes [122]. Nystatin is a potent antifungal drug for the treatment of fungal infections on the skin and oral cavity. One study encapsulated nystatin in niosomes to obtain a safe and effective formulation for parenteral administration for patients with neutropenia. Niosomes were prepared with Span 40, Span 60, cholesterol, and positive and negative charge inducing agents. Neutral and positively charged niosomes showed the highest EE, but *in vitro* release studies showed that both types of niosomes had sustained release profile. *In vivo* studies demonstrated that nystatin loaded niosomes showed less nephrotoxicity, hepatotoxicity and pronounced efficacy in the elimination of fungal burden in experimental animals infected with *Candida albicans* compared with those treated with a drug solution injected intraperitoneally [123].

Mullaicharam et al. investigated lung accumulation of rifampicin loaded niosomes following intravenous infusion in rats. Niosomes were prepared with Span 20, 40, 60 and 80 by thin film hydration method. The *in vivo* organ distribution pattern following intravenous injection was studied in albino rats to determine the potential of the delivery system for the site targeted delivery of rifampicin. A significant difference in the total drug concentration in the lung, liver, kidneys and blood serum was found between the rifampicin loaded niosomes and free rifampicin solution [80]. Pardakhty and co-workers prepared positively charged niosomal formulations containing sorbitan esters, cholesterol and cetyl trimethyl ammonium bromide by film hydration method for entrapment of autoclaved *Leishmania major* (ALM). Niosomes containing ALM and free ALM were subcutaneously injected to balb/c mice. Results showed that the ALM loaded niosomes had a moderate effect in the prevention of cutaneous leishmaniasis and can successfully delay the development of papules in studied animals [124]. The parenteral route is commonly used in chemotherapy to administer antineoplastic drugs. Using niosomes as carriers could achieve selective drug delivery to the tumor site, hence reduce toxicity and side effects. For instance, intravenous administration of hydroxycamptothecin loaded niosomes to sarcoma 180 ascites tumor-bearing mice lead to a total regression of tumor and a slower elimination from the systemic circulation [125]. pH-sensitive niosomes are also studied for parenteral delivery of anticancer drugs. The tumor targeting effect of these niosomes loaded with 5-fluorouracil was demonstrated by accumulation at the tumor site of mice transplanted with tumor cells [126]. Cisplatin niosomes (CP-NMs) were prepared with Span 40 and cholesterol, and their anticancer efficacy was investigated *in vivo* using rabbits bearing VX2 sarcoma. Rabbits were locally injected with either CP-NMs or a drug solution, a significant inhibition of tumor growth with much lower mortality, as well as inhibition of tumor metastasis to liver and inguinal lymph nodes were observed in the group treated with CP-NMs. The results indicated that CP-NMs could be developed as an effective anticancer preparation with low toxicity [127]. Recently, Shaker investigated tamoxifen citrate (TMC) loaded niosomes for localized cancer therapy through *in vitro* cancer cytotoxicity as well as *in vivo*

Table 7
Examples of niosomes that have been investigated for parenteral delivery.

Drug	Surfactant	Method of preparation	Reference
Acyclovir	Span 20, 40, 60 and 80	Thin film hydration	[122]
Autoclaved *Leishmania* Major	Span 20, 40, 60 80 and Tween 20, 40, 60, 80	Thin film hydration	[124]
Cisplatin	Span 40	Emulsion method	[127]
5-fluorouracil	pH-sensitive niosomes	Thin film hydration-probe ultrasound method	[126]
Gentamycin	Span and Tween surfactants	Thin film hydration	[66]
Hydroxycamptothecin	Span 60	Thin film hydration	[125]
Nystatin	Span 40 and 60	Thin film hydration	[123]
Rifampicin	Span surfactants	Thin film hydration	[80]
Tamoxifen	Span 40, 60, 80 and Tween 20	Thin film hydration	[43]

solid anti-tumor efficacy. Niosomal formulations were prepared with Span 40, 60, 80, Tween 20 and cholesterol at different molar ratios using the thin film hydration method. Niosomes prepared with Span 60 were spherical with an EE up to 92.3%. Sustained release of TMC was observed from the optimized niosomal formulation and *in vitro* studies showed enhanced cellular uptake and greater cytotoxicity. *In vivo* studies were performed using the Ehrlich carcinoma mice model and a reduced tumor volume of niosomal TMC was observed when compared to the free TMC solution [43].

7.6. Transmucosal drug delivery

Bioadhesion has been widely studied in the development of pharmaceutics to improve local and systemic absorption. Transmucosal drug delivery has gained impressive momentum in the past decade, especially with nano drug delivery systems [128–130]. Transmucosal drug delivery routes include ocular, nasal, oromucosal (buccal, sublingual and gingival), pulmonary, gastrointestinal and vaginal sites. Each site has distinct features, when designing a suitable drug delivery system, these features need to be considered. Niosomes are a versatile drug delivery system and due to their advantages, they have been studied for transmucosal delivery of various compounds through the oral, nasal and vaginal mucosa (Table 8). Benzocaine proniosomal gel formulations were prepared by El-Alim and co-workers using Span 80, Span 80, Span 85, and combinations of the three to achieve effective buccal delivery of benzocaine for local anesthesia. EE was found to improve with increasing ratio of Span 80 or Span 85, and *in vitro* drug release studies showed an initial burst release followed by a slower release. Formulations prepared with Span 80 and 85 showed better rate and extent of benzocaine permeation when examined using chicken pouch as a model mucosal membrane. Physical stability studies showed more than 90% of drug remaining after storage for one month at 4–8 °C. Benzocaine loaded proniosomes improved permeation through the mucosal membrane and could be used for managing mucosal pain [128]. There is increasing interest in the establishment of protective mucosal immunity, which could be achieved by vaccination via mucosal routes. Oral immunization is the safest and most convenient means to induce mucosal immunity [3]. Orally delivered antigens are taken up through the specialized epithelial cells. The selected antigen is then transported into the regional lymphoid tissue, stimulating specific B lymphocytes in the germinal canter [131]. Most antigens are poorly immunogenic when processed through the mucosal surface, stimulating only weak or no immunoglobulin response [132]. The effective mucosal response can be elicited with the use of adjuvants or novel carrier systems. Polysaccharide capped particles have several advantages such as increased stability against enzymatic attack and improved biochemical stability. Katare and co-workers developed polysaccharide-capped niosomes for oral mucosal vaccination of tetanus toxoid. In this study, niosomes were prepared by the reverse phase evaporation method using Span 60, Tween 20, stearylamine, and cholesterol, before being coated with pullulan derivative (O-palmitoyl pullan). Serum immunoglobulin level was measured to assess the immune stimulating effect of the niosomes following oral administration. The coated niosomes were able to produce an immune response equivalent to injected tetanus toxoid [94].

Transmucosal delivery through the nasal mucosa has been studied in order to bypass the blood-brain barrier for brain delivery. The use of this route will eliminate first pass metabolism, reduce side effects as a result of systemic circulation, and improve bioavailability. Niosomes that are less than 300 nm can cross the blood-brain barrier; as niosomes can carry both hydrophilic and hydrophilic compounds, they have been investigated for delivery of various active agents. The study conducted by Abdelrahman et al. formulated elastic niosomes known as spanlastics for brain delivery of risperidone. These are sorbitan-based nano particles, modified from conventional niosomes by incorporating an edge activator to impart flexibility to their membranes. The spanlastics were prepared with Span 60 and polyvinyl alcohol using the ethanol injection method. *Ex vivo* permeation was conducted using sheep nasal membrane to investigate the effect of spanlastics to improve permeation. The optimized formulation showed significantly higher transnasal permeation and better distribution to the brain when compared with the drug solution. The improvement in brain targeting and percentage of drug transported through the olfactory pathway suggests this may be a promising system that can effectively carry drug from nose to brain [129].

Chattaraj and colleagues investigated the nasal mucosal delivery of influenza antigens using niosomes. The dehydration-rehydration method was used to encapsulate vital influenza antigen, and the influence of the different proportion of surfactant, cholesterol and dicetyl phosphate on morphology, particle size, EE and *in vitro* release was studied. Stability of the antigen encapsulated in the vesicles was confirmed by using SDS-polyacrylamide gel electrophoresis and immunoblotting. Span 60 based niosomes were found to be best for antigen encapsulation [130]. Zidan and co-workers investigated the vaginal delivery of an anti-AIDS niosomal gel. This study aimed to improve mucoadhesion and skin permeation. According to the (BCS), tenofovir is a drug substance with high solubility and low permeability (BCS Class 3). Its poor permeation limits its antiretroviral potency. Chitosan was used as a mucoadhesive agent in the formulation, and a full factorial design was used to optimize the transmucosal delivery and mucoadhesion characteristics. The niosomal gels were characterized by investigating their vesicular size, shape and surface charge, drug EE, *in vitro* release and skin permeation. An *ex vivo* study using porcine vaginal tissue was also assessed. It was found that the mucoadhesion percentage was increased by five-fold and was further improved by decreasing the niosomal vesicular size and by increasing the surface charge. The formulation did not affect the viability of *Lactobacillus crispatus*, a common commensal bacterium found in the vagina, suggesting the niosomal gel could be promising for vaginal delivery of antiviral drugs [133]. Another study investigated cationic niosomes for intravaginal administration of metformin hydrochloride for the treatment of polycystic ovary syndrome (PCOS). In this study, the niosomes were loaded with thermosensitive gel to improve mucoadhesion on the vaginal mucosa. Oral administration of metformin is limited by impaired bioavailability and frequent dosing for patients with PCOS is required to maintain therapeutic effects, which can ultimately influence patient compliance and treatment outcomes. In this study, metformin loaded unmodified and cationic small unilamellar niosomes were incorporated with thermosensitive gel through the vaginal route. Both types of niosomes were prepared by the reverse phase evaporation

Table 8
Examples of niosomes that have been investigated for transmucosal delivery.

Drug	Surfactant	Method of preparation	Target delivery site	Reference
Benzocaine	Span 80 and Span 85	Reverse phase evaporation method	Buccal mucosa	[128]
Influenza antigens		Dehydration-rehydration method	Nasal mucosa	[130]
Metformin	Span 80	Reverse phase evaporation method	Vaginal mucosa	[28]
Risperidone	Span 60	Ethanol injection method	Nasal mucosa	[129]
Tenofovir	Span 20, 40 and 60	Proniosome derived niosome method	Vaginal mucosa	[133]
Tetanus toxoid	Span 60 and Tween 20	Reverse phase evaporation method	Oral mucosa	[94]

method and characterized to determine gelation time, gelling temperature, viscosity, mucoadhesiveness, and drug release. *In vivo* studies were conducted on PCOS rats, under a scheduled dosage regimen with oral metformin solution or intravaginal gels loaded with either small unilamellar niosomes or cationic small unilamellar niosomes. Results showed that the gels offered similar advantages as compared to oral metformin solution in the treatment of PCOS at lower dose-dosage regimen with negligible side effects. However, no significant difference was detected between the gels [28].

A clinical trial was conducted on niosomal propolis as an oromucoadhesive film for the treatment of recurrent aphthous ulceration (RAU). The films were prepared by loading propolis in niosomal vesicles and then incorporated into oromucoadhesive films. A total of 24 patients suffering from RAU were divided equally into medicated and placebo groups and participated in this study to examine the onset of ulcer size duration, complete healing and pain relief for two weeks. Results revealed the duration of film adherence lasted from 2 to 4 h in the two groups. The onset of ulcer size reduction in the medicated group was observed within the second and third day, pain relief lasted for more than 4 to 5 h after application, and five patients reported complete healing within the five days of treatment, and seven patients had complete ulcer healing within the period from day 5 to day 10 of treatment. On the other hand, no patients in the placebo group reported healing of ulcer during the first five days of treatment, and eight patients had complete ulcer healing from day 10 to day 15 of the treatment [134]. Priprem and co-workers conducted a clinical trial to investigate the pharmacokinetics of a melatonin niosomal oral gel in human subjects. Melatonin loaded niosomal oral gel has been formulated in order to overcome the problems associated with poor drug absorption and stability. This randomized, double-blind, three phase crossover design recruited 14 male volunteers. Melatonin oral gel was applied topically on labial mucosa at doses of 2.5, 5 and 10 mg with seven days washout for each period. The pharmacokinetic parameters that were determined included the maximum plasma concentration (C_{max}), area under the curve (AUC), time to peak concentration (T_{max}) and elimination half-life ($t_{1/2}$). Possible side effects including nausea, vomiting, headache, and irritability were also evaluated in the study. Results showed that the three different doses of melatonin niosomal oral gel provided dose-proportional pharmacokinetic profiles, extended the absorption process and improved plasma concentration, time to maximum plasma concentration and half-life compared to conventional immediate release oral dosage forms [135].

7.7. Cosmetic applications of niosomes

Niosomes were first developed and patented by a cosmetic company L'Oréal (Clichy, France) in 1975, and products were launched under the trade name of Lancôme (Paris, France) in 1987. Since then, a wide range of pharmaceutical applications and a variety of cosmetic products were developed and marketed with various functions, such as anti-wrinkle, skin whitening, moisturizing and sunscreen [136,137]. Some examples of commercialized cosmetic products containing bioactive compounds loaded in niosomes are listed in Table 9.

Niosomes have been widely investigated as a carrier system for cosmetic actives because of their advantages such as improved stability of entrapped active ingredients, enhanced skin penetration, bioavailability, improved surface adhesion and sustained release properties [138]. The usefulness of niosomes in cosmetic formulations has been evaluated with respect to conventional formulations such as emulsions. Niosomes showed lower toxicity, allowing controlled delivery of the loaded active ingredients that exhibit useful properties for skin moisturizing and tanning products [139]. Some bioactive ingredients extracted from plant materials are of particular interest in cosmetic research; these compounds possess beneficial effects such as antioxidant and anti-aging. A large number of plant-based bioactive compounds have been investigated using niosomes to improve their effects on the skin. Pando and co-workers prepared liposomes and niosomes for topical delivery of resveratrol; olein was used as a penetration enhancer for both vesicles. Negatively charged vesicles with a mean size around 200 nm were obtained. Results showed high accumulation and low transdermal delivery of resveratrol for both vesicles when compared with the control; this phenomenon was more significant for niosomes, which showed better behavior for cutaneous delivery of resveratrol [140]. Curcuminoids found in turmeric are major bioactive substances that possess antioxidant, anti-inflammatory and anti-cancer properties. These were encapsulated in niosomes for enhancement of skin permeation and an EE of 83% was obtained. An *in vitro* penetration study showed that niosomes significantly enhanced permeation of curcuminoids when compared with the control solution. The fluxes of curcumin, desmethoxycurcumin, and bis-desmethoxycurcumin were 1.117, 0.273 and 0.057, consistent with the lipophilicity of the three compounds, showing improved properties of curcuminoids by encapsulation in niosomes for skin delivery [141]. Elastic and non-elastic niosomes loaded with gallic acid isolated from *Terminalla chebula* galls were investigated for transdermal absorption. Both niosomes showed negative zeta potential in the size range of 200 to 400 nm. The percentages of gallic acid in non-elastic niosomes were higher than in elastic niosomes. An *in vivo* penetration study showed elastic niosomes exhibited higher percentages of gallic acid through rate skin than non-elastic niosomes. The authors concluded that niosomes, especially elastic niosomes, were able to enhance chemical stability and skin penetration of gallic acid and could be useful carriers for skin anti-aging molecules [65]. Niosomes loaded with caffeine for treatment of cellulite were formulated and evaluated by Mahmoud and co-workers for the treatment of cellulite. Histology revealed a significantly greater reduction in the size and thickness of the fatty layer of rat skin for the niosomal gel containing system, when compared to the commercial product Cellu Destock®. Further, a higher plasma concentration of caffeine was observed in the niosomal group, indicating that incorporation of caffeine into a niosomal system improved penetration through the skin and into the underlying fatty layer. This presents a promising approach for the formulation of a transdermal anti-cellulite product of caffeine in a niosomal gel system with improved transdermal bioavailability [142]. Similarly, a transdermal gel prepared with elastic niosomes loaded with papain has been investigated in comparison with polymeric nanoparticles. Elastic niosomes demonstrated enhanced penetration of papain in rat skin, better transdermal absorption, and reduced scar formation when compared with polymeric nanoparticles [24]. Ellagic acid (EA) is a potent antioxidant. However, its application is limited by poor solubility and low permeability. EA niosomes prepared with Span 60 and Tween 60 have been investigated in transdermal delivery. The

Table 9
Commercial cosmetic products containing niosomes.

Product name	Marketed by	Functions
Niosome plus	Lancôme® (Clinchy, France)	Foundation, clear and balance skin tone
Niosome plus perfected age treatment	Lancôme® (Clinchy, France)	Anti-wrinkle
Mayu niosome base cream	Laon Cosmetics® (Seoul, Korea)	Whitening and hydrating
Anti-age response cream	Nouvelle-HAS cosmetics® (Varese, Italy)	Anti-wrinkle
Identik masque floral repaire	Identik® (Paris, France)	Hair repair masque
Indentik shampooing floral repair	Identik® (Paris, France)	Hair repair shampoo
Eusu niosome makam pom whitening facial cream	Eusu® (Bangkok, Thailand)	Whitening
Anne möller anti-fatigue eye contour roll-on	Anne Möller® (Barcelona, Spain)	Anti-puffiness and moisturizing

results showed that the niosomal formulation could enhance skin penetration when compared to the EA solution, by improving its distribution in the human epidermis and dermis layer [116].

7.8. Targeted drug delivery

Targeted drug delivery by niosomal systems can be achieved by two approaches. Firstly, passive targeting of the reticuloendothelial system (RES), which is a part of the immune system that comprises phagocytic cells located in reticular connective tissue. The circulating serum factor, opsonin, marks the niosomes for clearance by macrophages [111]. Agrati et al. showed that Tween 20 niosomes have intrinsic selectivity to phagocytic cells such as macrophages. For this reason, niosomes can be used to treat infectious diseases in which the infecting organism resides in the RES. Secondly, niosomes can be conjugated with functionalized ligands to achieve targeting to specific organs or tissues [143]. Bragagni and colleagues developed a brain-targeted delivery system loaded with doxorubicin for cancer. Niosomes prepared in this work were conjugated with a glucose derivative N-palmitoyl glucosamine ligand. Intravenous injection of this formulation to rats resulted in reduced drug accumulation of doxorubicin in other organs such as the heart, longer blood circulation time and an increased brain concentration with respect to the commercial formulation of the drug [144]. The same functionalized niosomes were also studied for brain-targeted delivery for dynorphin-B. *In vivo* studies in mice by intravenous injection of the niosomal formulation showed a significantly higher antinociceptive effect compared with the drug solution at the same concentration [47]. Another study explored the possibility of a combination of the PEGylated niosomes and active targeting function of transferrin by transferrin receptor-mediated endocytosis to promote drug delivery to solid tumor following intravenous injection with hydroxycamptothecin as the model drug. Niosomes were prepared by thin film hydration method, and periodate-oxidated transferrin was coupled to polyethylene glycol to produce the active targeting niosomes (Tf-PEG-NS). The strongest cytotoxicity to three carcinomatous cell lines *in vitro* was demonstrated by Tf-PEG-NS when compared with drug solution, non-stealth niosomes, PEGylated niosomes, Tf-PEG-NS showed the most powerful anti-tumor activity with the inhibition rate of 71% against S180 tumor in mice, suggesting transferrin modified PEGylated niosomes could be promising for delivering anti-tumor drugs to tumor [81].

8. Delivery of bioactive compounds

Nanocarriers such as liposomes, solid lipid nanoparticles and niosomes have been investigated to deliver vitamins, plant constituents and other bioactive compounds. Modifying the pharmacokinetics of phytochemicals may enhance or modulate delivery to the target site and achieve better effect upon administration. Various natural products have been loaded into niosomes, such as ginkgo biloba extract, curcumin, rutin, and rice bran extract. Table 10 lists the application of niosomes in bioactive delivery [24,72,107,145–148]. These formulations were prepared for various routes of administration, including dermal, oral, subcutaneous and rectal. Ginkgo biloba extract (GbE) loaded niosomes showed improved *in vivo* distribution after oral administration when compared to conventional GbE tablets [145]. Silymarin is an active extract from milk thistle, a complex of flavonolignans and polyphenols that has poor bioavailability. A niosomal formulation was developed and *in vivo* studies performed in albino rats showed a significant reduction in both transaminase level as well as in serum alkaline phosphatase level after subcutaneous injection when compared with silymarin suspension [148]. Moreover, the biochemical markers assessed showed an excellent antioxidant activity of the niosomal formulation [149].

Table 10
Examples of niosomes that have been investigated for bioactive delivery.

Natural product	Surfactant	Method of preparation	Reference
Curcumin	Span 60, 80 and Tween 20	Proniosome derived niosome method	[150]
Ginkgo biloba extract	Span 80 and Tween 80	Thin film hydration	[145]
Rice bran extract	Tween 61	Thin film hydration	[72]
Silymarin	Span 60 and 40	Thin film hydration	[148]
Rutin	Span 60	Thin film hydration	[147]
Resveratrol	Span 60 and Span 80	Thin film hydration	[7]
Embelin	Span 60	Thin film hydration	[149]

9. Limitations and perspectives

Niosomes have attracted a great deal of attention in controlled drug delivery because of many advantages, such as biodegradable, biocompatible, chemical stability, able to improve the therapeutic performance of drug molecules by modulating drug release. Despite numerous studies and with respect to the fact that niosomes have a long way to become a clinical reality, there are still multiple and serious challenges regarding the niosomes. The major obstacle that hinders the utilization of niosomes as potential drug delivery system is sterilization. Heat sterilization such as dry heat and steam sterilization are inappropriate and destructive for lipid or surfactant-based formulations with a gel liquid transition temperature lower than the temperature used in the sterilization process, as heat can cause extensive drug leakage from the vesicles due to the destruction of the bilayer membranes [3]. Similarly, membrane filtration is not suitable for niosomes that are larger than the pore size (0.22 μm) of the membrane filters. Preparation under aseptic conditions could be a possible solution, as well as methods that generate minimal heat such as gamma irradiation. Niosomes can be prepared under aseptic conditions by filtering all organic solvent, buffer, surfactant solution, and drug solution through anti-bacterial filters, autoclaving glassware and working under aseptic conditions in a laminar fume hood that produces sterile airflow. The gamma sterilization process uses Cobalt 60 radiation to kill microorganisms, which yields quick turnaround time and can easily penetrate packaging and products as a minimal amount of heat is generated. Many marketed pharmaceutical products such as eye ointments, drops and injectable preparations are gamma radiation sterilized [151]. This method could potentially be applied onto niosomes, and hence the effect of gamma irradiation on the physical and chemical stability of niosomes can be studied in future work.

Surfactants as building components of niosomes have the most critical role in the formation and properties of these carriers, and potential toxicity of surfactants is another limitation. Segregation of surfactants may cause some degree of toxicity; there is not enough research about the toxicity of niosomes as minimal studies have been conducted on this topic. Hofland et al. evaluated the inhibition of human keratinocyte cell proliferation by different niosomal formulations, in particular, the effect of surfactants and concentration of cholesterol. The surfactants were of different hydrocarbon chain length and polyoxyethylene chain length. Ether- and ester-type surfactants were also investigated. The study reported that both the hydrocarbon chain and the polyoxyethylene chain length had minor effects on cell proliferation. However, the bond by which the alkyl chain was linked to the polyoxyethylene head group significantly influenced cell proliferation. Ester-type surfactants were less toxic compared to the ether-type surfactants, which was attributed to enzymatic degradation of the ester bond. Cholesterol in the bilayers has not been found to affect cell proliferation [152,153]. Niosomes prepared using Bola-surfactants showed safety and tolerability both *in vitro* on human keratinocytes up to incubation of 72 h and on human volunteers, with no skin erythema observed when topically treated with drug-free Bola niosomes [154].

Recently, the ocular toxicity of niosomes has been investigated by measuring conjunctival and corneal irritation potential of Span 60 niosomes and surface modified Span 60 niosomes using hen's egg chorioallantoic membranes and excised bovine corneal opacity and permeability models. The study showed minimal ocular irritations and suggesting good ocular tolerability for niosomes [26]. Currently, data related to the cytotoxicity of niosome as well as surfactant molecules have been reported by many papers; however, there are no specific studies aimed to investigate toxicity after administration in animal models, particularly in long term studies. Filling the gap in research on long term tolerability of using surfactant-based systems would be fundamental before reaching clinical reality.

From the vast literature on niosomes, it appears that not much attention was focused on exploring the possibility of using amphiphilic molecules are biologically active or can serve as targetable ligands, into bilayer vesicles. However, very few materials with dual qualities such as amphiphilicity and biological activity may be available. Therefore, it would be useful to synthesize such amphiphilic materials which can be converted into bilayer vesicles for drug delivery. Uchegbu and co-works were working on these compounds; for example, they synthesized palmitoyl muramic acid and *N*-palmitoyl glucosamine and prepared niosomes with these materials [155]. 1-*O*-Alkyl glycerols isolated from shark liver oil have several biological activities, including macrophage activation and natural killer cell activation. They also have a prominent effect on blood barrier permeability and studies have shown that they markedly improve brain uptake of anti-cancer agents [156]. Due to their surface-active properties, Gopinath and his group have converted them into bilayer vesicles called algosomes. These vesicles are spherical and are capable of encapsulating drugs in the aqueous regions of the bilayer. However, they are osmotically sensitive, vulnerable to electrolytic destabilization and are stable for only a few days. Later, the same group developed ascorbyl palmitate vesicles (aspasomes) using ascorbyl palmitate. Several ester derivatives of ascorbic acid were synthesized to transfer the peculiar antioxidant properties of ascorbic acid in lipophilic media and to improve its stability, all of them retained the antioxidant property of the ascorbyl moiety and are amphiphilic. Ascorbyl palmitate is one of the derivatives, more stable than ascorbic acid and its lipophilic character is beneficial for skin penetration. Aspasomes prepared with this compound showed better antioxidant property when compared to ascorbic acid, and enhanced penetration of across the rat skin [29]. The antioxidant property and skin permeation enhancing properties of aspasomes indicate a promising future for application as transdermal drug delivery systems in disorders implicate with reactive oxygen species. Thus, vesicles with biological activity or with a targeting function in addition to carrier properties will have an added advantage to increase the efficiency of niosomes, which can be an exciting area to study in the future.

Currently, there are four main approaches to develop and extend the application of niosomes in the pharmaceutical field. The first approach aims to enhance the efficiency of targeted drug delivery by decorating niosomes with ligands. Encapsulation of drug in nano-vesicles is not enough for the successful delivery of drugs to areas such as the central nervous system; specific targeting is required to elevate the specific uptake and permeability of drugs across the blood-brain-barrier. The second approach focuses on developing and optimizing novel techniques that improve the quality of niosomes and provide the possibility for scale-up in industrial production. Most niosomes are prepared by traditional methods, such as thin film rehydration, reverse phase evaporation, and ether injection method. These methods require the removal of organic solvents and they are expensive and time-consuming. To overcome these problems, Khan et al. developed a simple probe sonication method, which is an eco-friendly green technique with no addition of organic solvents [157]. Besides, it is a low-cost and straight forward technique. In this method, only aqueous phase of the drug is mixed with surfactant, cholesterol and other surface additives, and subjected to ultra-sonication with a probe. Niosomes prepared by this technique were smaller with higher monodispersity and faster drug release as compared to niosomes prepared by traditional methods. By the third approach, new generations of niosomes for drug delivery and development of cosmeceutical products in practice have been continuously discovered and introduced with numerous outstanding features: better stability, deformability, elasticity, enhanced skin permeation, the newer generation of niosomes including proniosomes, aspasomes, elastic niosomes and cationic niosomes. Proniosomes exhibits excellent stability owing to its potential to surmount physical instability including aggregation or fusion, leaking of entrapped drugs and sedimentation. They provide an additional convenience of transportation, distribution, storage and dosing. However, most of publications were focused on the utilization of proniosomes in transdermal drug delivery. Application of proniosomes can be further explored in areas such as aerosol drug delivery due to their unique properties. Elastic niosomes formed with the addition of edge activators such as sodium cholate and ethanol, they are superior to conventional niosomes for transdermal delivery due to its flexibility and deformability of being able to squeeze itself through pores on the skin which are much smaller than its diameter. The fourth approach involves the development of hybrid systems consists of niosomes and vehicles such as gel matrices. The hybrid system not only aims to improve drug release profile but also to obtain an adequate formulation with better patient acceptability. These four approaches of development will continuously be developed to adapt to the higher advancement of the pharmaceutical industry; more advanced niosomes will continuously be introduced in order to achieve targeted and site-specific drug delivery.

10. Conclusion

In recent years, niosomes have been extensively studied for various applications, from topical, transdermal, oral to brain-targeted drug delivery. They are easy to prepare at a low cost as well as being able to achieve higher EE than their analog system, liposomes. This versatile drug delivery system has great potential in the fields of pharmaceutical and cosmetic sciences. Niosomes are promising delivery systems, their potential can be further enhanced by novel preparation, modification methods and novel formulation components, which allow them to achieve targeted delivery, better drug entrapment efficiency and develop vesicles with special structures.

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Declaration of Competing Interest

None.

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