

Review Article

Niosomes as Nanoparticulate Drug Carriers: Fundamentals and Recent Applications

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Drug delivery systems are defined as formulations aiming for transportation of a drug to the desired area of action within the body. The basic component of drug delivery systems is an appropriate carrier that protects the drug from rapid degradation or clearance and thereby enhances drug concentration in target tissues. Based on their biodegradable, biocompatible, and nonimmunogenic structure, niosomes are promising drug carriers that are formed by self-association of nonionic surfactants and cholesterol in an aqueous phase. In recent years, numerous research articles have been published in scientific journals reporting the potential of niosomes to serve as a carrier for the delivery of different types of drugs. The present review describes preparation methods, characterization techniques, and recent studies on niosomal drug delivery systems and also gives up to date information regarding recent applications of niosomes in drug delivery.

1. Introduction

Delivering drug with a controlled rate and targeted delivery received much attention in recent years. The application of nanotechnology to medicine has provided the development of multifunctional nanoparticles that, acting as drug carriers, can be loaded with different drugs. Nanocarriers present a great approach in drug delivery with promising features such as protection of drug from degradation and cleavage, controlled release, and in case of targeted delivery approaches the delivery of drug molecules to the target sites [1].

Niosomes are one of the promising drug carriers that have a bilayer structure and are formed by self-association of nonionic surfactants and cholesterol in an aqueous phase. Niosomes are biodegradable, biocompatible, and nonimmunogenic. They have long shelf life, exhibit high stability, and enable the delivery of drug at target site in a controlled and/or sustained manner [2]. In recent years, the potential of niosomes as a drug carrier has been extensively studied [3–5]. Various types of nonionic surfactants have been reported to form niosomes and enable the entrapment of a large number of drugs with a wide range of solubility [6–8]. The

composition, size, number of lamellae, and surface charge of niosomes can be varied and optimized to enhance the performance of niosomes for drug delivery.

The aim of this review is to present the fundamentals of niosome preparation and characterization as well as a description of their use in drug delivery, with particular attention to more recent studies. This review will provide an overview on the increasing interest on niosomes in the field of drug delivery.

2. Structure and Components of Niosomes

The main components of niosomes are nonionic surfactants, hydration medium and lipids such as cholesterol. The list of materials used in the preparation of niosomes has been shown in Table 1. The self-assembly of nonionic surfactants in aqueous media results in closed bilayer structures (Figure 1). A high interfacial tension between water and the hydrophobic tails of the amphiphile causes them to associate. The steric and hydrophilic repulsion between the head groups of nonionic surfactant ensure that hydrophilic termini point outwards and are in contact with water. The assembly into closed

TABLE 1: The materials used in niosome preparation.

Nonionic surfactants	Examples	References
<i>Alkyl ethers</i>		
(i) Alkyl glycerol ethers	Hexadecyl diglycerol ether (C16G2)	[9]
(ii) Polyoxyethylene glycol alkyl ethers (Brij)	Brij 30, Brij 52, Brij 72, Brij 76, Brij 78	[10–12]
<i>Crown ethers</i>	Bola	[13, 14]
<i>Alkyl esters</i>		
(i) Sorbitan fatty acid esters (Spans)	Span 20, Span 40, Span 60, Span 80, Span 65, Span 85	[15–18]
(ii) Polyoxyethylene sorbitan fatty acid esters (Tweens)	Tween 20, Tween 40, Tween 60, Tween 80, Tween 65, Tween 85	[7, 19, 20]
<i>Alkyl amides</i>		
(i) Glycosides	C-Glycoside derivative surfactant (BRM-BG)	[21]
(ii) Alkyl polyglucosides	Octyl-decyl polyglucoside (OrCG110), decyl polyglucoside (OrNS10)	[22]
<i>Fatty alcohols or fatty acids</i>		
(i) Fatty alcohols	Stearyl alcohol, cetyl alcohol, myristyl alcohol	[23]
(ii) Fatty acids	Stearic acid, palmitic acid, myristic acid	[23]
<i>Block copolymer</i>		
(i) Pluronic	Pluronic L64, Pluronic 105	[24, 25]
<i>Lipidic components</i>		
<i>Cholesterol</i>		[26]
<i>l-α-Soya phosphatidyl choline</i>		[27]
<i>Charged molecule</i>		
<i>Negative charge</i>	Diacetyl phosphate, phosphatidic acid, lipoamino acid, dihexadecyl phosphate	[28, 29]
<i>Positive charge</i>	Stearylamine, stearyl pyridinium chloride, cetyl pyridinium chloride	[29]

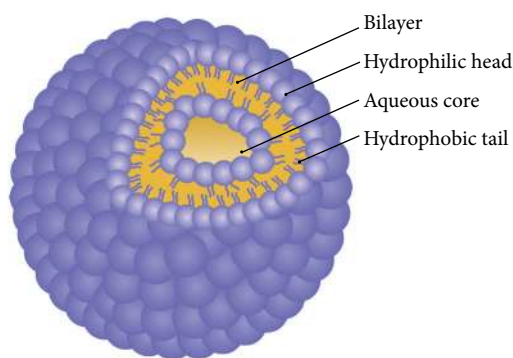


FIGURE 1: Structure of niosomes.

bilayers usually requires some input of energy such as mechanical or heat. Niosomes can be categorized in three groups according to their sizes and bilayers. Small unilamellar vesicles (SUV) (10–100 nm), large unilamellar vesicles (LUV) (100–3000 nm), and multilamellar vesicles (MLV) where more than one bilayer is present.

2.1. Nonionic Surfactants. Nonionic surfactants are a class of surfactants, which have no charged groups in their

hydrophilic heads. They are more stable and biocompatible and less toxic compared to their anionic, amphoteric, or cationic counterparts [41]. Therefore they are preferred for formation of stable niosome for *in vitro* and *in vivo* applications. Nonionic surfactants are amphiphilic molecules that comprise two different regions: one of them is hydrophilic (water-soluble) and the other one is hydrophobic (organic-soluble). Alkyl ethers, alkyl esters, alkyl amides, fatty acids are the main nonionic surfactant classes used for niosome production. The hydrophilic-lipophilic balance (HLB) and critical packing parameter (CPP) values play a critical role in the selection of surfactant molecules for niosome preparation.

2.1.1. Hydrophilic-Lipophilic Balance (HLB). HLB is a dimensionless parameter, which is the indication of the solubility of the surfactant molecule. The HLB value describes the balance between the hydrophilic portion to the lipophilic portion of the nonionic surfactant. The HLB range is from 0 to 20 for nonionic surfactants. The lower HLB refers to more lipophilic surfactant and the higher HLB to more hydrophilic surfactant. Surfactants with a HLB between 4 and 8 can be used for preparation of vesicle [42]. Hydrophilic surfactants with a HLB value ranging from 14 to 17 are not suitable to form a bilayer membrane due to their high aqueous solubility [43].

However with the addition of an optimum level of cholesterol, niosomes are indeed formed from polysorbate 80 (HLB value = 15) and Tween 20 (HLB value = 16.7) [44, 45]. Tween 20 forms stable niosome in the presence of equimolar cholesterol concentration. The interaction occurs between the hydrophobic part of the amphiphile next to head group and the 3-OH group of cholesterol at an equimolar ratio and this interaction could explain the effect of cholesterol on the formation and hydration behavior of Tween 20 niosomal membranes [46, 47].

Drug entrapment efficiency of the niosomes is also affected by HLB value of surfactant [48]. Shahiwala et al. have incorporated nimesulide into niosomes using lipid film hydration technique by changing the HLB. They found that as the HLB value of surfactant decreases from 8.6 to 1.7, entrapment efficiency decreases [43, 49].

2.1.2. Critical Packing Parameter (CPP). During the niosomal preparation, the geometry of the vesicle depends upon the critical packing parameter. On the basis of the CPP of a surfactant, the shape of nanostructures formed by self-assembly of amphiphilic molecules can be predicted. Critical packing parameter depends on the symmetry of the surfactant and can be defined using following equation [50, 51]:

$$\text{CPP} = \frac{\nu}{l_c \times a_0}, \quad (1)$$

where ν is hydrophobic group volume, l_c is the critical hydrophobic group length, and a_0 is the area of hydrophilic head group. If $\text{CPP} \leq 1/3$ corresponding, for example, to a bulky head group, small hydrophobic tail spherical micelles may form. Nonspherical micelles may form if $1/3 \leq \text{CPP} \leq 1/2$, and bilayer vesicles can occur if $1/2 \leq \text{CPP} \leq 1$. Inverted micelles form if $\text{CPP} \geq 1$ when the surfactant is composed of a voluminous tail and a small hydrophobic tail [47]. CPP could be considered as a tool for realizing, rationalizing, and predicting the self-assembled structure and its morphological transition in amphiphilic solutions [52].

2.2. Cholesterol. In the bilayer structure of niosomes, cholesterol forms hydrogen bonds with hydrophilic head of a surfactant [19, 53]. Cholesterol content of niosomes thereby influences the structures of niosomes and physical properties such as entrapment efficiency, long time stability, release of payload, and biostability [17, 46]. Cholesterol improves the rigidity of vesicles and stabilizes niosomes towards destabilizing effects induced by plasma and serum components and decreases the permeability of vesicles for entrapped molecules thus inhibiting leakage [54].

Drug entrapment efficiency plays an important role in niosomal formulations and it can be altered by varying the content of cholesterol. Agarwal et al. demonstrated that cholesterol improves the stability of enoxacin loaded niosome with increasing cholesterol content, resulting in increases of entrapment efficiency [55]. The effect of cholesterol on flurbiprofen entrapment was studied by Mokhtar et al. and cholesterol was found to have little effect on the flurbiprofen entrapment into Span 20 and Span 80 niosomes. However,

a significant increase in entrapment efficiency of flurbiprofen was obtained when 10% of cholesterol was incorporated into niosomes prepared from Span 40 and Span 60 followed by a decrease in encapsulation efficiency of the drug upon further increase in cholesterol content [56]. According to the reported results, the addition of cholesterol and its amounts needs to be optimized depending on the physical-chemical characteristic of surfactants and loaded drugs.

2.3. Charged Molecule. Charged molecules increase the stability of the vesicles by the addition of charged groups to the bilayer of vesicles. They increase surface charge density and thereby prevent vesicles aggregation. Dicetyl phosphate and phosphatidic acid are most used negatively charged molecules for niosome preparation and, similarly, stearylamine and stearyl pyridinium chloride are well-known positively charged molecules used in niosomal preparations. Normally, the charged molecule is added in niosomal formulation in an amount of 2.5–5 mol%. However increasing the amount of charged molecules can inhibit niosome formation [29].

3. Methods of Preparation

3.1. Thin-Film Hydration Method (TFH). Thin-film hydration method is a simple and well-known preparation method. In this method, the surfactants, cholesterol, and some additives such as charged molecules are dissolved in an organic solvent in a round bottomed flask. Then the organic solvent is removed using a rotary vacuum evaporator to obtain thin film on the inside wall of the flask. An aqueous solution of drug is added and the dry film is hydrated above the transition temperature (T_c) of the surfactant for specified time with constant shaking [57, 58]. Multilamellar niosomes are formed by this method.

3.2. Ether Injection Method (EIM). In ether injection method, the surfactants with additives are dissolved in diethyl ether and injected slowly through a needle in an aqueous drug solution maintained at a constant temperature, which is above the boiling point of the organic solvent. The organic solvent is evaporated using a rotary evaporator. During the vaporization the formation of single layered vesicles occurs [59–61].

3.3. Reverse Phase Evaporation Method (REV). In this method, niosomal ingredients are dissolved in a mixture of ether and chloroform and added to aqueous phase containing the drug. The resulting mixture is sonicated in order to form an emulsion and the organic phase is evaporated. Large unilamellar vesicles are formed during the evaporation of the organic solvent [62–64].

3.4. Microfluidization Method. The microfluidization method is based on submerged jet principle. In this method, the drug and the surfactant fluidized streams interact at ultrahigh velocities, in precisely defined micro channels within the interaction chamber. The high speed impingement and the energy involved leads to formation of niosomes. This method

offers greater uniformity, smaller size, unilamellar vesicles, and high reproducibility in the formulation of niosomes [65, 66].

3.5. Supercritical Carbon Dioxide Fluid (scCO₂). Manosroi et al. have described the supercritical reverse phase evaporation technique for niosome formation [67, 68]. They added Tween 61, cholesterol, glucose, PBS, and ethanol into the view cell and the CO₂ gas was introduced into the view cell. After magnetic stirring until equilibrium, the pressure was released and niosomal dispersions were obtained [67]. This method enables one step production and easy scale-up.

3.6. Proniosome. Proniosome technique includes the coating of a water-soluble carrier such as sorbitol and mannitol with surfactant. The coating process results in the formation of a dry formulation. This preparation is termed "Proniosomes" which requires to be hydrated before being used. The niosomes are formed by the addition of the aqueous phase. This method helps in reducing physical stability problems such as the aggregation, leaking, and fusion problem and provides convenience in dosing, distribution, transportation, and storage showing improved results compared to conventional niosomes [69].

3.7. Transmembrane pH Gradient. In this method, surfactant and cholesterol are dissolved in chloroform and evaporated to form a thin lipid film on the wall of a round bottomed flask. The film is hydrated with a solution of citric acid (pH = 4) by vortex mixing and the resulting product is freeze-thawed for niosome formation. The aqueous solution of drug is added to this niosomal suspension, after that phosphate buffer is added to maintain pH between 7.0 and 7.2 [70]. According to this method, the interior of niosome has a more acidic pH value than the outer medium. The added unionized drug passes through the niosome membrane and enters into the niosome. The drug ionizes in an acidic medium and cannot escape from the niosomal bilayer [71].

3.8. Heating Method. This is a patented method which was created by Mozafari et al. [72, 73]. Surfactants and cholesterol are separately hydrated in buffer and the solution is heated to 120°C with stirring to dissolve cholesterol. The temperature is reduced and surfactants and other additives are then added to the buffer in which cholesterol is dissolved while stirring continues. Niosomes form at this stage, are left at room temperature, and then are kept at 4-5°C under nitrogen atmosphere until use [53].

3.9. The "Bubble" Method. In this method, surfactants, additives, and the buffer are added into a glass flask with three necks. Niosome components are dispersed at 70°C and the dispersion is mixed with homogenizer. After that, immediately the flask is placed in a water bath followed by the bubbling of nitrogen gas at 70°C. Nitrogen gas is passed through a sample of homogenized surfactants resulting in formation of large unilamellar vesicles [74].

4. Characterization of Niosomes

The characterization of niosome is essential for the clinical applications. Characterization parameters have a direct impact on the stability of niosomes and a significant effect on their *in vivo* performance. Therefore these parameters such as morphology, size, polydispersity index (PI), number of lamellae, zeta potential, encapsulation efficiency, and stability must be evaluated.

4.1. Size and Morphology. Dynamic light scattering (DLS) [75], scanning electron microscopy (SEM) [76], transmission electron microscopy (TEM) [77], freeze fracture replication-electron microscopy (FF-TEM) [68], and cryotransmission electron microscopy (cryo-TEM) [67] are the most used methods for the determination of niosome sizes and morphology. DLS provides simultaneously cumulative information of particle size and valuable information on the homogeneity of the solution. A single sharp peak in the DLS profile implies existence of a single population of scatterers. The PI is helpful in this respect. It less than 0.3 corresponds to a homogenous population for colloidal systems [75]. The microscopic approaches are generally used to characterize the morphology of the niosomes.

4.2. Zeta Potential. Surface zeta potential of niosomes can be determined using zetasizer and DLS instruments. The surface charge of niosome plays an important role in the behavior of niosomes. In general, charged niosomes are more stable against aggregation than uncharged vesicles. Bayindir and Yuksel prepared paclitaxel loaded niosomes and investigated the physicochemical properties such as zeta potential of niosomes. They found that negative zeta potential values ranging between -41.7 and -58.4 mV are sufficiently high for electrostatic stabilization of niosomes [12].

4.3. Bilayer Characterization. Bilayer characteristics of niosomes have an importance on drug entrapment efficiency. The number of lamellae can be determined by AFM, NMR, and small angle X-ray scattering (SAXS) for multilamellar vesicles [54]. Membrane rigidity of niosomal formulations can be measured by means of the mobility of fluorescence probe as a function of temperature [20]. DPH (1,6 diphenyl-1,3,5-hexatriene) is most used fluorescent probe and added to niosomal dispersion. DPH normally exists in hydrophobic region in the bilayer membrane. The microviscosity of niosomal membrane is determined by fluorescence polarization. High fluorescence polarization means high microviscosity of the membrane [78]. Moreover, the bilayer thickness can be characterized using the latter method, together with the *in situ* energy-dispersive X-ray diffraction (EDXD) [79].

4.4. Entrapment Efficiency. Entrapment efficiency (EE%) is defined as the portion of the applied drug which is entrapped by the niosomes. Unencapsulated free drug can be removed from the niosomal solution using centrifugation [80], dialysis [24], or gel chromatography [81]. After this step the loaded drug can be released from niosomes by destruction of

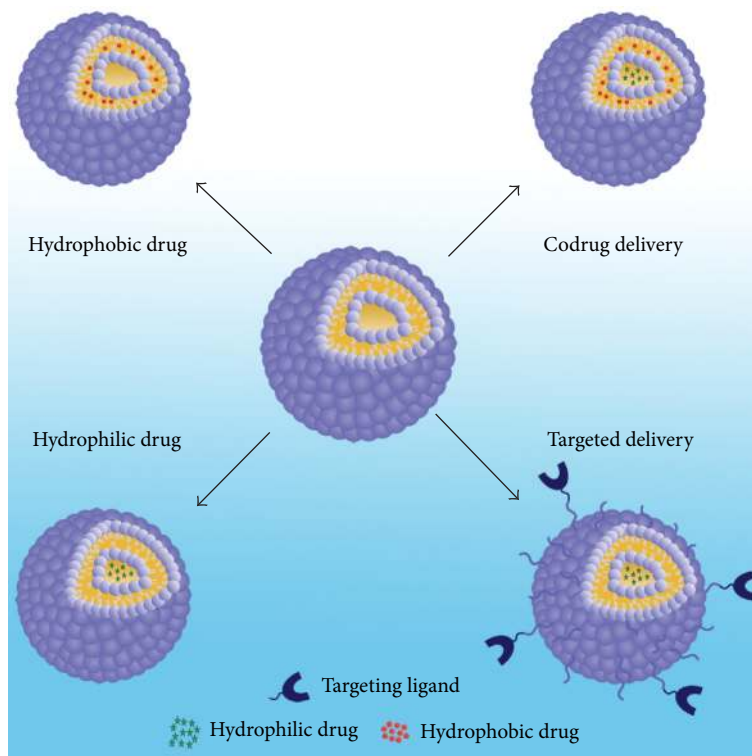


FIGURE 2: Niosomes in drug delivery.

vesicles. Niosomes can be destroyed with the addition of 0.1% Triton X-100 or methanol to niosomal suspension. The loaded and free drug concentration can be determined by a spectrophotometer [82] or high-performance liquid chromatography (HPLC) [83].

4.5. Stability. The stability of niosomes can be evaluated by determining mean vesicle size, size distribution, and entrapment efficiency over several month storage periods at different temperatures. During storage the niosomes are sampled at regular intervals of time and the percentage of drug which is retained into the niosomes is analyzed by UV spectroscopy or HPLC methods [82, 84].

4.6. In Vitro Release. One often applied method to study *in vitro* release is based on using of dialysis tubing. A dialysis bag is washed and soaked in distilled water. After 30 mins, the drug loaded niosomal suspension is transferred, into this bag. The bag containing the vesicles is immersed in buffer solution with constant shaking at 25°C or 37°C. At specific time intervals, samples were removed from the outer buffer (release medium) and replaced with the same volume of fresh buffer. The samples are analyzed for the drug content by an appropriate assay method [17].

5. Niosomes as Drug Carriers

Niosomes are very promising carriers for the delivery of numerous pharmacological and diagnostic agents. A number

of publications have reported the preparation, characterization, and use of niosomes as drug carriers. Because of their nonionic nature, they offer excellent biocompatibility and low toxicity. The unique structure of niosomes allows the development of effective novel drug delivery systems with ability of loading both hydrophilic and lipophilic drugs. Hydrophilic drugs and lipophilic drugs are entrapped into the aqueous core and membrane bilayer of niosome respectively (Figure 2).

5.1. Anticancer Drug Delivery. The current treatment for cancer is usually chemotherapy. The therapeutic efficacy of many anticancer drugs is limited by their poor penetration into tumor tissue and by their severe side effects on healthy cells. Various attempts have been made to overcome these drawbacks, including the use of niosomes as a novel drug delivery system.

5.1.1. Melanoma. Artemisone is a 10-amino-artemisinin derivative exhibiting antimalarial activity and also possessing antitumor activity. Dwivedi et al. encapsulated artemisone in niosomes using thin-film hydration method. The formulations showed highly selective cytotoxicity towards the melanoma cells with negligible toxicity towards the normal skin cells [85]. 5-Fluorouracil (5-FU), largely used in the treatment of different forms of skin cancers, was encapsulated in an innovative bola-niosomal system made up of α,ω -hexadecyl-bis-(1-aza-18-crown-6) (bola-surfactant), Span 80, and cholesterol. The percutaneous permeation of 5-FU-loaded bola-niosomes was evaluated by using human stratum

corneum and epidermis membranes. Bola-niosomes provided an increase of the drug penetration of 8- and 4-fold with respect to free drug aqueous solution [13]. The use of cisplatin is limited due to its severe toxic effects. Gude et al. synthesized niosomal cisplatin by using Span 60 and cholesterol and investigated the antimetastatic activity in experimental metastatic model of B16F10 melanoma. Their results suggest that cisplatin encapsulated in niosomes has significant antimetastatic activity and reduced toxicity when compared to free cisplatin [86].

5.1.2. Breast Cancer. 5-FU-loaded polyethylene glycol- (PEG-) coated and uncoated bola-niosomes were prepared by Cosco et al. and were tested on breast cancer cell lines (MCF-7 and T47D). Both bola-niosome formulations provided an increase in the cytotoxic effect with respect to the free drug. *In vivo* experiments on MCF-7 xenograft tumor SCID mice models showed a more effective antitumor activity of the PEGylated niosomal 5-FU at a concentration ten times lower (8 mg/kg) than that of the free solution of the drug (80 mg/kg) after a treatment of 30 days [87]. Cantharidin-entrapped niosomes were prepared by injection method. Their potential in enhancing the antitumor activities of the drug and reducing its toxicity was evaluated on human breast cancer cell line MCF-7. Moreover, *in vivo* therapeutic efficacy was investigated in S_{180} tumor-bearing mice. Mice treated with 1.0 mg/kg niosomal cantharidin showed the most effective antitumor activity, with an inhibition rate of 52.76%, which was significantly higher than that of the same concentration of free cantharidin (1.0 mg/kg, 31.05%) [88]. Recently, tamoxifen citrate niosomes were prepared by film hydration technique for localized cancer therapy through *in vitro* breast cancer cytotoxicity as well as *in vivo* solid antitumor efficacy. The optimized niosomal formulation of tamoxifen showed significantly enhanced cellular uptake (2.8-fold) and exhibited significantly greater cytotoxic activity on MCF-7 breast cancer cell line. *In vivo* experiments showed enhanced tumor volume reduction induced by niosomal tamoxifen when compared to free tamoxifen [89].

5.1.3. Ovarian Cancer. Uchegbu et al. prepared doxorubicin loaded niosomes. The activity of doxorubicin in hexadecyl diglycerol ether ($C_{16}G_2$) and Span 60 niosomes was studied against a human ovarian cancer cell line and its doxorubicin resistant subline. According to the results, there was a slight reduction in the IC_{50} against the resistant cell line when the drug was encapsulated in Span 60 niosomes in comparison to the free drug in solution [90].

5.1.4. Lung Cancer. Adriamycin was encapsulated into the niosome using a monoalkyl triglycerol ether by Kerr et al. and the activity of niosomal adriamycin compared with free adriamycin solution on human lung tumor cells grown in monolayer and spheroid culture and in tumor xenografted nude mice. The growth delay (i.e., the time taken for the tumor volume to double) was significantly longer for adriamycin (15 days) and niosomal adriamycin (11 days) than for control (5.8 days). It is possible that the therapeutic ratio of adriamycin could be further enhanced by

administration in niosomal form [91]. In another study, pentoxifylline loaded niosomes were prepared by lipid film hydration method. Intravenous administration of niosomal pentoxifylline (6 mg/kg and 10 mg/kg) resulted in significant reduction in lung nodules in an experimental metastatic B16F10 model suggesting accumulation of pentoxifylline in a distant target. Light microscopic observation of histologic sections showed a decrease in number of tumor islands in the lung [92].

5.2. Targeted Delivery. The efficiency and particularly the specificity of cellular targeting of niosomal drug delivery systems can be further improved by active targeting for tumor therapy, by using a ligand coupled to the surface of niosomes, which could be actively taken up, for example, via a receptor-mediated endocytosis. Niosome surfaces can be conjugated with small molecules and/or macromolecular targeting ligands to enable cell specific targeting [93]. Proteins and peptides, carbohydrates, aptamers, antibodies, and antibody fragments are the most commonly used molecules that bind specifically to an overexpressed target on the cell surface [94–96]. Bragagni et al. developed brain targeted niosomal formulation using with the glucose-derivative as a targeting ligand. They formulated niosomal doxorubicin composed of span : cholesterol : solulan : N-palmitoylglucosamine. Preliminary *in vivo* studies in rats showed that intravenous administration of a single dose of the developed targeted-niosomal formulation with respect to the commercial one was able to significantly reduce the hearth accumulation of the drug and to keep it longer in the blood circulation and also to allow the achievement of well detectable doxorubicin brain concentrations [30]. Moreover, an efficient tumor-targeted niosomal delivery system was designed by Tavano et al. Niosomes were prepared from a mixture of Pluronic L64 surfactant and cholesterol and doxorubicin was entrapped into the niosome. After the preparation, transferrin was conjugated to niosomes surface using EDC (N-[3-(dimethylamino)propyl]-N-ethylcarbodiimide hydrochloride) chemistry. Doxorubicin-loaded niosome anticancer activity was achieved against MCF-7 and MDA-MB-231 tumor cell lines, and a significant reduction in viability in a dose and time related manner was observed [24]. The information about some recent studies on niosomal targeted drug delivery is summarized in Table 2.

5.3. Codrug Delivery. In recent years, nanoparticles have emerged as a promising class of carriers in codelivery of multiple drugs for combination therapy [97]. Combinational therapies enhance therapeutic efficacy and decrease dosage while obtaining equal or greater levels of efficacy and reducing drug resistance [98]. Anticancer drugs often have serious side effects. With multidrug delivery system Pasut et al. achieved higher anticancer activity for carcinoma cells, whereas multidrug delivery system decreased cytotoxicity against endothelial cells and cardiomyocytes, with respect to free drug treatment. In their system, they have developed simultaneous anticancer drug epirubicin and nitric oxide carrying system, in which nitric oxide and epirubicin were covalently conjugated to each terminal of PEG. Nitric oxide acts

TABLE 2: Niosomes in targeted drug delivery.

Targeted tissue	Loaded therapeutic agent	Composition	Preparation method	Surface modification	Targeting molecule	References
Brain	Doxorubicin	Span 60, cholesterol, solulan C24, N-palmitoyl glucosamine	TLE-paddle method	—	N-Palmitoyl glucosamine	[30]
	Dynorphin-B	Span 60, cholesterol, solulan C24, N-palmitoyl glucosamine	Sonication	—	N-Palmitoyl glucosamine	[26]
	Vasoactive intestinal peptide	Span 60, cholesterol, solulan C24, N-palmitoyl glucosamine	Sonication	—	N-Palmitoyl glucosamine	[31]
Breast cancer	Doxorubicin	Oxidate pluronic L64, cholesterol	Thin-film hydration	EDC Chemistry	Transferrin	[24]
Chronic myelogenous leukemia	Doxorubicin	Tween 60, pluronic L64	Thin-film hydration	—	Magnetite	[32]
Epidermoid carcinoma	Hydroxycamptothecin	Span 60, cholesterol	Thin-film hydration	Periodate oxidation	Transferrin	[33]
	Doxorubicin	Span 60, cholesterol, solulan C24, N-palmitoyl glucosamine	Sonication	—	N-Palmitoyl glucosamine	[34]
Melanoma	Doxorubicin	Span 60, cholesterol, dicetyl phosphate, N-lauryl glucosamine	Ethanol injection method	—	N-Lauryl glucosamine	[35]

as not only protecting reagent against anthracycline induced cardiomyopathy but also sensitizer of anticancer drug treatment. In order to increase anticancer efficacy and enhance cardiocyte protecting ability of codelivery system, they used branched PEG as polymer backbone instead of linear one [99]. Multidrug resistance (MDR) of malignant neoplasm is the survival ability of cancer cells under the treatment with structurally and functionally diverse anticancer drugs. Increased drug efflux is mostly mediated by ATP-driven extrusion pump proteins of the ATP-binding cassette (ABC) superfamily, such as P-glycoprotein (P-gp) encoded by MDR-1, multidrug resistance (MDR) proteins (MRPs/ABCC) and breast cancer resistance protein (BCRP/ABCG2). These drug efflux pumps noticeably decrease the intracellular concentration of numerous therapeutic agents [100]. Chemosensitizers, such as Verapamil, Elacridar, Tariquidar, and cyclosporine A mainly act as antagonist for P-gp and suppress drug efflux and consequently recover chemosensitivity of MDR cancer cells. Paclitaxel was coencapsulated with cyclosporine A within actively targeted polymeric lipid-core micelles. P-gp inhibition with cyclosporine A caused an enhanced cytotoxicity of paclitaxel. Micelles loaded with this dual cargo demonstrated significantly higher cytotoxicity in the MDCKII-MDR1 cells than micelles loaded with paclitaxel alone [101].

Niosomes are promising nanocarriers in multidrug delivery applications [102]. Recently Sharma et al. reported the dual encapsulation of hydrophobic curcumin and hydrophilic doxorubicin in niosomes for cancer multidrug delivery [44]. Results showed that dual-drug loaded niosomes had higher cytotoxicity on HeLa cells when compared to free drugs. In another study, gallic acid, ascorbic acid, curcumin, and quercetin were encapsulated into the niosome as single agents or in combination and the effect of the drugs coencapsulation on the physicochemical properties of the carriers, on their antioxidant properties and capability to release the encapsulated materials, was evaluated [103]. Furthermore, Marianecci et al. prepared, characterized, and applied multidrug niosomes using lidocaine and ibuprofen. Results suggest the potential application of niosomes in dermal administration of the two drugs at the same time in the same pharmaceutical formulation, as useful carriers for the treatment of various skin diseases, such as acute and chronic inflammations in presence of pain [104].

5.4. Antibiotics. Niosomal carriers are also suitable for the delivery of antibiotics and anti-inflammatory agents. These carriers have been used extensively to improve poor skin penetration and as well as enhance skin retention of the drugs. Begum and coworkers designed rifampicin, a broad spectrum antibiotic, encapsulated in a niosomal delivery system. They investigated the activity of this system in *in vitro* conditions and this study showed that niosomal formulation of rifampicin is able to provide consistent and prolonged release of the drug [105]. In another study to increase efficacy of the antibiotics and reduce the dose, Akbari et al. synthesized ciprofloxacin loaded niosomes using different non-ionic surfactants and cholesterol in various concentrations by film hydration method. Drug release through bilayers and antibacterial activity of the niosomes were examined.

The results showed that cholesterol content and phase transition temperature of the surfactants influenced the performance of niosomes. Besides, all formulations presented more antibacterial activity as compared to free ciprofloxacin [106].

Vesicular systems, niosomes and liposomes, are mostly used in ophthalmic controlled delivery. Abdelbary and El-Gendy examined the feasibility of the niosomes as a carrier for the ophthalmic controlled delivery of gentamicin antibiotic. Various surfactants (Tween 60, Tween 80, or Brij 35) were combined with cholesterol and a negative charge inducer dicetyl phosphate in different molar ratios. The ability of these vesicles to entrap the selected drug was evaluated and the obtained results showed that entrapment efficiency and the release rate of gentamicin is affected by cholesterol content, type of surfactant, and the presence of charge inducer. Gentamicin loaded niosomes composed of Tween 60, cholesterol, and dicetyl phosphate were the most effective in terms of prolongation of *in vitro* drug release [107].

5.5. Anti-Inflammatory Drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) loaded niosomes have been prepared by several groups. These drugs may cause adverse effects such as mucosal irritation. Topically applied NSAIDs loaded niosomes can substantially improve drug permeation. To investigate the potential application of the niosomes for delivery of anti-inflammatory agents, Marianecci et al. synthesized ammonium glycyrrhizinate (AG) loaded niosomes using several surfactants and cholesterol at various concentrations. Drug entrapment efficiency, anisotropy, cytotoxicity and skin tolerability, and some further analysis have been performed for characterization. The AG-loaded niosomes demonstrated no toxicity and good skin tolerability and were able to improve the anti-inflammatory activity in mice. Moreover, an enhancement of the anti-inflammatory activity of the niosome delivered drug was observed on chemically induced skin erythema in humans [7].

5.6. Antiviral Drugs. Niosomes have also demonstrated the capability to deliver various antiviral agents. Ruckmani and Sankar synthesized zidovudine, which is the first anti-HIV compound approved for clinical use, encapsulated niosomes, and examined their entrapment efficiency and as well as sustainability of release. The niosomes were formulated by combining the proportions of Tween, Span, and cholesterol. Niosomes composed Tween 80 entrapped large amounts of zidovudine and the addition of dicetyl phosphate enhanced drug release for a longer time [108]. The drug leakage from Tween 80 formulations stored at room temperature was significant compared to niosomes stored at 4°C for 90 days. Besides, the results of a pharmacokinetic study in rabbits also confirmed that Tween 80 formulations with dicetyl phosphate were cleared from the circulation within five hours [109].

6. Recent Studies

Over the past three decades, niosomes have been successfully used as a drug carriers to overcome some major biopharmaceutical problems such as insolubility, side effects, and

TABLE 3: Recent studies on niosomes in drug delivery.

Type of the drug	Name of the drug	Composition	Experimental model	Year	References
Angiotensin receptor blockers	Candesartan cilexetil	Span 60, cholesterol, dicetyl phosphate, maltodextrin	<i>In vitro</i> dissolution test for proniosomal tablets, <i>in vivo</i> evaluation of proniosomal tablets, pharmacokinetic analysis	2016	[36]
Anti-inflammatory	Naproxen	Tween 80, Tween 20, cholesterol	<i>In vitro</i> drug release study, preformulation study	2016	[37]
	Dexamethasone	Span 60, cholesterol	Characterization of niosomes, <i>in vitro</i> release studies, stability test	2015	[38]
Antibacterial	Moxifloxacin	Tween 60, cholesterol	<i>In vitro</i> release studies, antimicrobial activity	2016	[39]
	Cefixime	C-Glycoside derivative surfactant, cholesterol	<i>In vitro</i> release study, biocompatibility and bioavailability studies using experimental animals	2016	[21]
Anticancer	Doxorubicin	Span 60, cholesterol, dicetyl phosphate, N-lauryl glucosamine	Optimization studies for formulation, skin irritancy, histopathological investigation of rat skin	2016	[35]
	Paclitaxel	Span 40, cholesterol, dicetyl phosphate	Formulation studies, Pharmacokinetic and tissue distribution studies	2015	[6]
Antiviral	Nevirapine	Tyloxapol, cholesterol	Diffusion kinetics of drug, microviscosity studies, <i>in vitro</i> release study	2015	[8]
H ₂ receptor antagonist	Famotidine	Span 60, cholesterol	Kinetic analysis of drug-release profiles, <i>ex vivo</i> permeability study	2016	[40]

poor chemical stability of drug molecules [110]. Table 3 summarizes the most recent applications of niosomes as drug delivery systems.

7. Strengths and Limitations of Niosomes in Drug Delivery

One of the most important strengths of niosomes compared with liposomes is their chemical stability. Niosomes are more stable against chemical degradation or oxidation and have long storage time compared to liposomes [51]. The surfactants which are used for niosomes preparation are biodegradable, biocompatible, and nonimmunogenic [83]. Handling and storage conditions of surfactants do not need any specifications. Moreover composition, size, lamellarity, stability, and surface charge of niosomes can be controlled by the type of preparation method, surfactant, cholesterol content, surface charge additives, and suspension concentration [66].

On the other hand niosomes show physical stability problems. During storage of dispersion niosomes are at risk of aggregation, fusion, drug leakage, or hydrolysis of encapsulated drugs. Furthermore the sterilization of niosomes needs much effort. Heat sterilization and membrane filtration are unsuitable for niosomes. Thus, these areas need further research to produce commercially niosomal preparations.

8. Conclusion

Niosomes are novel nano drug carriers to design effective drug delivery systems. They offer a great opportunity for loading hydrophilic, lipophilic drugs, or both drugs together.

Numbers of studies have been performed with different types of niosomes in delivery of the anticancer agents, anti-inflammatory agents, anti-infective agents, and so forth. The relevant studies demonstrated that niosomes improve the stability of the entrapped drug, reduce the dose, and enable targeted delivery to a specific type of tissue. The structural properties and characteristics of the niosomes can be enhanced by using novel preparations, loading, and modification methods for particular routes of administration. Thus, niosomes present itself as promising tools in commercially available therapeutics.

Competing Interests

The authors declare that there are no competing interests regarding the publication of this paper.

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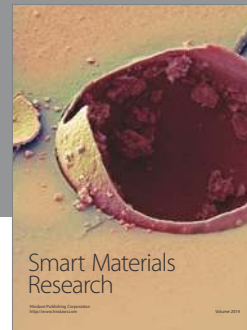
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