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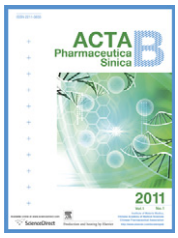

REVIEW

Nonionic surfactant vesicular systems for effective drug delivery—an overview

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Abstract Vesicular systems are a novel means of drug delivery that can enhance bioavailability of encapsulated drug and provide therapeutic activity in a controlled manner for a prolonged period of time. Liposomes were the first such system but they suffer from a number of drawbacks including high cost and lack of stability at various pHs. Niosomes are a nonionic surfactant vesicular system, which can be easily and reliably made in the laboratory. Many factors affect noisome formation such as the method of manufacture, nature of surfactant and encapsulated drug, temperature at which the lipids are hydrated and the critical packing parameter. This review describes all aspects of niosomes including their different compositions, the various methods of preparation, the effect of changing manufacturing parameters, methods of characterization, factors that affect their stability, their use by various routes of administration, their therapeutic applications and the most important patents. The review also provides detailed information of the various types of niosomes that provide effective drug delivery.

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1. Introduction

Vesicles are colloidal particles in which a concentric bilayer made-up of amphiphilic molecules surrounds an aqueous compartment[1–3]. They are a useful vehicle for drug delivery of both hydrophobic drugs, which associate with the lipid bilayer and hydrophilic drugs, which are encapsulated in the interior aqueous compartment. In general, vesicles made of natural or synthetic phospholipids are called liposomes whereas those made of nonionic surfactants (e.g. alkyl ethers and alkyl esters) and cholesterol constitute a nonionic surfactant vesicular system called niosomes[3–5]. Modified liposomal systems include transferosomes that, besides phospholipids, contain a single chain surfactant as an edge activator[1,6–8] and ethosomes that contain ethanol as an edge activator[9]. There are also niosomes containing bile acids called bilosomes that show enhanced stability in the presence of bile salts in the gastrointestinal tract.

The composition of vesicles affects their physicochemical characteristics such as their size, charge, lamellarity, elasticity and thermodynamic phase. The vesicular structure can also be modified to provide sustained or controlled drug delivery for prolonged periods[3,10,11]. Liposomes can encapsulate a wide variety of drugs such as many cytotoxic drugs, antimicrobial drugs, proteins and genetic material[12,13] and deliver them to the target site. They have a number of advantages over other drug delivery systems but also some disadvantages such as high cost and limited shelf life due to the rancidification of lipids[14]. Niosomes (Fig. 1) are a very useful drug delivery system with numerous applications as described below[2,3,10,12,14].

Nonionic surfactants can improve the solubility of some poorly soluble drugs[15]. Formulation in niosomes can also improve their bioavailability as shown for acyclovir and griseofulvin[16,17]. The stability of peptide drugs can be significantly increased by encapsulation in niosomes[18]. For instance, insulin loaded niosomes have high resistance to proteolytic enzymes and exhibit good stability in the presence of sodium deoxycholate[19]. Transdermal delivery of various drugs such as minoxidil, enoxacin, aceclofenac and estradiol are enhanced by encapsulation in niosomes[20–23]. Finally encapsulation in niosomes can provide sustained release of drugs to prolong their duration of action. Examples include estradiol and withaferin[23,24]. Similarly formulation of timolol maleate in niosomes prepared using chitosan prolonged its effect on intraocular tension[25].

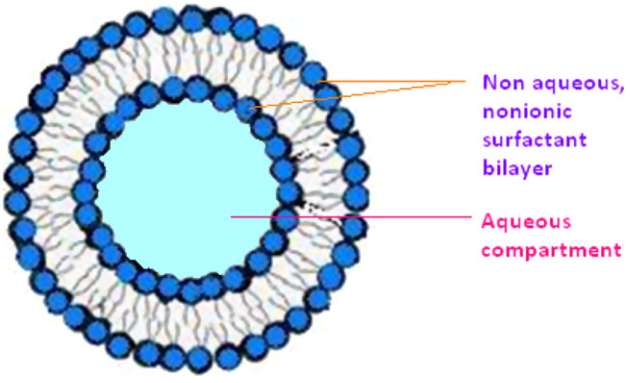

Figure 1 Structure of a nonionic surfactant vesicle (niosome).

2. Formulation aspects

It is necessary to understand the role of the basic structural components of niosomes before preparation. These components include the nonionic amphiphiles/surfactants and the hydration medium.

2.1. *Nonionic amphiphiles/surfactants*

Nonionic surfactants are the most common type of surface active agent used in preparing vesicles due to the superior benefits they impart with respect to stability, compatibility and toxicity compared to their anionic, amphoteric or cationic counterparts[26–28]. They are generally less toxic, less hemolytic and less irritating to cellular surfaces and tend to maintain near physiological pH in solution. They have many functions including acting as solubilizers, wetting agents, emulsifiers and permeability enhancers. They are also strong P-glycoprotein inhibitors, a property useful for enhancing drug absorption and for targeting to specific tissues[29] as shown for anticancer drugs such as doxorubicin and daunorubicin[30], steroids such as hydrocortisone and dexamethasone[31], HIV protease inhibitors such as ritonavir and saquinavir[32,33], cardiovascular drugs such as digoxin and quinidine[34] and beta-blockers such as acebutolol and timolol[35].

Nonionic surfactants are comprised of both polar and nonpolar segments and possess high interfacial activity. The formation of bilayer vesicles instead of micelles is dependent on the hydrophilic–lipophilic balance (HLB) of the surfactant, the chemical structure of the components and the critical packing parameter (CPP)[3]. On the basis of the CPP of a surfactant, the type of vesicle, which it will form, can be predicted as shown in Fig. 2[3]. The method of calculating CPP from the volume of the hydrophobic group, area of the hydrophilic head group and length of the lipophilic alkyl chain of the surfactant is also shown in Fig. 2[3].

The chain length and size of the hydrophilic head group of the nonionic surfactant affect the entrapment efficiency of drug. Nonionic surfactants with stearyl (C18) chains show higher entrapment efficiency than those with lauryl (C12) chains. The Tween series of surfactants bearing a long alkyl chain and a large hydrophilic moiety in combination with cholesterol in a 1:1 ratio have the highest entrapment efficiency of water soluble drugs[3,4,36].

The HLB value of a surfactant plays a key role in controlling drug entrapment of the vesicle it forms. A surfactant with an

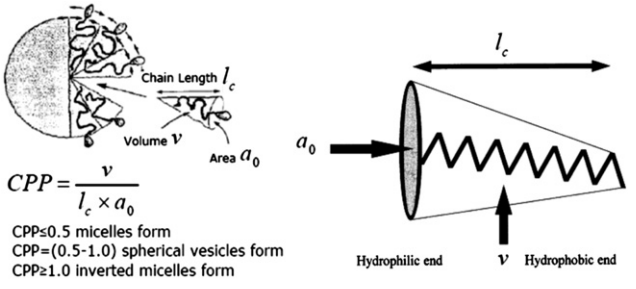

Figure 2 Critical packing parameter (CPP) of an amphiphile where v is the hydrophobic group volume, l_c the critical hydrophobic group length and a_0 the area of the hydrophilic head group.

HLB value in the range 14–17 is not suitable to produce niosomes whereas one with an HLB value of 8.6 gives niosomes with the highest entrapment efficiency. Entrapment efficiency decreases as the HLB value decreases from 8.6 to 1.7[37–39]. For HLB > 6, cholesterol must be added to the surfactant in order to form a bilayered vesicle[37] and for lower HLB values, cholesterol enhances stability of vesicles. It is also seen that the addition of cholesterol enables more hydrophobic surfactants to form vesicles, suppresses the tendency of the surfactant to form aggregates, and provides greater stability to the lipid bilayer by promoting the gel liquid transition temperature of the vesicle[37]. The entrapment efficiency is affected by the phase transition temperature (Tc) of the surfactant. Thus Span 60 with a high Tc exhibits the highest entrapment efficiency[38]. The most common nonionic amphiphiles used for vesicle formation are alkyl ethers, alkyl esters, alkyl amides and esters of fatty acids[3].

2.1.1. *Alkyl ethers and alkyl glyceryl ethers*

Alkyl ethers are good vesicle forming nonionic surfactants. They are stable, relatively non-irritant to the skin and compatible with other surfactants[40]. Due to their high stability they can be used to encapsulate proteins and peptides although it was shown that their encapsulation capacity is reduced when combined with cholesterol[19].

2.1.1.1. Polyoxyethelene 4 lauryl ether (Brij 30). This surfactant has an HLB value of 9.7 and a phase transition temperature $< 10\ ^{\circ}C$[41,42]. Unlike other alkyl ether derivatives, which reduce vesicle formation in the presence of cholesterol, Brij 30 forms large unilamellar vesicles when combined with 30 mmol/L cholesterol. However, it cannot be used to formulate some drugs and iodides, mercury salts, phenolic substances, salicylates, sulfonamides and tannins. Polyoxyethylene alkyl ethers are also incompatible with benzocaine, tretinoin and oxidizable drugs since, with such substances, it causes oxidation leading to discoloration of product[41,42]. However, Manconi et al.[43,44] prepared niosomes of tretinion using polyoxythelene 4 lauryl ether and reported that it formed large unilamellar vesicles with high entrapment efficiency.

2.1.1.2. Polyoxyethylene cetyl ethers (Brij 58). Brij 52, 56 and 58 are cetyl derivatives of polyoxyethylene with vesicle forming capability. Among them, Brij 58 has got special importance due to its ability to form inverted vesicles, which are useful for studying ion-pumping activity (H^+-ATPase and Ca^{2+}-ATPase) at the plasma membrane. This ability is the result of 'non-detergent behavior' associated with its large head group (E20-23)[45]. Brij 58 is commercially available under a variety of trade names including poly(oxyethylene) cetyl ether, Brij W1, polyethylene oxide hexadecyl ether, polyethylene glycol cetyl ether, Brij 38, Brij 52, poly(oxyethylene) palmityl ether, Brij 56, Atlas G 3802, cetocire, cetyl alcohol ethoxylate, Nikkol BC 40, etc. The HLB value of Brij 58 is 15.7[41].

2.1.1.3. Polyoxyethylene stearyl ethers (Brij 72 and 76). They are stearyl derivatives of polyoxyethylene ether with good vesicle forming properties. In particular, Brij 72 forms multilamellar vesicles with high encapsulation efficiency. Thus, vesicles made of Brij 72 encapsulated more finasteride than those formulated using Brij 76[46]. This is probably because of its low HLB value of 4.9 compared to that of Brij 76 of 12.4[41]. Chloramphenicol sodium succinate loaded Brij 72 niosomes have also found application in intracellular chemotherapy[47]. However, higher drug entrapment of minoxidil was reported in vesicles prepared using Brij 76[22].

2.1.2. *Sorbitan fatty acid esters*

These derivatives of polyoxyethylene esters are often used in cosmetics to solubilize essential oils in water-based products. Esters of plain (non-PEG-ylated) sorbitan with fatty acids are usually referred to as Spans. Their gel transition temperature increases as the length of the acyl chain increases. Thus sorbitan monolaurate (Span 20) with a C9 chain is liquid at room temperature; sorbitan monopalmitate (Span 40) with a C13 chain has a gel transition temperature of 46–47 °C; sorbitan monostearate (Span 60) with a C15 chain has a gel transition temperature of 56–58 °C. Vesicles made with these higher molecular weight Spans are less leaky and more stable to osmotic gradients[5].

The molar ratio of cholesterol to Span may affect the entrapment of drugs into niosomes. Thus higher encapsulation of acyclovir was reported in niosomes made using a cholesterol: Span 80 ratio of 1:3[10] although high encapsulation of colchicine and 5-flourouracil was reported in niosomes made with a cholesterol:Span ratio of 1:1[48]. Fang et al.[21] reported Span 40 was required in a proniosomal formulation of estradiol to enhance its permeation across the skin. A decrease in entrapment efficiency of retinyl palmitate was reported as the length of the lipophilic chain increased in the order Span 40 > Span 60 > Span 85[49]. In developing niosomes for ocular delivery of acetazolamide, Ahmed et al.[50] found Span 60 formed multilamellar vesicles with high encapsulation efficiency.

2.1.3. *Polyoxyethylene fatty acid esters*

Polysorbates are liquids derived from PEG-ylated sorbitan esterified with fatty acids. The distribution of zidovudine after an intravenous bolus injection of niosomes prepared using Tween 80 to mice was seen in lungs, kidney, heart, liver and spleen and was comparatively higher than from niosomes made using dicetyl phosphate or Tween 80[51]. The slow release of paclitaxel from Tween 28 niosomes was beneficial in reducing its toxic side effects[52].

2.2. *Hydration medium*

Phosphate buffer at various pHs is the most commonly used hydration medium for preparation of niosomes. The actual pH of the hydration medium depends on the solubility of the drug being encapsulated[3]. Thus pH 5.5 phosphate buffer was used in the preparation of ketoconazole niosomes[53] whereas pH 7.4 phosphate buffer was used in the preparation of meloxicam niosomes[54].

3. Methods of preparation

The general method of preparation of niosomes involves evaporation to produce a lipid film followed by hydration with the hydration medium. However, there are variants of this method that are described here in detail.

3.1. Transmembrane pH gradient method

Equal proportions of surfactant and cholesterol are dissolved in chloroform and evaporated under reduced pressure to produce a thin lipid film on the wall of a round-bottomed flask. The film is hydrated with a solution of an acidic compound (generally citric acid) by vortex mixing. The resulting product is subjected to freeze-thaw cycles after which an aqueous solution of drug is added and the mixture vortexed. The pH of the sample is then raised to 7–7.2 using a disodium hydrogen phosphate solution[55,56]. Bhaskaran and Lakshmi[11] prepared niosomes using this method and reported an entrapment efficiency of 87.5%.

3.2. Lipid layer hydration

The thin film, prepared as described above, is hydrated with an aqueous solution of drug at a temperature slightly above the phase transition temperature of the surfactants for a specified time with constant mild shaking[11,55–59]. Process variables to be validated include the mass per batch, angle of evaporation and rotation speed of the vacuum rotary evaporator and the hydration process. The latter is developed by varying the solvent (water, phosphate buffer (PB) and PB/drug) and hydration temperature below and above the gel transition temperature. Using thin film hydration under reduced pressure, Sathali and Rajalakshmi[60] developed multilamellar vesicles containing terbinafine which, upon sonication, produced small unilamellar niosomes with an entrapment efficiency of about 85%. Bhaskaran and Lakshmi[11] reported that about 78% of the drug was entrapped in the aqueous compartment of niosomes which was prepared using the hand shaking process.

3.3. Reversed phase evaporation

The surfactants are dissolved in a mixture of ether and chloroform to which an aqueous phase containing the drug is added. The resulting two-phase system is then homogenized and the organic phase evaporated under reduced pressure to form niosomes dispersed in the aqueous phase[11]. Spherical stable uniform vesicles containing lansoprazole were prepared using this method[61]. Guinedi et al.[50] also used this method to develop niosomes containing acetazolamide and reported that spherical vesicles were produced with less drug entrapment than in multilamellar vesicles. Gyanendra et al.[62] developed isoniazid niosomes by reversed phase evaporation.

3.4. Microfluidization

Microfluidization is the process where a solution of surfactants and drug is pumped under pressure from a reservoir through an interaction chamber packed in ice at a rate of 100 mL/min. From the interaction chamber, the solution is passed through a cooling loop to remove the heat produced during microfluidization and returned to the reservoir for recirculation or allowed to exit the system. The process is repeated until a vesicle of the desired size is produced[63,64].

3.5. Ether injection

In this method, the lipids and drug are dissolved in diethyl ether and injected slowly into an aqueous phase, which is heated above the boiling point of the organic solvent. This produces large unilamellar vesicles, which are further subjected to size reduction[3,11,57]. Bhaskaran and Lakshmi[11] prepared salbutamol niosomes by ether injection with an entrapment efficiency of 67.7%.

3.6. Bubbling of nitrogen

In this method nitrogen gas is passed through a sample of homogenized surfactants to give large unilamellar vesicles. These are then subjected to size reduction to give small unilamellar vesicles[65].

3.7. The Handjani–Vila method

Here a homogeneous lamellar phase is produced by mixing a lipid or lipid mixture with an aqueous solution containing an equivalent amount of active substance. The resultant mixture is homogenized at a controlled temperature by means of ultracentrifugation or agitation[66].

3.8. The enzymatic method

Niosomes may also be formed by an enzymatic process from a mixed micellar solution. In this method ester links are cleaved by esterases leading to breakdown products such as cholesterol and polyoxyethylene, which in combination with dicetyl phosphate and other lipids produce multilamellar niosomes. The surfactants used are polyoxyethylene stearyl derivatives and polyoxyethylene cholesteryl sebacetate diacetate[3].

3.9. The single pass technique

This is a patented technique involving a continuous process that comprises the extrusion of a solution or suspension of lipids through a porous device and subsequently through a nozzle. It combines homogenization and high pressure extrusion to produce niosomes with a narrow size distribution in the range 50–500 nm[67].

4. Factors affecting niosome formation

4.1. Effect of cholesterol

Cholesterol influences the physical properties and structure of niosomes possibly due to its interaction with the nonionic surfactants[68]. The interaction is of biological interest since cholesterol is always present in biological membranes where it influences membrane properties such as aggregation, ion permeability, fusion processes, elasticity, enzymatic activity, size and shape[68]. The effect of cholesterol in lipid bilayers is mostly to modulate their cohesion and mechanical strength and their permeability to water[4,68,69]. Through the addition of cholesterol, the fluidity of niosomes is changed considerably[68]. Cholesterol imparts rigidity to vesicles, which is very important under severe stress conditions[70]. The interaction of cholesterol with Span 60

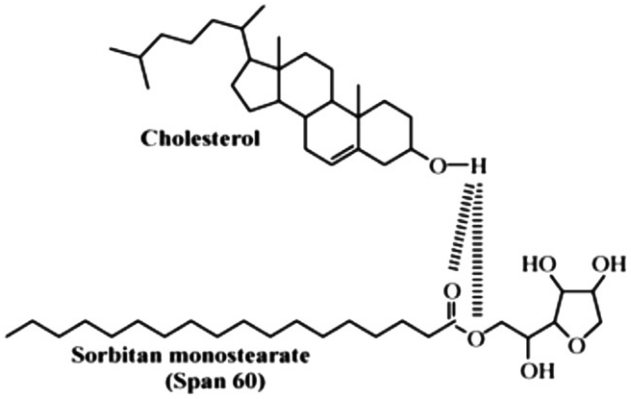

Figure 3 Structural interaction between Span 60 and cholesterol.

in the bilayer of niosomes is due to hydrogen bonding as shown in Fig. 3.

The amount of cholesterol to be added depends on the HLB value of the surfactants. As the HLB value increases above 10, it is necessary to increase the minimum amount of cholesterol to be added in order to compensate for the larger head groups[3]. Higher entrapment of minoxidil occurred in Brij 76 niosomes in the presence of a higher content of cholesterol whereas no significant increase in entrapment efficiency occurred in Brij 52 (HLB 5.3) niosomes. In fact, above a certain level of cholesterol, entrapment efficiency decreased[22] possibly due to a decrease in volume diameter ($CPP < 0.05$)[19].

4.2. *Nonionic surfactant structure*

Vesicle aggregation of niosomes may be prevented by the inclusion of compounds that introduce repulsive steric or electrostatic forces. An example of steric stabilization is the inclusion of Solulan C24 (a cholesteryl poly-24-oxyethylene ether) in doxorubicin sorbitan monostearate (Span 60) niosome formulations. Examples of electrostatic stabilization are the inclusion of dicetyl phosphate in 5(6)-carboxyfluorescein loaded Span 60 based niosomes and the inclusion of stearyl amine in rifampicin loaded niosomes[3].

4.3. *Surfactant and lipid amount*

The maximum amount of surfactant/lipid used to prepare niosomes is generally 10–30 mmol/L (1–2.5%, *w*/*w*). Alterations in the surfactant:water ratio during the hydration step may affect the structure and properties of the niosomes produced. As the surfactant/lipid level increases, the amount of drug to be encapsulated also increases leading to an increase in the viscosity of the system[3].

4.4. *Effect of encapsulated drug*

Another factor to be considered is whether the drug to be encapsulated is amphiphilic. The best example of such a drug is doxorubicin. When encapsulated in niosomes, aggregation occurred and was overcome by the addition of a steric stabilizer[30]. The increase in encapsulation of a drug that occurs when more is added could be the result of saturation of the medium. This suggests that the solubility of certain poorly soluble drugs can be increased by formulation in niosomes but only up to a certain limit above which drug precipitation will occur[22]. An increase in the encapsulation of flurbiprofen due to saturation of drug in the hydration medium has been reported[71]. However, when niosomes were prepared using higher amounts of minoxidil, optical microscopy revealed minoxidil crystals dispersed in between the niosomal particles[22].

4.5. *Effect of temperature*

Temperature of the hydration medium plays a major role in the formation of vesicles and affects their shape and size. The temperature should always be above the gel to liquid phase transition temperature of the system. Temperature affects the assembly of surfactants into vesicles and also induces changes in vesicle shape[3,68]. For example, polyhedral vesicles formed by C16:solulan C24 (91:9) at 25 °C transformed into spherical vesicles upon heating to 48 °C but, on cooling from 55 °C, formed a cluster of smaller spherical niosomes at 49 °C and changed to a polyhedral structure at 35 °C. In contrast, vesicles formed by C16:cholesterol:solulan C24 (49:49:2) showed no shape transformations on heating or cooling[36]. Volume of the hydration medium and duration of hydration of the lipid film also affect vesicle structure and yield[68].

4.6. *Effect of pH of the hydration medium*

Entrapment efficiency of niosomes is greatly affected by the pH of the hydration medium. High entrapment of flurbiprofen was reported at acidic pH with a maximum encapsulation efficiency of 94.6% at pH 5.5. The fraction of flurbiprofen encapsulated increased to about 1.5 times as pH decreased from 8 to 5.5 and decreased significantly at $pH > 6.8$. The lowest entrapment of flurbiprofen occurred at pH 7.4 and 8 with no significant difference between them. The increase in encapsulation efficiency of flurbiprofen at lower pH is presumably due to its ionizable carboxylic acid group. At lower pH, the proportion of unionized flurbiprofen increases and partitions more readily into the lipid bilayer than the ionized species[71]. At lower pH, niosome formulations should be examined by optical microscopy for the presence of drug precipitates both before and after centrifugation and washing. This will help to determine the concentration of drug in the hydration medium giving optimum encapsulation in niosomes.

5. Characterization

Vesicle structure and shape can be characterized by various types of microscopy such as optical[12], freeze fracture electron[72], surface electron, scanning electron, negative staining transmission electron, cryo-electron, fluorescence and confocal[73]. The interfacial surface tension of a vesicular system determines the structure of the supramolecular elements of multilamellar vesicles[74].

5.1. Size and vesicle charge

Size and charge of vesicles have a significant effect on their stability and drug encapsulation. Size and charge can be assessed using a multifunctional zeta potential analyzer[11] where size of vesicles is the result of repulsion forces between the bilayers and the entrapped drug. Manosroi et al.[75] found that the size of niosomes loaded with gallidermin was smaller for anionic niosomes than cationic niosomes due to neutralization of their negative charge by the positive charge of entrapped gallidermin. Correspondingly, cationic niosomes were larger due to repulsion between the positive charges of the niosomes and gallidermin.

5.2. Entrapment efficiency

This is determined by measuring the difference between the unentrapped and total amounts of drug. Unentrapped drug is determined by various techniques such as exhaustive dialysis[57], gel filtration[6,7,46] and centrifugation[3]. Total amount of drug can be determined by digesting a specific amount of a preparation and analyzing with a suitable analytical method. Percent entrapment can then be calculated in the usual way[76].

5.3. In vitro release

In-vitro release studies are carried out by dialysis through a semipermeable membrane. A niosome preparation is incorporated in an open end dialysis membrane and placed in a receptor compartment containing buffer. Samples are periodically collected and analyzed using a suitable analytical method[55,75,76]. Alternatively Hu's method can be used[77,78].

6. Stability

The main problems associated with storage of vesicles are aggregation, fusion and leakage of drug. Ammar et al.[79] defined stable formulations of tenoxicam as those showing high entrapment efficiency (>60%) and retention (>90%) over a period of months. At the end of each month, only stable formulations were selected to continue for another month. It was found that there was no significant change in the mean size of vesicles after 90 days when compared with those of freshly prepared sucrose stearate niosomes. However, the entrapment efficiency was affected (10%) following storage[80].

The stability of niosomes is also assessed under conditions, which promote photodegradation such as exposure to UV irradiation and fluorescent light[43]. For the former, drug is analyzed after the drug solution and vesicle preparation are maintained at room temperature and exposed to UV radiation for 1 h at 25 °C. Such studies have been reported for niosomes loaded with tretinoin, a metabolite of vitamin A[43]. For the latter, the samples are exposed to artificial light at room temperature for a specific period and the drug concentration determined[81].

7. Delivery strategies

The administration of niosomes by various routes has been reported and it is clear that the route is important in designing a vesicular formulation. For example, enoxacin, a fluoroquinolone antibiotic with a broad spectrum of activity, has a plasma half-life after oral administration of only 3–6 h such that frequent dosing is necessary for effective antibiotic therapy. Subsequently, the oral formulation was withdrawn due to a high frequency of drug interactions and adverse effects[20] and a transdermal delivery system based on niosomes was developed. This is now the preferred formulation because it reduces the adverse effects of oral administration and provides a long duration of action[20].

7.1. Oral route

The oral route is generally preferred leading to a research emphasis on delivery of niosomes via the oral route. A niosome formulation of acyclovir providing a Higuchi pattern of drug release was found to enhance sustained release of drug in an *in vivo* study in rabbits. In this study, the oral bioavailability and MRT of acyclovir were increased more than 2-fold compared to a tablet dosage form. Similarly, a Span 60 niosome formulation of fluconazole with an encapsulation efficiency>91% showed sustained release by zero order followed by first order kinetics[82]. Griseofulvin loaded niosomes have been subjected to an *in vitro–in vivo* correlation study, which showed that niosomes were an efficient way to enhance the bioavailability and sustained delivery of griseofulvin via the oral route[17]. These studies all indicate that niosomes are a promising delivery systems for sustained drug release[16]. However, the main obstacles to oral delivery are hepatic first pass metabolism and GI irritation, limitations that can be overcome using other routes of administration. For oral immunization, mannosylated nonionic surfactant based vesicles have been developed for the efficient delivery of plasmid DNA encoding small subunit proteins of hepatitis B virus. Rifampicin and gatifloxacin loaded niosomes were effective against the tubercle bacilli for prolonged periods and were better than the conventional dosage form because of the reduced dose and greater patient compliance[83].

7.2. Topical route

7.2.1. Ocular delivery

The penetration of drug molecules into the eye depends on the physicochemical properties of both the drug and vehicle[6]. Vesicular systems provide prolonged duration of action at the corneal surface by preventing ocular metabolism by enzymes in the lachrymal fluid[84,85]. Because of this, niosomes have gained popularity in ocular drug delivery research and are a potential delivery system for the effective treatment of glaucoma[86] and various other conditions. Allam et al.[84] reported that acyclovir loaded niosomes were effective for the treatment of herpes simplex keratitis, a condition that can lead to blindness. Similarly, gentamicin loaded niosomes provided controlled, opthalmic delivery[87] and brimonidine loaded niosomes were therapeutically effective with a long duration of action due to slow and prolonged zero order release of drug[88]. Bioavailability of ofloxacin in the eye was improved to

73.8%[89] and niosomes promoted ocular absorption of cyclopentolate, which is essential in pediatric eye examinations[90].

7.2.2. Transdermal delivery

The major obstacle to topical delivery of drugs is the barrier function of the stratum corneum. Vesicular delivery through the skin is advantageous in that drugs, which permeate through the skin reach the systemic circulation. Niosomes are the best vesicular system for transdermal delivery because they act as a reservoir of drug for a prolonged period of time and enhance skin penetration. Thus estradiol loaded niosomes made with the inclusion of cholesterol facilitated estradiol transdermal permeation[21]. A high cumulative drug penetration and steady state transdermal flux was observed from an aceclofenac niosomal gel preparation compared to a plain gel formulation[23]. Similarly a meloxicam niosomal gel produced a greater reduction in edema in albino rats when compared to the conventional meloxicam gel due to the penetration of niosomes into the deeper layers of the skin[54].

8. Types of niosomes

Many types of niosomes are mentioned in the literature including discomes, proniosomes, elastic niosomes and surfactant ethosomes.

8.1. Proniosomes

Proniosomes are dry niosomes, which are hydrated immediately before use to yield an aqueous niosome dispersion. Being dry, they reduce problems associated with the physical stability of niosomes such as aggregation, fusion and leaking and, in addition offer benefits in terms of transportation, distribution, storage and dosing. Proniosomes, hydrated by agitation in an aqueous phase for a short period of time, offer a versatile vesicular delivery system with the potential for drug delivery via the transdermal route[91,92]. This involves the topical application of proniosomes under occlusive conditions during which they are converted to niosomes due to hydration by water in the skin itself. Compared to niosomes, a proniosome gel appeared to deliver estradiol efficiently by the transdermal route[21]. Similarly a niosomal gel containing ketoprofen was therapeutically superior to a plain ketoprofen gel[93]. Proniosomal gel preparations of contraceptive hormones such as estradiol, ethinyl estradiol and levonorgestrel may also be useful for population control programmes[21,76,94]. Proniosomes allow the nebulized delivery of cromolyn sodium and provide enhanced controlled drug release and physical stability[80].

8.2. Surfactant ethosomes

Touitou et al.[95] were the first to prepare ethosomes, a lipid vesicular system incorporating ethanol at relatively high concentrations. Ethosomes contain nonionic surfactants, a high concentration of ethanol or isopropyl alcohol and water. Unlike other vesicular systems, surfactant ethosomes were shown to permeate through the stratum corneum and possess significantly higher transdermal flux in comparison to liposomes or nisosmes[95]. The exact mechanism by which they enhance permeation into deeper skin layers remains unclear. The synergistic effect of the nonionic surfactant and high concentration of ethanol is suggested to be responsible for this deeper distribution and penetration in skin lipid bilayers[91,92,95–99].

8.3. Elastic niosomes

Elastic niosomes are composed of nonionic surfactants, ethanol and water. They are superior to conventional niosomes because they enhance penetration of a drug through intact skin by passing through pores in the stratum corneum, which are smaller than the vesicles. In fact, their elasticity allows them to pass through channels that are less than one-tenth of their own diameter[8,9]. Thus they can deliver drugs or compounds of both low and high molecular weight. Furthermore, they can provide prolonged action and demonstrate superior biological activity compared to conventional niosomes[100]. The transport of these elastic vesicles is concentration independent and driven by trans-epidermal hydration[1,100,101]. Van den Bergh et al.[100,101] developed the first detergent-based elastic nanovesicles called elastic or deformable niosomes consisting of surfactant L-595 (sucrose laurate ester) and the micelle forming surfactant PEG-8-L (octaoxyethylene laurate ester). Manosroi et al.[102] developed topical diclofenac diethylammonium loaded elastic niosomes and reported high transdermal flux in rat and high antiinflammatory activity in the rat ear edema assay.

8.4. Discomes

These are the large discoid structures, which exist under certain conditions of the phase diagram of nonionic surfactant vesicles. Uchebu et al.[103] prepared niosomes from hexadecyl diglycerol ether (C16), cholesterol and dicetyl phosphate by mechanical shaking and sonication followed by incubation with soluble polyoxyethylene cholesteryl ether, Solulan C24, at 74 °C. A partial phase diagram was constructed for the system in which four phases could be identified; a lamellar phase, a micellar phase, an uncharacterized phase, and a novel phase, which they called the 'discome' phase. Vesicles in the discome phase were large (volume distribution mean diameter 12–60 mm) and slowly increased in size immediately after sonication. Discomes were shown to entrap water soluble solutes[102]. Discomes of 5(6)-carboxyfluorescein (CF) were developed and were found to retain 50% of entrapped CF over a 24 h period at room temperature.[103] The drug delivery potential of discomes in the field of ophthalmology was highlighted by Vyas et al.[25] who reported that timolol maleate discomes gave a threefold increase in ocular absorption of timolol compared to a solution.

9. Therapeutic applications of niosomes

Niosomes are a versatile drug delivery system with many pharmaceutical applications. Some of them are described below.

9.1. Pulmonary delivery

Inhalation therapy is frequently used in asthmatic patients but is limited by poor permeation of drug through hydrophilic mucus. To overcome this, Terzano et al.[104] developed polysorbate 20 niosomes containing beclomethasone dipropionate

for pulmonary delivery to patients with chronic obstructive pulmonary disease. They reported that the niosomes provided sustained and targeted delivery, improved mucus permeation and amplified therapeutic effect.

9.2. *Protein and peptide delivery*

The delivery of proteins to the systemic circulation after their oral administration is hindered by numerous barriers including proteolytic enzymes, pH gradients and low epithelial permeability. The oral administration of recombinant human insulin in a niosomal formulation was demonstrated in a study involving niosomes based on polyoxyethylene alkyl ethers. Entrapment of insulin in the bilayer structure of niosomes was shown to protect it against proteolytic activity of α-chymotrypsin, trypsin and pepsin *in vitro*. Even higher protection was provided by Brij 92/cholesterol niosomes in which only about 26% of entrapped insulin was released over 24 h in simulated intestinal fluid[19]. The kinetics of drug release was described by the Baker and Lonsdale equation indicating a diffusion based delivery mechanism. These results suggest that niosomes can be developed as sustained release oral dosage forms for delivery of peptides and proteins[19,105].

Vasoactive intestinal peptide (VIP) has diverse therapeutic applications because of its antiinflammatory and immunomodulatory effects and its ability to regulate cell growth and differentiation and participate in the development of neural tissue[18]. VIP has been tested in the treatment of Alzheimer's disease but, like most endogenous peptides, its therapeutic potential is limited by its failure to cross the blood–brain barrier (BBB) and by its rapid elimination after intravenous administration[106]. Dufes et al.[105] reported glucose-bearing niosomes encapsulating VIP for delivery to specific brain areas[105]. They concluded that glucose-bearing vesicles represent a novel tool to deliver drugs across the BBB.

9.3. *Cancer chemotherapy*

Niosomes are an effective means of targeting delivery of anticancer drugs to tumors. Paolino et al.[107] developed bola surfactant niosomes containing 5-fluorouracil to treat skin cancer. They reported enhanced drug penetration compared to an aqueous solution of drug and to a suspension of empty bola-niosomes in an aqueous solution of drug. Niosomes of doxorubicin prepared from C16 monoalkyl glycerol ether with and without cholesterol were reported by Uchegbu et al.[108]. Compared to simple drug solution, methotrexate loaded niosomes produced increased antitumor activity against tumors in serum and lung but not in liver and spleen[109].

9.4. *Carrier for hemoglobin*

Niosomes can be used as a carrier for hemoglobin. Vesicles were permeable to oxygen and could be modified to produce a hemoglobin dissociation curve similar to that of non-encapsulated hemoglobin[110]. In addition, a niosomal suspension showed a visible spectrum superimposable onto that of free hemoglobin.

9.5. *Treatment of HIV-AIDS*

Zidovudine is commonly used to treat patients with AIDS but is limited by its toxicity and low potency. A noisome formulation that may overcome these drawbacks has been proposed by Ruckmani and Sankar[111]. They concluded that zidovudine loaded niosomes would provide sustained delivery of drug and a more effective AIDS therapy.

9.6. *Vaccine and antigen delivery*

A number of surfactants have immunostimulatory properties[112] and have been used as vaccine adjuvants. The adjuvanticity of niosomes prepared from 1-monopalmitoyl glycerol: cholesterol: dicetyl phosphate (5:4:1) was demonstrated in mice administered a subcutaneous injection of ovalbumin or a synthetic peptide containing a known T-cell epitope[113] and bovine serum albumin[114]. Intraperitoneal administration of the same niosome formulation was also shown to act as a vaccine adjuvant in immune reconstituted SCID-human mice[115].

9.7. *Transdermal delivery*

Transdermal delivery of NSAIDs is the best way to avoid gastric disturbances. Transferosomes and elastic niosomes are novel types of vesicles for transdermal delivery[116] with the latter having the advantage of low cost of manufacturing. Manosroi et al.[102] reported novel elastic niosomes containing diclofenac diethylammonium for topical use and concluded that they illustrated the promise of such formulations of NSAIDs for topical non-invasive treatment of inflammation. Srikanth et al.[54] developed a meloxicam niosomal gel and studied its antiinflammatory activity in the carrageenan induced rat paw method. They concluded that the niosomal gel was superior to a conventional gel formulation because of the ability of niosomes to penetrate into the deeper layers of the skin. However, for transdermal delivery of other drugs, penetration of niosomes into the deeper layers of the skin remains a problem. Hopefully, the design of elastic noisome formulations will extend the application of this route of drug delivery[117].

10. Conclusion

Nonionic surfactant vesicular systems, otherwise known as niosomes, are a novel and efficient approach to drug delivery. Their vesicular membrane is mainly composed of nonionic surfactants and cholesterol and the enclosed interior usually contains a buffer solution at appropriate pH. Niosomes may be prepared by various methods, which affect their formations along with the properties of the drug, cholesterol content and amount, structrue and type of surfactant. As a drug delivery device, niosomes are osmotically active and stable. They also improve the stability of the entrapped drug during delivery. They do not require special conditions for handling, protection, storage or industrial manufacturing. In addition, they can be prepared with different structural characteristics (composition, fluidity and size), and can be designed for particular routes of administration. Overall, niosomes are a very effective tool for drug delivery and targeting of numerous therapeutically active moieties. They have the potential to provide better treatment than conventional drug delivery systems.

Table 1 Important patents related to niosomes.

Patent publication number	Inventors	Title	Patent description in brief	References
US2010/0068264 A1	Norma Alclantar, Eva C Williams and Ryan Toomey	Niosome hydro gel drug delivery	Drug encapsulated in niosomes made of a biodegradable polymer with a temperature and pH-sensitive hydro gel network (cross linked chitosan) providing controlled release of drug	118
US2010/0226932 A1	Gail Smith, Dinesh B. Shenoy and Robert W. Lee	Adjuvant and vaccine compositions	Addition of aluminum salts; encapsulation in niosomes improves the stability of antigens in vaccine for a specific immunological response	119
US2008/0050445 A1	Norma Alclantar, Kristina Dearborn, Michael Van Aukar, Ryan Toomey and Elizabeth Hood	Niosome hydro gel drug delivery	Drug encapsulated in niosomes made of a biodegradable polymer hydro gel network providing a two-fold increase in controlled release rate	120
US2006/0292211 A1	Elizabeth Hood, Joel A. Strom and Michael Van Aukar	Ultrasound enhancement of drug release across nonionic surfactant membranes	Ultrasound enhances the delivery of drug encapsulated in niosomes when given non-invasively by altering the niosome membrane structure	121
US2007/0172520 A1	Michael Van Aukar, Anna Plaas and Elizabeth Hood	Immuno targeting of nonionic surfactant vesicles	Niosomes provide targeted delivery of antigens to the host by retaining the bioactive agent in the cytoplasm of target cells	122
US2005/0239747 A1	Chih-Chiyang Yang, Yuan-Chih le and Chao-Cheng Liu	Compositions and methods of enhanced transdermal delivery of steroidal compounds and preparation methods	Niosomes are a delivery system that increases permeation of steroidal drugs across dermal tissue	123

11. Patents

Because niosomes are becoming increasingly popular for clinical use, the number of patents for niosomal formulations is increasing enormously. A short summary of some of the important patents pertaining to the encapsulation of various drugs in niosomes is indicated in Table 1.

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