

NIOSOMES FORMULATION STRATEGIES AND ITS APPLICATIONS: A

REVIEW

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ABSTRACT

Target-specific drug-delivery systems for the administration of pharmaceutical compounds enable the localization of drugs to diseased sites. Various types of drug-delivery systems utilize carriers, such as immunoglobulins, serum proteins, synthetic polymers, liposomes, and microspheres. The vesicular system of niosomes, with their bilayer structure assembled by nonionic surfactants, is able to enhance the bioavailability of a drug to a predetermined area for a period. The amphiphilic nature of niosomes promotes their efficiency in encapsulating lipophilic or hydrophilic drugs. Other additives, such as cholesterol, can be used to maintain the rigidity of the niosomes' structure. This narrative review describes fundamental aspects of niosomes, including their structural components, methods of preparation, limitations, and current applications to various diseases.

Keywords: drug-delivery system, medical applications, methods of preparation, niosomes, structure

INTRODUCTION

The concept of a drug-delivery system refers to a process of administering pharmaceutical compounds at a predetermined rate to achieve a therapeutic effect in humans or animals at a diseased site, and at the same time, reducing the concentration of the medication in surrounding tissues. Localized drug action enhances the efficacy of drug and reduces systemic toxic effects to tissues [1]. Paul Ehrlich proposed the idea of targeted delivery directly to the diseased cell without damaging healthy cells in 1909, and this strategy has been known as the “magic bullet” [2]. Since then, a number of drug carrier systems have emerged, including immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, and niosomes [1]. Among these systems, liposomes and niosomes are well-documented vesicular drug-delivery systems [3–6]. In general, a vesicular system is a drug-delivery platform that enables effective bioavailability of drugs through controlled release of therapeutic drugs for a prolonged period [7–10]. The vesicles consist of bilayer amphiphilic molecules that surround an aqueous compartment [8, 11, 12]. Niosomes are vesicles of nonionic surfactant (for example, alkyl ester and alkyl ether) and

cholesterol that act as a carrier for amphiphilic and lipophilic drugs [7, 8, 13, 14]. Niosomes improve the therapeutic performance of encapsulated drug molecules by protecting the drug from harsh biological environments, resulting in their delayed clearance [15]. Novel drug development is both time consuming and expensive. The development of a new drug costs an estimated \$120 million, and the journey from discovery, clinical testing, and development to regulatory approval takes decades [16–19]. Specific drug-delivery systems alleviate the urgency for bringing new drugs into the market by increasing drug selectivity and the therapeutic index, while lowering the effective dose. This narrative review discusses the role of niosomes as a drug-delivery system and details of their structure, preparation, properties, and applications.

Niosomes

Structure of niosomes

Niosomes are spherical and consist of microscopic lamellar (unilamellar or multilamellar) structures (Figure 1). The bilayer is formed by nonionic surfactants, with or without cholesterol and a charge inducer [20, 21]. Different types of surfactants at variable combinations and molar ratios are used to form niosomes [22]. Examples of surfactants include

alkyl ethers, alkyl glyceryl ethers, sorbitan fatty acid esters, and polyoxyethylene fatty acid esters [7]. Addition of cholesterol maintains the rigidity of the bilayer, resulting in less leaky niosomes. Meanwhile, charge inducers provide charge to the vesicles and increase vesicle size, increasing drug entrapment efficiency. Negative charge inducers, including dicetyl phosphate, dihexadecyl phosphate, and lipoamino acid, and positive charge inducers, including stearylamine and cetylpyridinium chloride, help to stabilize the vesicles [23, 26]. Nonionic surfactants in niosomes tend to orient themselves in such a way that hydrophilic end faces outward (toward the aqueous phase), whereas the hydrophobic end faces inward to each other to form a closed bilayer structure, which encloses solutes in an aqueous solution [20]. As a result, the closed bilayer structure of niosomes has hydrophilic inner and outer surfaces, with a sandwiched lipophilic area in between [8, 26]. To form the closed bilayer structure, energy such as heat or physical agitation is required. Various forces inside the vesicles were found to play an important role in maintaining the vesicular structure, for example, van der Waals and repulsive forces that exist among the surfactant molecules. Varying the vesicle's components (including type, composition,

and concentration), size, surface charge, or volume will likely modify the properties of resultant niosomes [20, 21, 27].

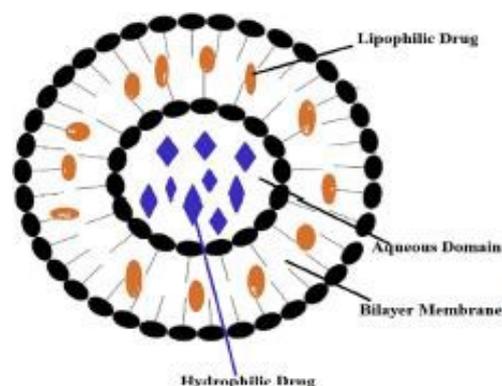


Figure 1: Bilayer structure of niosome showing entrapment area of hydrophilic and hydrophobic drug

Niosomes can be categorized into 3 groups based on their vesicle size, namely, small unilamellar vesicles (0.025–0.05 μm), multilamellar vesicles ($>0.05 \mu\text{m}$), and large unilamellar vesicles ($>0.10 \mu\text{m}$) [27].

METHODS OF PREPARATION

Preparation of niosomes begins with the hydration of a surfactant and lipid mixture at elevated temperatures, followed by optional niosome size reduction in order to obtain a colloidal suspension [28]. There are several well-studied standard methods for the preparation of niosomes. Ether injection, hand shaking, sonication, and microfluidization methods are a few examples [7, 27, 29]. Subsequently, the untrapped drug is separated from the entrapped drug by centrifugation, gel filtration, or dialysis [28].

The first step in niosome production by ether injection is through the dissolution

of surfactant in diethyl ether. The solution is then injected through a 14-gauge needle into an aqueous solution of drug maintained at 60°C. Subsequently, single-layer vesicles with diameters ranging from 50 to 1000 nm are formed because of the vaporization of ether [20]. However, a small amount of residual ether frequently persists in the niosomal suspension [27].

In the hand-shaking method, also known as thin-film hydration technique, surfactant and cholesterol are dissolved in a volatile organic solvent and transferred to a rotary evaporator. After evaporation, a thin layer of solid mixture is deposited on the wall of the flask. The dried layer is then hydrated with an aqueous phase containing the drug of interest. This process may be carried out at room temperature with gentle agitation [15, 27].

Niosomes can also be produced through sonicating a mixture of surfactant, cholesterol, and aqueous phase containing the drug at 60°C for 3 min. The vesicles produced through this method are usually small and uniform in size [15, 27]. Microfluidization is another reproducible technique that achieves this size uniformity. Operationally, 2 fluidized streams move forward through a precisely defined micro-channel, and these 2 streams interact with each other at an

ultrahigh velocity [20, 27, 30].

Alternative methods have since been defined for the preparation of niosomes. The multiple membrane extrusion method uses surfactant, cholesterol, and dicetyl phosphate in chloroform, and the mixture is evaporated to produce a thin film. The film is then hydrated with aqueous drug solution, and the suspension produced is extruded through polycarbonate membranes, which are placed in series for up to 8 passages [20, 27, 31].

The reverse-phase evaporation technique uses a mixture containing surfactant and cholesterol in a 1:1 ratio, in addition to ether and chloroform. An aqueous phase containing the target drug is added to the mixture followed by sonication at 4–5°C. Sonication is continued after adding a small amount of phosphate-buffered saline to the mixture. The organic solvent is removed at 40°C under a low pressure, and the remaining suspension is diluted with phosphate-buffered saline. After heating the mixture at 60°C for 10 min, the final product of niosomes is obtained [20, 27, 32]. The preparation of niosomes using the reverse-phase evaporation technique is illustrated in **Figure 2**.

Niosomes can be produced without the use of organic solvents using the “bubble” method. A “bubbling unit” consists of a round-bottomed flask

with 3 necks positioned in a water bath; a water-cooled reflux condenser and thermometer are positioned in the first and second necks, respectively, while nitrogen is supplied through the third neck. Surfactant and cholesterol that are mixed at 70°C in a buffer are homogenized and bubbled at 70°C using the bubbling unit [20, 33]. The preparation of niosomes using this technique is illustrated in Figure 3.

In another variation of preparation of niosomes, a thin film resulting from evaporation of surfactant and cholesterol dissolved in chloroform is hydrated with 300 mM citric acid (pH 4.0). Then, the suspension is subjected to 3 successive freeze-thaw cycles. After sonication, the aqueous solution containing the drug is added to the suspension and vortexed. Disodium phosphate (1 M) is added to the mixture to increase the pH to $7.0-7.2$. This mixture is later heated at 60°C for 10 min to produce niosomes. This method is known as the transmembrane pH gradient (inside acidic) drug uptake process [20, 27, 34]. Niosomes obtained by this method showed better entrapment efficiency and retention of drugs [35, 36]. Figure 4 shows the steps for the preparation of niosomes using this technique.

The emulsion method, which uses an oil-in-water emulsion prepared from an

organic solution of surfactant, cholesterol, and an aqueous solution of drug, is another technique for preparation of niosomes. The organic solvent is evaporated to obtain the final product [8, 27, 37]. By contrast, a mixture of lipids and surfactant is melted and injected into a heated aqueous phase containing the drug in the lipid injection method [27].

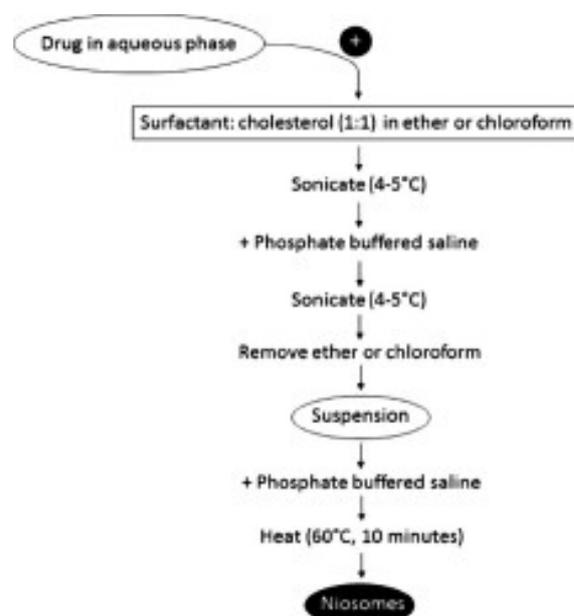


Figure 2: A Schematic diagram of preparation of niosomes using the reverse-phase evaporation technique

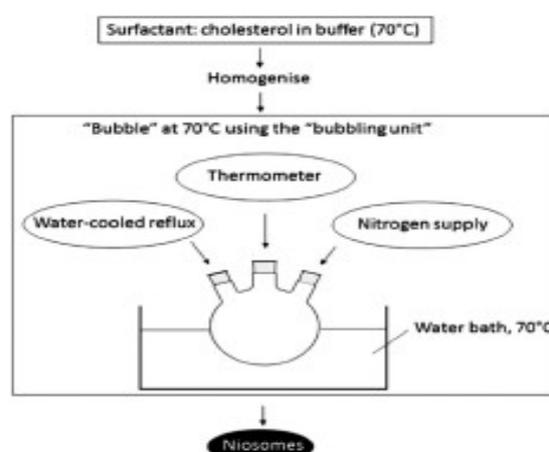


Figure 3: A Schematic diagram of preparation of niosomes using the bubble method

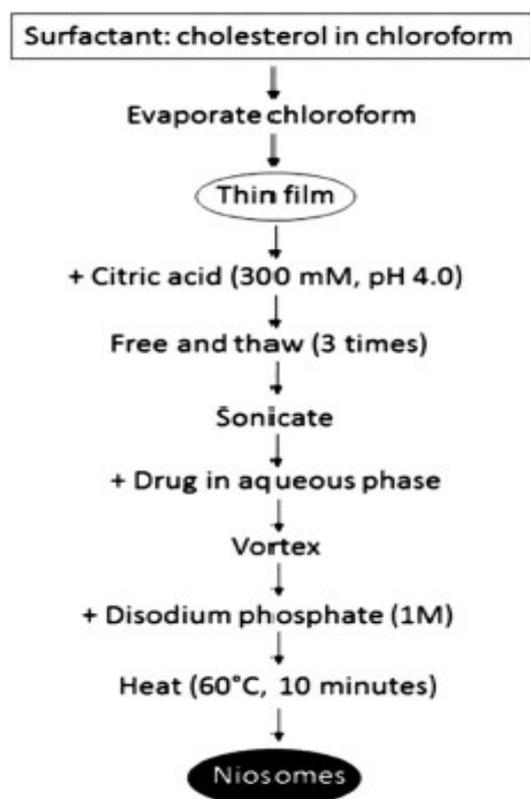


Figure 4: Schematic diagram of preparation of niosomes by transmembrane pH gradient (inside acidic) drug uptake process

Salient properties of niosomes

Surfactant-based niosomes are biodegradable, biocompatible, and nonimmunogenic [23]. They act as a drug depot in the body, whereby they release drugs in a controlled manner through their closed bilayer structure, resulting in a sustained release of the enclosed drug to the target site [38]. The therapeutic effects of drugs enclosed in niosomes are improved by reduced clearance and specific targeting [15]. Because of their hydrophilic, amphiphilic, and lipophilic nature, niosomes are able to accommodate a wide variety of drugs with a wide range of solubility [39]. Bioavailability of otherwise poorly soluble drugs may be improved, and the efficacy of topical

applications would be enhanced with the use of niosomes. Furthermore, labile and sensitive drugs may be delivered with greater ease as niosomes protect the encapsulated active pharmaceutical ingredients from deleterious conditions both inside and outside of the body [38].

The stability of niosomes is mainly affected by the type of surfactant, properties of the encapsulated drug, temperature of hydration, detergent, membrane-spanning lipids, polymerization of surfactant monomers, and charged molecules [20, 21, 27]. It is crucial for the surfactant used for the preparation of niosomes to consist of a hydrophilic head and a hydrophobic tail. Generally, surfactants possessing hydrophobic tails with an alkyl (chain length from C12 to C18), perfluoroalkyl, or steroidal groups are suitable for the preparation of niosomes [8]. Ester-type surfactants are less suitable because they are easily degraded by esterases *in vivo*, making them unstable in the body.

Comparatively, ether-type surfactants are a better choice. The size of niosomes increases proportionally with the increase in hydrophilic-lipophilic balance (HLB) of surfactants. If the HLB value falls between 4 and 8, niosome vesicle formation is considered relatively stable and optimal [8, 27, 40]. Addition of different types of additives together with the drug entrapped

in niosomes is able to improve niosome stability. For instance, addition of cholesterol provides rigidity and reduces leaking in niosomes [41].

Hydration temperature plays an important role in the assembly of surfactants into vesicles and the shape and size formation of niosomes. Ideally, the temperature chosen should be above the temperature of the gel-to-liquid phase transition [8, 27, 42]. Encapsulated drugs usually interact with the head group of the surfactant and thus indirectly influence the charge and rigidity of the bilayer structure of the niosome. Hydrophobic drugs generally improve the stability of niosomes, while hydrophilic drugs decrease their stability. Interestingly, amphiphilic drugs have no obvious effect on the niosomes' bilayer structure [27, 43].

Common problems related to preparation of niosomes include aggregation, fusion, and leaking, which are affected by the physicochemical properties of vesicles including their size, charge, lamellarity, elasticity, and thermodynamic phase. Preparation of proniosomes, which are a dried form of niosomes, might overcome the limitations mentioned because proniosomes hydrate immediately before use to yield an aqueous niosome dispersion [44]. Studies have found that proniosomes carried better therapeutic efficacy for anti-inflammatory drugs (flurbiprofen and

piroxicam) administered via a transdermal route [45, 46].

Niosomes are generally nontoxic to humans [27]. Researchers studied the toxic effect of surfactants in a topical niosome formulation on the proliferation of keratinocytes. The results show that ester was less toxic than ether because of enzymatic degradation of ester bonds. It had been proven that the physical form of niosomes (liquid crystal vs gel) did not influence their toxicity [47].

Niosomes: a superior drug-delivery system compared with liposomes

Niosomes possess a bilayer structure, which is similar to liposomes. However, the materials used to prepare niosomes confer better stability on them [20]. Niosomes are prepared from uncharged single chain surfactant and cholesterol. By contrast, liposomes are prepared from neutral or charged double chain phospholipids. The concentration of cholesterol is higher in liposomes than in niosomes. As a result, the drug entrapment efficiency of liposomes is less than that of niosomes. Niosomes are cost-effective for industrial manufacture and do not require special storage conditions, which are essential while manufacturing liposomes. The cost of liposome preparation is high because of the unstable chemical ingredients (phospholipids), which

undergo oxidative degradation. Liposomes therefore require special handling methods [27]. Niosomes possess a longer shelf life than liposomes [47]. They prolong the circulation of encapsulated drugs and increase metabolic stability in an emulsified form, whereas liposomes have limited shelf life because of rancidification of their lipid components [7, 47–50].

Current applications of niosomes

Drug-delivery systems using niosomes through transdermal, parenteral, and ophthalmic routes are well studied [27, 51, 52]. Niosomal delivery via transdermal routes is able to overcome the slow penetration rate of conventional transdermal approaches. The bioavailability and therapeutic efficacy of drugs such as diclofenac, flurbiprofen, and nimesulide increase by their incorporation into niosomal formulations. For ophthalmic drug delivery, chitosan-coated niosomal formulation of timolol maleate exhibits a greater effect in reducing intraocular pressure compared with marketed formulations, with less cardiovascular side effects [52]. Because of their many desirable properties, niosomal formulations have been used in many other therapeutic applications, as discussed in the following sections.

Leishmaniasis

Leishmaniasis is a parasitic disease

invading the liver and spleen transmitted through the bite of a female sandfly. Therapeutic efficacy of amarogentin (an antileishmanial, secoiridoid glycoside isolated from Indian medicinal plant *Swertia chirata*) was examined in an experimental model of leishmaniasis in hamster. The efficacy of amarogentin was compared using liposomes and niosomes as tools of delivery to the infected site. Amarogentin encapsulated in niosomes was more efficacious than that in liposomes at the same level of membrane microviscosity [25]. Toxicity studies including blood pathology, histology, and specific enzyme levels related to normal liver function showed that the niosomal formulation had no apparent toxic effect [53].

Acquired immune deficiency syndrome

Acquired immune deficiency syndrome (AIDS) is characterized by a severe damage to the immune system caused by the human immunodeficiency virus (HIV). Zidovudine (AZT), a pioneering anti-HIV compound, is approved for clinical use, either alone or in combination with other antiviral agents, for the treatment of AIDS and AIDS-related complex. However, there are some setbacks in AZT administration, including hematological toxicity, poor bioavailability, high first-pass metabolism, and short half-life [54]. A study revealed that niosomal AZT

formulation prolonged the drug half-life in rabbit serum [55]. In another study, niosomes manufactured with Tween 80 were able to encapsulate a high amount of AZT, and addition of dicetyl phosphate enhanced drug release for a pro-longed period (88.72% over 12 h). Changes in the micromolar ratios of nonionic surfactants with a constant ratio of cholesterol during the preparation of niosomes were associated with the changes in the encapsulation efficiency and controlled release of AZT [56].

Neoplasia

Common drawbacks of cancer chemotherapy are the side effects and low therapeutic efficacy. Doxorubicin, a broad-spectrum anthracycline used for antitumor activity, has shown a dose-dependent irreversible cardiotoxic effect [26]. However, niosomal delivery of this drug to mice bearing S-180 tumor showed increased life span and decreased proliferation of sarcoma. This might be the result of the high efficiency of niosomes in encapsulating the drug, causing a prolonged circulation in addition to alteration in drug metabolism [26, 57]. Another well-known anticancer drug, daunorubicin hydro-chloride, exhibited an enhanced antitumor efficacy in its niosomal encapsulated form when compared to the free drug. The niosomal formulation destroyed Dalton's ascitic

lymphoma cells effectively in a short time. Bleomycin, a potent anticancer drug, was found to be accumulated in higher levels at the tumor site when it was encapsulated in niosomes containing 47.5% cholesterol as compared with its free drug form [52].

Methotrexate is an established toxic synthetic antineoplastic agent used in chemotherapy, either alone or combined with other medications, to treat various types of cancers. Studies have shown that intravenous administration of methotrexate encapsulated in niosomes to S-180 tumor-bearing mice resulted in a total regression of tumor, slower drug clearance, and a higher plasma level of methotrexate [58]. Enhanced drug penetration was noted when 5-fluorouracil was formulated in bola-surfactant niosomes to treat skin cancer [59]. Despite enhanced antitumor activity, in some instances, encapsulation of the drug in niosomal vesicles reduces the toxicity in normal cells, as demonstrated in a study of preparation of niosome containing vincristine. Common side effects of the drug, such as neurological toxicity, diarrhea, and alopecia, were alleviated, while antitumor activity was increased in a mouse model of S-180 sarcoma following intravenous administration of the niosome-encapsulated vincristine [5].

Tocotrienol, first reported for its anticancer activity in the early 1990s [60],

was encapsulated in niosomes by Fu *et al.* using a film hydration method. The niosomal tocotrienol showed at least 2-fold enhancement of its cytotoxic effect in killing breast cancer cells, with 2.5-fold increase in the drug uptake in the cells. The antitumor effect of the formulation was also observed in female BALB/c nude mice implanted with breast cancer cells [61].

Curcumin is known to show multiple therapeutic applications including anticancer properties [62]. A novel niosome system composed of Span 80, Tween 80, and poloxamer 188 was shown to possess high encapsulating efficiency (92.3%) for curcumin. When niosomal curcumin was added to ovarian cancer A2780 cells, enhanced cytotoxic and apoptotic effects were noted compared with freely dispersed curcumin. This might be the result of the efficient controlled release of curcumin from niosomes [63]. Sharma *et al.* prepared niosomes with Tween 80 and cholesterol using a film hydration method. Two active molecules, curcumin and doxorubicin hydrochloride, were encapsulated into the prepared niosomes; curcumin was found accumulated in the shell, whereas doxorubicin hydrochloride accumulated in the inner aqueous core of the niosomes. Enhanced cytotoxicity toward cervical cancer cells (HeLa) was observed for the

dual-drug-loaded niosomes [64].

Artemisinin, isolated from the Chinese herb *Artemisia annua* commonly used in the treatment of fevers and chills [65], was also found to possess antitumor properties [66]. However, the use of artemisinin has some restrictions because it has low solubility in water and oil and poor bioavailability. Furthermore, it has short half-life in vivo [67]. To improve the efficacy of artemisinin, Dwivedi *et al.* encapsulated the compound in nanovesicular niosomes. Results show that the encapsulated artemisinin was cytotoxic toward melanoma cells with negligible toxicity toward normal skin cells, suggesting its potential as a useful therapeutic strategy for the treatment of melanoma [68].

Tamoxifen citrate is a hormone antagonist administered to breast cancer patients with estrogen receptor-positive tumors [69]. However, issues such as localization, efficiency, sustained delivery, and side effects of drugs are the major challenges for this type of cancer therapy. As such, Shaker *et al.* loaded the drug into niosomes and evaluated its cellular uptake, cytotoxicity, and efficiency in vivo. Niosomal tamoxifen showed enhanced cellular uptake and greater cytotoxicity against the MCF-7 breast cancer cell line and enhanced reduction in tumor volume in vivo [70].

Mitoxantrone has been used in chemotherapy for leukemia, lymphoma, breast and prostate cancers, and multiple sclerosis. However, administration of the drug is usually associated with severe systemic toxicity, particularly cardiotoxicity. Tila *et al.* formulated pH-sensitive, polymer-modified, and plasma-stable niosomes to carry the drug. Cytotoxicity of mitoxantrone niosomes was evaluated against human ovarian cancer (OVCAR-3), human breast cancer (MCF-7), and human umbilical vein endothelial cell lines. Mitoxantrone contained in the pH-sensitive niosomes showed higher cytotoxicity than conventional niosomes on the cancer cells but a lowered cytotoxic effect on the endothelial cell line. These findings indicate that the niosomal formulations may be useful in reducing the side effects of mitoxantrone [71].

Cisplatin, a widely used anticancer drug, acts by inducing apoptosis and necrosis. However, cisplatin usage is found to be associated with various unwarranted side effects such as nephro- and neurotoxicity [72]. Furthermore, development of drug resistance toward cisplatin in patients is a major concern in cancer treatment. Niosomal cisplatin prepared by reverse-phase evaporation technique showed a 1.5-fold increase in cytotoxic effect against BT-20 breast cancer cells compared with the unencapsulated drug

[73]. Anticancer effects of the niosomal formulations mentioned are summarized in **Table 1**.

Lung diseases

Inhalation therapy utilizing glucocorticosteroids such as beclomethasone dipropionate (BDP) in chronic obstructive pulmonary disease (COPD) is promising, but the common drawback of the medication is poor permeation through hydrophilic mucus to reach the glucocorticoid receptors of bronchial epithelial cells [74]. Niosomes developed from poly-sorbate 20 containing BDP are well suited as a drug-delivery system for COPD patients through pulmonary delivery. This is because of the advantages offered by the niosomes, such as high drug encapsulation efficiency, strong mucus permeation, and sustained delivery to the target site [75]. Thus, the use of niosomes overcame weaknesses of the drug and other conventional inhalation therapies. Niosomes may offer a better targeted-delivery system for patients with COPD as these nonionic vesicles remarkably increased the permeation rate of BDP through the mucosal membrane barrier. Clinical efficacy of an inhalation therapy is usually dependent on the aerodynamic size distribution of the aerosol and drug output from a nebulizer. Niosomal dispersion provides a better aerodynamic diameter than the commercial products'

dispersion. Under all conditions of nebulization, niosomes provide a higher efficacy, thus offering better targeting of corticosteroids in the treatment of COPD [74].

Niosomal encapsulation of isoniazid was found to effectively treat tuberculosis, with 62% of cellular uptake by macrophages. In addition, the niosomal formulation decreased the dose required and reduced the level of toxicity; these contributed to improved patient compliance. The additional advantages of the niosomal formulation are that it was site specific to where tuberculosis bacteria were harbored and it was able to maintain steady drug concentrations for up to 30 h [76]. Another study showed that intravenous and intraperitoneal administration of rifampicin encapsulated in niosomes prepared using surfactants of sorbitan ester class:cholesterol (50:50 percent mole fraction ratio) could be used for the treatment of tuberculosis [77]. Positive results were noted with rifampicin encapsulated in Span 85 (sorbitan trioleate)-based niosomes. The rifampicin was found accumulated in the lungs of mice, therefore offering possibility of improved antituberculosis therapy [8, 78]. Gentamycin sulfate used in the treatment of nosocomial pneumonia displays short half-life and has various side effects. Niosomal formulations may ensure that an efficient concentration of the drug is achieved in the lungs without

inducing systemic effects. Gentamycin sulfate in niosomes prepared with polyoxyethylene sorbitan esters showed a significantly higher accumulation in lungs than the plain drug, indicating that niosomes are an enhanced drug- delivery system for this therapy [79].

Inflammation

Niosomal formulations of diclofenac sodium, nimesulide, and flurbiprofen exhibit greater anti- inflammatory activity than the free drugs [52]. Niosomal formulations of diclofenac diethylammonium, aceclofenac, meloxicam, and lornoxicam used for topical application also show good anti-inflammatory activity because of the penetration of niosomes into the deeper layers of the skin [7, 80–82]. Additionally, mefenamic acid-loaded niosomes prepared by Kamboj *et al.* [83] demonstrated enhanced inhibition of inflammation *in vivo*. Serratiopeptidase is controversially used in the treatment of arthritis, fibrocystic breast disease, chronic bronchitis, and carpal tunnel syndrome to alleviate pain and inflammation. Orally administered serratiopeptidase has been reported to show systemic side effects. Therefore, a topical formulation of serratiopeptidase that potentially reduces adverse effects and increase local effects have been developed by Shinde and Kanojiya using niosomes. The results showed that the newly formulated serratiopeptidase niosomal gel had anti-

inflammatory activity comparable to that of diclofenac gel [84].

A number of compounds isolated from natural products have recently emerged as potential anti-inflammatory agents. Compounds isolated from *Glycyrrhiza glabra* L. and *Zingiber cassumunar* Roxb. are a few examples. Extracts of *G. glabra* are purported to be useful in the treatment of dermatitis, eczema, and psoriasis [85, 86]. The plant's active compound, ammonium glycyrrhizinate, showed strong anti-inflammatory effects in various models [87, 88]. When ammonium glycyrrhizinate was encapsulated in niosomes prepared by using Tween 85, Span 20, and cholesterol in various molar ratios, improved anti-inflammatory activities were observed in chemically induced skin erythema in mice and humans [89]. (E)-4-(3',4'-dimethoxyphenyl)but-3-en-1-ol (also known as compound D) is the active compound isolated from *Z. cassumunar*. Encapsulation of compound D in niosomes enhanced its chemical stability and skin permeation with anti-inflammatory effects comparable to commercial anti-inflammatory drugs when applied on the skin of mice [90]. *Z. cassumunar*-encapsulated niosomes were also effective for local subcutaneous inflammation when used in combination with therapeutic ultrasound [91].

Resveratrol is a polyphenolic compound found in grape skin, peanuts, and the roots of

Polygonum cuspidatum [92]. Topical application of resveratrol has shown to improve some types of skin conditions such as inflammation. However, the therapeutic potential of resveratrol is limited because of its poor bioavailability, low water solubility, chemical instability, and limited skin permeability [93, 94]. Recently, a resveratrol-loaded niosomal hydrogel system, which could enhance the permeation and deposition of resveratrol in skin, had been developed by Negi *et al.* Administration of this niosomal gel reduced edema with prolonged therapeutic action, as evaluated with a model of edema induced in rat paw by carrageenan injection [95].

Flurbiprofen is commonly used in the treatment of ocular inflammatory diseases [96]. However, challenges arise with the use of the ocular drugs, including limited ocular bioavailability because of nasolacrimal drainage, the corneal barrier, and unintentional absorption of the drugs to the systemic circulation [97]. As a result, not more than 5% of applied drugs can reach intraocular tissues [98]. Therefore, to enhance the ocular bioavailability of flurbiprofen, the drug was encapsulated in niosomes consisting of nonionic surfactant Span 60 using the thin-film hydration technique. The encapsulated flurbiprofen was found to rapidly reduce eye inflammation of New Zealand albino rabbits, with a higher ocular bioavailability than that

of a flurbiprofen solution [99].

Bacterial or fungal infections

Itraconazole is the drug of choice for treating fungal infections caused by *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, and *Coccidioides immitis*. It is used in the treatment of pseudallescheriasis, sporotrichosis, tinea corporis, tinea versicolor, and toenail onychomycosis. However, it has poor solubility and permeation that hinder its absorption through skin. Incorporation of the drug in niosomes enhanced its therapeutic efficacy, as evidenced by a study in which the itraconazole niosomes demonstrated greater antimycotic activity against *Candida albicans* than marketed formulations [100]. Another potentially antifungal drug called diallyl disulfide was found to be entrapped in niosomes prepared efficiently using Span 80. When the niosomal diallyl disulfide was administered to *C. albicans* infected mice, it cleared the fungal burden and increased the survival rate of the mice; the effect was better than the drug in free form [101]. Fluconazole, which is commonly available in parental and oral dosage forms, is used in the treatment of cutaneous candidiasis. However, the drug is well known for its adverse effects such as taste disturbances and gastrointestinal irritation. When the drug is given in an oral form, a high dose is usually required to reach therapeutic

concentrations. Therefore, a topical formulation of the drug was developed. Fluconazole loaded niosomal gels were formulated as a topical ocular drug-delivery system for corneal fungal infections. Fluconazole was incorporated into poloxamer or chitosan niosomal gel, and the antifungal effects of the 2 gels were compared. Fluconazole in the poloxamer gel showed a better effect than it did in the chitosan gel [102]. In another study, miconazole loaded in proniosomal vesicles was proven to be effective against *Trichophyton rubrum* in the treatment of tinea infections [103].

Nisin is an antimicrobial agent used in food and pharmaceutical applications [104]. However, its effectiveness is limited because of its inaccessibility to an inner membrane of bacteria. Hence, ethylene-diaminetetraacetic acid (EDTA) is used to improve the efficacy of nisin [105]. Niosomes encapsulating both nisin and EDTA were evaluated for their anti-bacterial activity. The encapsulated form of nisin and EDTA showed a better and longer-lasting effect in inhibiting *Staphylococcus aureus* than their free forms [106]. Gallidermin, an antibiotic that has effects similar to erythromycin or fusidic acid, is effective against endocarditis, abscesses, skin infections, and acne [107]. When gallidermin is loaded in anionic niosomes and incorporated in gel, it accumulated in the skin with no risk of a

systemic effect and displayed better antibacterial effects, particularly against *Propionibacterium acnes* and *S. aureus* [108]. Propolis is considered to have broad-spectrum antimicrobial properties [109]. Its antimicrobial effect was enhanced when it was incorporated into niosomes that were prepared with varying concentrations of Span 60 and cholesterol. This is because niosomes are able to interact with the bacterial cell envelope, thereby facilitating the diffusion of constituents of propolis across the cell wall [110].

Gatifloxacin is widely used for ocular infections. Patients are required to apply the medicine several times a day, and this greatly inconveniences the patients. Therefore, Zubairu et al. designed and formulated a novel delivery system for gatifloxacin that could help in reducing the dosing frequency. A chitosan-coated niosomal formulation of gatifloxacin developed by researchers showed a longer retention time on the eyes, suggesting the potential use of the drug in the form of transcorneal delivery [111]. Another group of scientists developed chitosan gel-embedded moxifloxacin niosomes, and the drug formulation was used for topical microbial infections [112].

Pseudomonas aeruginosa causes highly resistant infections through biofilm formation, which inhibits the entry of antibiotics [113]. Synergistic combination

therapy is believed to be more effective in the treatment of infections related to biofilms. Hence, a niosomal drug formulation consisting of bismuth-ethanedithiol and tobramycin was developed and its antibacterial effect was tested through the inhibition of biofilm formation and reduction of N-acyl homoserine lactone in *P. aeruginosa*. Results showed that the formulation may be useful in the treatment of infections caused by this pathogen [114]. Antibacterial and antifungal effects of the niosomal drugs/compounds mentioned are summarized in **Table 2**.

Table 1. Drugs/compounds encapsulated in niosomes and their anticancer effects

Drug/compound(s)	Effects	Reference(s)
Doxorubicin	Decreased proliferation of sarcoma cells	[26, 57]
Daunorubicin hydrochloride	Destroyed Dalton's ascitic lymphoma cells	[52]
Bleomycin	Accumulated in higher levels at the tumor site	[52]
Methotrexate	Enhanced antitumor activity against sarcoma	[58]
5-Fluorouracil	Enhanced drug penetration in the treatment of skin cancer	[59]
Vincristine	Enhanced antitumor activity against sarcoma	[5]
Tocotrienol	Enhanced cytotoxicity toward breast cancer cells	[61]
Curcumin	Enhanced cytotoxic and apoptotic effects toward ovarian cancer cells	[63]
Curcumin and doxorubicin hydrochloride	Enhanced cytotoxicity toward cervical cancer cells	[64]
Artemisinin	Cytotoxic toward melanoma cells	[68]
Tamoxifen citrate	Greater cytotoxicity against breast cancer cell line	[70]
Mitoxantrone	Greater cytotoxicity against human ovarian cancer and breast cancer cell lines	[71]
Cisplatin	Enhanced cytotoxicity toward breast cancer cells	[73]

Table 2. Drugs/compounds encapsulated in niosomes and their antibacterial or antifungal effects

Drug/compound(s)	Effects compared with unencapsulated form	Refer
Itraconazole	Greater activity against <i>Candida albicans</i>	
Diallyl disulfide	Greater activity against <i>C. albicans</i>	
Fluconazole	Effective against corneal fungal infections	
Miconazole	Effective against <i>Trichophyton rubrum</i>	
Nisin and ethylenediaminetetraacetic acid	Better effect in inhibiting <i>Staphylococcus aureus</i>	
Gallidermin	Better antibacterial effects against <i>Propionibacterium acnes</i> and <i>S. aureus</i>	
Propolis	Enhanced antimicrobial effect	
Gatifloxacin	Effective against ocular infections	
Moxifloxacin	Used for topical microbial infections	
Bismuth-ethanedithiol and tobramycin	Effective against <i>Pseudomonas aeruginosa</i>	

Niosomal formulations have been used extensively in many other applications such as transdermal delivery. For example, 8-methoxypsoralen, a compound used in psoralen ultraviolet. A therapy [115], had been formulated into niosomal vesicles and delivered topically to increase its local efficacy and safety [116]. Another group of investigators has attempted to develop a niosomal gel formulation with acyclovir that has a superior topical bioavailability [117]. Acyclovir is used in the treatment of herpes simplex, varicella zoster, and herpes zoster viral infections. Its usual route of oral administration is plagued by poor bioavailability and short elimination half-life [118]. Usual topical delivery is limited by the poor intrinsic permeation of acyclovir into the basal epidermis. A goal of topical delivery is that the drug is transported through the stratum corneum, thereby effectively reaching the target tissue. The niosomal gel developed by Jacob *et al.* [117] demonstrated successful delivery of acyclovir through topical administration.

Niosomes could also potentially serve as gene delivery system. Niosomes prepared by using cationic lipid N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride and the nonionic surfactant polysorbate 60, with or without lycopene, were used to

encapsulate promoter of cytomegalovirus-enhanced green fluorescent protein (pCMS-EGFP)-based plasmids. The niosomes generated were then used in the transfection of ARPE-19 human retinal pigment epithelial cells. The higher transfection efficiency obtained indicates the potential use of this gene delivery system for various inherited retinal diseases [119]. Opanasopit *et al.* also investigated the use of niosomes using this approach. They reported that cationic niosomes composed of Span 20, cholesterol, and spermine-based cationic lipids encapsulating pDNA encoding EGFP contributed to a high transfection efficiency of HeLa human cervical cells [120].

Other uses of niosomes include the treatment of glaucoma using dorzolamide niosomes [121], specific niosomal drug-delivery systems that target the liver [122] and induction of angiogenesis using growth factor-loaded nano-niosomal gel formulations [123]. Moghassemi *et al.* [124] formulated bovine serum albumin-loaded niosomes that have potential use in pharmaceutical and cosmetic applications.

CONCLUSIONS

Niosomes, a nonionic surfactant vesicular system, is a novel and efficient approach to drug delivery. With the incorporation of appropriate nonionic surfactant and cholesterol in the vesicular membrane, a

wide range of drugs can be encapsulated into niosomes. In addition, niosomes possess enhanced stability and reduced toxic drug effects, with sustained release of the encapsulated drug. Furthermore, no special conditions are required for handling and storage of niosomes, compared with other drug-delivery systems such as liposomes. Appropriate modifications of niosomes, resulting in structures such as proniosomes, enable them to be used in special routes of administration. In summary, niosomes represent a highly effective tool for drug delivery in the therapeutic regime of numerous diseases and have the potential to provide more efficacious treatment than conventional drug-delivery platforms.

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