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**Review Article**

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# Niosome: A Mini Review on Its Structure, Properties, Methods of Preparation and Medical Applications

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**ABSTRACT**

*Drug delivery system in administration of pharmaceutical compounds enabled localisation of drug to the diseased site. There are different types of drug delivery system utilising immunoglobulin, serum protein, synthetic polymer, liposome, microsphere and others. Vesicular system of niosome with bilayer structure assembled by non-ionic surfactants is able to enhance bioavailability of a drug to a predetermined area for a period of time. The amphiphillic nature of noisome promotes its efficiency in encapsulating lipophilic or hydrophilic drugs. Other additives such as cholesterol can be used to maintain the rigidity of the niosome's structure. This review describes the basic aspects of noisome include its structural components, preparation methods, limitations and current applications in various diseases.*

**Keywords:** Niosome; Drug delivery system

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## INTRODUCTION

The concept of drug delivery system refers to a process of administrating pharmaceutical compound in a predetermined rate to achieve therapeutic effect in human or animals at diseased site and at the same time reducing concentration of the medication in the remaining tissues. Localised drug action enhances efficacy of drug and reduces systemic toxic effect to tissues [1]. Paul Ehrlich proposed an idea of targeted delivery directly to the diseased cell without damaging healthy cells in 1909; and this has been known as "magic bullet" [2]. Since then, a number of drug carrier systems emerged which include immunoglobulin, serum protein, synthetic polymer, liposome, microsphere and niosome [1]. Among all, liposome and niosome are well documented vesicular drug delivery systems [3-6]. In general, vesicular system is a type of drug delivery system that enables effective bioavailability of drug by providing therapeutic effect in a controlled manner for prolong period of time [7-10]. The vesicle consists of bilayer of amphiphilic molecules that surrounding an aqueous compartment [8, 11, 12]. To be specific, niosome is a vesicle made of non-ionic surfactant (for example alkyl ester and alkyl ether) and cholesterol that acts as a carrier for amphiphilic and lipophilic drugs [7, 8, 13, 14]. Niosomes improve therapeutic performance of encapsulated drug molecule by protecting the drug from biological environment, thus resulting in delayed clearance from circulation [15].

Specific drug delivery system aims to increase drug selectivity and therapeutic index and in the meantime reduce dose of drug required. However, development of new drug is time consuming and expensive. Estimated cost of $120 million is needed in bringing new drugs through discovery, clinical testing, development and regulatory approval [16-19]. Nevertheless, effective drug delivery system to carry drug to a specific site is vital. Thus, this review provides details of niosome as a better drug delivery system in the aspect of its structure, preparation, properties and applications.

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## NIOSOME

### Structure of noisome

Niosomes have spherical shape and consist of lamellar structure (unilamellar or multilamellar) which is microscopic in size. The bilayer is formed by non-ionic surfactant, with or without cholesterol and charge inducer [20, 21]. Different types of surfactants at the different combinations in different molar ratios can be used to form niosomes [22]. Examples include alkyl ethers, alkyl glyceryl ethers, sorbitan fatty acid esters and polyoxyethylene fatty acid esters [7]. Addition of cholesterol maintains rigidity of the bilayer structure, hence resulting in a less leaky form of noisome. Meanwhile, charge inducers provide charge to the vesicles and increases the vesicles' size, hence increases the drug entrapment efficiency. Dicetyl phosphate, dihexadecyl phosphate and lipoamine acid are negative charge inducers while sterylamine and cetyl pyridinium chloride are positive charge inducers. They help in stabilisation of the vesicles [23-26]. Non-ionic surfactants in niosome tend to orient themselves in such way that hydrophilic end faces outward toward aqueous phase whereas hydrophobic end faces inward to each other to form a closed bilayer structure which encloses aqueous solution of solutes [20]. As a result, the closed bilayer structure of niosome has both inner and outer surfaces to be hydrophilic with sandwiched lipophilic area in between [8,26]. To form the closed bilayer structure, energy like heat or physical agitation is needed. Various forces inside the vesicle were found to have an important role in maintaining the vesicular structure, for example, Van der Waals and repulsive forces that are existed among the surfactant molecules. In order to modify the property of niosome produced, varying the vesicle's components (including type, composition and concentration), size, surface charge or volume could be considered [20,21,27].
Niosomes can be categorised into three groups based on their vesicle size. They are small unilamellar vesicles (SUV, size = 0.025-0.05 μm), multilamellar vesicles (MLV, size > 0.05 μm), and large unilamellar vesicles (LUV, size > 0.10 μm) [27].

### Methods of preparation

Preparation of niosome is started with the hydration of surfactant/lipid mixture at elevated temperature followed by optional size reduction in order to obtain a colloidal suspension [28]. There are several standard methods which are well studied and reviewed in the preparation of niosomes. Ether injection, hand shaking, sonication and microfluidisation methods are a few of the examples [7, 27, 29]. Afterward, un-entrapped drug is separated from the entrapped drug by centrifugation, gel filtration or dialysis [28].
Production of niosome by ether injection method is started by dissolving surfactant in diethyl ether. The solution is then injected through 14-gauge needle into an aqueous solution of drug maintained at 60°C. Subsequently, single layer vesicles with diameter ranged from 50 to 1000 nm are formed due to the vaporisation of ether [20]. However, a small amount of ether that is difficult to be removed is frequently present in the niosomal suspension [27]. In hand shaking method, which is also known as thin film hydration technique, surfactant and cholesterol are dissolved in a volatile organic solvent and transferred to a rotary evaporator. After the evaporation, a thin layer of solid mixture is deposited on the wall of the flask. The dried layer is then hydrated with aqueous phase containing drug. The process can be carried out at room temperature with gentle agitation [15, 27]. Niosome can also be produced through sonication of mixture of surfactant, cholesterol and aqueous phase containing drug at 60°C for 3 minutes. The vesicles produced are usually small and uniform in size [15, 27]. Micro fluidisation is another better and reproducible technique used to prepare vesicles which are uniform and smaller in size. Operationally, two fluidised streams move forward through precisely defined micro channel, and these 2 streams interact with each other at an ultra-high velocity [20,27,30].
There are others methods available for the preparation of niosomes. 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. The suspension produced is subsequently extruded through polycarbonate membranes, which are placed in series for up to 8 passages [20, 27, 31]. Reverse phase evaporation technique uses a mixture containing surfactant and cholesterol in 1 to 1 ratio, as well as ether and chloroform. An aqueous phase containing drug is added to the mixture and sonication at 4-5°C is carried out. After adding a small amount of phosphate buffered saline, the mixture is continued to be sonicated. The organic solvent is removed at 40°C under low pressure and the remaining suspension is diluted with phosphate buffered saline. After heating the mixture at 60°C for 10 minutes, the final product, niosome is obtained [20, 27, 32].
Without using the organic solvent, niosomes can be produced through the "bubble" method. A "bubbling" unit consists of a round-bottomed flask with three necks is positioned in water bath, and water-cooled reflux and thermometer are positioned in the first and second neck respectively while nitrogen is supplied through the third neck. Surfactant and cholesterol that are mixed at 70°C in a buffer is homogenised and "bubbled" at 70°C using the "bubbling" unit [20,33].
In another technique of niosome preparation, 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 undergone 3 times of repeated freeze-thaw cycles. After sonication, aqueous solution containing drug is added to the

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suspension and vortexed. Disodium phosphate (1M) is added to the mixture to increase the pH to 7.0-7.2. This mixture is later heated at 60°C for 10 minutes to produce niosomes. This method is known as "tans-membrane pH gradient (inside acidic) drug uptake process" [20, 27, 34]. Niosomes obtained by this method showed better entrapment efficiency and retention of drug [35, 36]. Emulsion method which uses oil in water emulsion prepared from an organic solution of surfactant, cholesterol and an aqueous solution of drug is another preferable technique for niosome preparation. The organic solvent is evaporated to get the final product [8, 27, 37]. On the other hand, mixture of lipids and surfactant is melted and injected into a heated aqueous phase containing drug in the lipid injection method [27].

**Salient properties of niosome**

Surfactant-based niosome is biodegradable, biocompatible and non-immunogenic [23]. It acts as a drug depot in human body where it releases drug in a controlled manner through its closed bilayer structure, resulting in sustained release of enclosed drug to the target site [38]. Therapeutic effects of drug enclosed in niosome are improved by reduced clearance rate and specific targeting [15]. Due to the hydrophilic, amphiphilic and lipophilic nature, niosome is able to accommodate large number of drugs with a wide range of solubility [39]. Bioavailability of poorly soluble drug can be improved and topical application can be enhanced with the use of niosomes. Furthermore, labile and sensitive drugs can be delivered easily as niosome protects the enclosed active pharmaceutical ingredient from deleterious conditions both inside and outside of body [38].

Stability of niosome is mainly affected by the type of surfactant, properties of encapsulated drug, temperature of hydration, detergent, membrane spanning lipids, polymerisation of surfactant monomers and charged molecules [20, 21, 27]. It is important that surfactant used for preparation of niosome consists of hydrophilic head and hydrophobic tail. Generally, surfactants that have hydrophobic tail with alkyl (chain length from $C_{12}$ to $C_{18}$), perfluoroalkyl or steroidal group is suitable for the preparation of niosome [8]. Ester type surfactants are less suitable because they are degraded by esterase easily *in vivo*, making it unstable in the body. Comparatively, ether type surfactants are 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, 41]. Addition of different types of additive together with the drug entrapped in niosome is able to improve the stability of noisome. For instance, addition of cholesterol provides rigidity and reduces leaking to niosome [40]. Hydration temperature plays an important role in the assembly of surfactants into vesicles as well as shape and size formation of niosomes. Ideally, temperature chosen should be above the temperature of the gel to liquid phase transition [8, 27, 42]. Encapsulated drug usually interacts with the head group of the surfactant and thus indirectly influences the charge and rigidity of the bilayer structure of noisome. Hydrophobic drugs generally improve the stability of niosomes while hydrophobic drugs decrease the stability. Interestingly, amphiphilic drugs have no obvious effect on the niosomes' bilayer structure [27, 43].

Niosomes have some common problems such as aggregation, fusion and leaking that are affected by the physiochemical properties of vesicles including size, charge, lamellarity, elasticity and thermodynamic phase. Preparation of proniosome which is a dried form of niosome might be able to overcome the limitations mentioned because it hydrated immediately before use to yield aqueous niosome dispersion [44]. Studies have found that proniosome carried better therapeutic efficacy for anti-inflammatory drugs (flurbiprofen and piroxicam) administrated via transdermal route [45, 46].

Niosomes are generally non-toxic to human body [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 due to enzymatic degradation of ester bonds. Besides, it had been proven that physical form of niosome (liquid crystal *vs* gel) did not influence the toxicity of niosome [47].

**Niosome as a better drug delivery system compared to liposome**

Niosomes possess bilayer structure which is similar with liposomes. However, the materials used to prepare niosomes make them more stable than liposomes [20]. Niosomes are prepared from uncharged single chain surfactant and cholesterol. On the other hand, liposomes are prepared from neutral or charged double chain phospholipid. The concentration of cholesterol is higher in the liposomes compared with niosomes. As a result, drug entrapment efficiency of liposomes is lesser than niosomes. Niosomes are cost effective for industrial manufacture and do not require special storage condition whereas the cost of liposomes preparation is high due to the unstable chemical ingredient (phospholipid) which undergoes oxidative degradation. Besides, liposomes require special storage condition and method of handling [27]. Niosomes possess longer shelf life than liposomes [47]. They prolong the circulation of entrapped drug and even increase metabolic stability in emulsified form whereas liposomes have limited shelf life due to rancidification of lipid [7, 47-50].

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## CURRENT APPLICATIONS OF NOISOME

Drug delivery system using niosome through transdermal, parenteral and ophthalmic routes is well studied [27, 51,52]. Niosomal formulation via transdermal route is able to overcome slow penetration rate of the conventional transdermal approach. The bioavailability and therapeutic efficacy of drugs like diclofenac, flurbiprofen and nimesulide increased with niosomal formulation. For ophthalmic drug delivery, chitosan-coated niosomal formulation of timolol maleate exhibited greater effect in reducing intraocular pressure compared to the marketed formulation with less cardiovascular side effects [52]. Besides, niosomal formulations have been used in many other therapeutic applications, as listed in the following section.

**Leishmaniasis**

Leishmaniasis is a parasitic disease invading liver and spleen that spread through the bite of female sandfly. Therapeutic efficacy of amarogentin (anti-leishmanial, a secoiridoid glycosides isolated from Indian medicinal plant *Swertiachirata*) was examined in an experimental hamster model infected with leishamaniasis. The efficacy of amarogentin was compared using liposome and niosome as tool of delivery to the infected site. Results show that amarogentin encapsulated in niosome was more efficacious than liposome at the same membrane micro-viscosity level [25]. Besides, toxicity studies including blood pathology, histological staining of tissue and specific enzyme levels related to normal liver function show that the niosomal formulation had no toxic effect [53].

**Acquired immune deficiency syndrome (AIDS)**

AIDS is characterised by severely damaged immune system that caused by human immunodeficiency virus (HIV). Zidovudine (AZT), a pioneering anti-HIV compound, is approved for clinical use, either used alone or in combination with other anti-viral agents, for the treatment of AIDS and AIDS-related complex. However, there are some disadvantages of prescribing the drug including haematological toxicity, poor bioavailability, high first-pass metabolism and short half-life [55]. Previous study revealed that niosomal AZT formulation prolonged drug half-life in rabbit serum [56]. In another study, the niosome made with Tween 80 was able to entrap high amount of AZT drug and addition of dicetylphosphate enhanced the drug release for a prolong period of time (88.72 % over 12 hours). Changes in the micromolar ratios of nonionic surfactants with a constant ratio of cholesterol during the preparation of niosome were associated with the changes of the entrapment efficiency and controlled release of AZT [54].

**Neoplasia**

Common drawbacks of cancer chemotherapy are the side effects and low therapeutic efficacy. Doxorubicin, a broad spectrum anthracyclic medicine used for anti-tumour activity has shown a dose-dependent irreversible cardio toxic effect [26]. However, niosomal delivery of this drug to mice bearing S-180 tumour showed increased life-span and decreased proliferation of sarcoma. This might be due to the high efficiency of niosome in entrapping the drug that caused a prolonged drug circulation in addition to the alteration of drug metabolism [26, 57]. Another famous anticancer drug, daunorubicin hydrochloride exhibited an enhanced antitumor efficacy in its niosomal encapsulated form when compared to the free drug. The niosomal formulation destroyed the Dalton's ascitic lymphoma cells effectively in a short duration. Bleomycin, a potent anti-cancer drug, was found accumulated in higher level at the tumour site when it was encapsulated in niosome containing 47.5% cholesterol, as compared to its free drug form [52].

Methotrexate is a well-known toxic synthetic anti-neoplastic agent used in chemotherapy either alone or in combination with other medications to treat various types of cancer. Studies have shown intravenous administration of methotrexate entrapped in niosome to S-180 tumour bearing mice resulted in a total regression of tumour, slower clearance rate and higher plasma level [58]. In another report, enhanced drug penetration was noted when 5-fluorouracil was formulated in bola surfactant niosomes for the treatment of skin cancer [59]. Despite the enhanced anti-tumour activity, in some instances, encapsulation of drug in niosomal vesicle reduces the toxicity to normal cells, as demonstrated in a study of preparation of noisome containing vincristine. It decreased common side effects of the drug such as neurological toxicity, diarrhoea and alopecia and increased anti-tumour activity in S-180 sarcoma mouse model following intravenous administration [60].

Tocotrienol, a compound which was first reported for its anti-cancer activity in the early 1990s [61], was encapsulated in niosomes prepared using film hydration method by Fu *et al*. (2016). The niosomal tocotrienol showed at least 2-fold enhancement of cytotoxic effect in killing breast cancer cells, with 2.5-fold increment of the drug uptake in the cells. The good anti-tumour effects of the formulation were also observed in female BALB/c nude mice implanted with breast cancer cells [62]. Curcumin has been known to have multiple therapeutic applications including anticancer [63]. A novel niosome system composed of Span 80, Tween 80 and poloxamer 188 has shown to possess high entrapment efficiency (92.3%) of curcumin. When the niosomal curcumin was added to ovarian cancer A2780 cells, enhanced cytotoxic and apoptotic effects were noted

compared to the free dispersed curcumin. This might be due to the efficient controlled release of curcumin from niosome [64]. Sharma *et al.* (2015) prepared niosomes by using Tween 80 and cholesterol through film hydration method. Two active molecules, curcumin and doxorubicin hydrochloride were encapsulated into the niosomes prepared, and the curcumin was found accumulated in the shell whereas doxorubicin hydrochloride accumulated in the inner aqueous core of the niosome. Enhanced cytotoxicity towards cervical cancer cells (HeLa) was observed for the dual-drug loaded niosomes [65]. Artemisinin isolated from Chinese herb *Artemisia annua* which is commonly used in the treatment of fevers and chills [66], was found to possess antitumour properties [67-70]. However, the use of artemisinin has some restrictions because it has low solubility in water and oil and showing poor bioavailability. Furthermore, it has short half-life *in vivo* [71, 72]. To improve the efficacy of artemisinin, Dwivedi *et al*. (2015) encapsulated the compound in nano-vesicular niosomes. Results show that the encapsulated artemisinin was cytotoxic towards melanoma cells with negligible toxicity towards normal skin cells, suggesting its potential as a useful therapeutic strategy for the treatment of melanoma [73].

Tamoxifen citrate (TMC) is a hormone antagonist given to breast cancer patients that are estrogen receptor positive [74]. However, issues such as localisation, efficiency, sustained delivery and side effects of drug are the major challenges for this type of cancer therapy. As such, Shaker *et al*. (2015) loaded the drug into niosome and evaluated its cellular uptake, cytotoxicity and efficiency *in vivo*. The niosomal TMC showed enhanced cellular uptake, greater cytotoxicity against MCF-7 breast cancer cell line and enhanced tumour volume reduction in *in vivo* experiment [75]. Mitoxantrone has been used in chemotherapy for leukaemia, lymphoma, breast and prostate cancer and multiple sclerosis. However, administration of the drug is usually associated with severe systemic toxicity, particularly cardiotoxicity. Hence, Tila *et al*. (2015) has formulated the pH-sensitive, polymer modified and plasma stable niosomes to carry the drug. Cytotoxicity of the mitoxantrone niosomes was evaluated against human ovarian cancer (OVCAR-3), human breast cancer (MCF-7) and human umbilical vein endothelial (HUVEC) cell lines. As a result, drug contained in the pH-sensitive niosome showed higher cytotoxicity than the conventional niosome on the cancer cells, but lower cytotoxic effect on the HUVEC cell line. These findings indicate that the niosomal formulation might help reducing the side effects of mitoxantrone [76].

**Lung diseases**

Inhalation therapy utilising glucocorticosteroid such as beclometasone 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 receptor of bronchial epithelial cells [77]. Previous study has shown that niosome made of polysorbate 20 that contained BDP is well suited as a drug delivery system for COPD patients through pulmonary delivery. This is due to the advantages offered by the noisome such as high drug entrapment efficiency, strong mucus permeation and sustained delivery to target site [78]. Thus, the use of niosome has overcome the weakness of the drug or other conventional inhalation therapies. Niosome hence offers a better target delivery system for COPD patients as this non-ionic vesicle 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 aerosol and drug output from nebuliser. Niosomal dispersion in fact provides better aerodynamic diameter in comparison to the commercial products. In all conditions of nebulisation, niosome provides higher efficacy thus offering a better targeting of corticosteroid in the treatment of COPD [77].

Niosomal entrapment of isoniazid was found to effectively treat tuberculosis, with 61.80% of cellular uptake by macrophages. In addition, the niosomal formulation showed to decrease the dose required and reduce level of toxicity; and these contributed to the improved patient compliance. The additional advantages of niosomal formulation are that it was site specific where tuberculosis bacteria were harboured; and it was able to maintain steady drug concentration for up to 30 hours [79]. Another study showed that intraveneous and intraperitoneal administrations of rifampicin encapsulated with niosome prepared using surfactants of sorbitan ester class:cholesterol (50:50 percent mole fraction ratio) could be used for the treatment of tuberculosis [80]. Positive results were also noted with rifampicin encapsulated in Span 85 (sorbitan tri-oleate)-based noisome. The drug was found accumulated in the lungs of mice, therefore offering possibility of improved anti-tuberculosis therapy [8, 81].

Gentamycin sulphate used in the treatment of nosocomial pneumonia displays short half-life and has various side effects. Hence, niosomal formulation to ensure an efficient concentration of the drug is achieved in the lungs without inducing systemic effect is highly in demand. Gentamycin sulphate in niosomes prepared with polyoxyethylene sorbitan esters showed significantly higher accumulation in lungs as compared with the plain drug, indicating niosomes are better drug delivery system for the treatment [82].

**Inflammation**

Niosomal formulations of diclofenac sodium, nimesulide and flurbiprofen exhibit greater anti-inflammation activity as compared to the free drug [52]. Niosomal formulations of diclofenac diethylammonium, aceclofenac,

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meloxicam and lornoxicam that used for topical application also show good anti-inflammatory activity due to penetration of niosomes into the deeper layers of the skin [7, 83-86]. Mefenamic acid-loaded niosomes prepared by Kamboj *et al.* (2013) also showed good inhibition of inflammation in *in vivo* model [87].

Serratiopeptidase (SRP) is widely used in the treatment of arthritis, fibrocystic breast disease, chronic bronchitis and carpal tunnel syndrome; basically alleviating pain and inflammation among patients. However, orally administered SRP has been reported to show systemic side effects. Therefore, topical formulation of SRP that might reduce the side effects and increase local effects has been developed by Shinde and Kanojiya (2014) using niosomes. Results showed that the newly formulated SRP niosomal gel had a comparable anti-inflammatory activity to that of dicolfenac gel [88].

A number of compounds isolated from natural products have emerged as potential anti-inflammatory agents nowadays. Compounds isolated from *Glycyrrhiza glabra* L. and *Zingiber cassumunar* Roxb. are a few to be listed. Extracts of *G. glabra* are useful in the treatment of dermatitis, eczema, and psoriasis [89, 90]. The plant's active compound, ammonium glycyrrhizinate showed great anti-inflammatory effects in various experimental models [91-93]. The compound, when encapsulated in niosomes prepared by using Tween 85, Span 20 and cholesterol in different molar ratios, showed improved anti-inflammatory activities as observed in chemically induced skin erythema in mice and humans [94]. (E)-4-(3',4'-dimethoxyphenyl)but-3-en-1-ol (or known as compound D) is the active compound isolated from *Z. cassumunar*. Encapsulation of the compound in niosomes enhanced its chemical stability and skin permeation with comparable anti-inflammatory effects to the commercialised anti-inflammatory drugs when applied on the skin of mice [95].

**Bacterial or fungal infections**

Itraconazole is a drug of choice for treating fungal infections caused by *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Paracoccidioides brasiliensis* and *Coccidioides immitis*. It is often used in the treatment of pseudallescheriasis, sporotrichosis, tinea corporis, tinea versicolor and toenail onychomycosis. However, it has low solubility and low permeation that hinders its absorption through skin. Incorporation of the drug in niosomes enhanced its therapeutic efficacy, as evidenced by a scientific research in which the itraconazole niosome had greater antimycotic activity against *Candida albicans* than marketed formulations [96]. Another potential anti-fungal drug, diallyl disulfide (DADS) was found to be entrapped in niosomes prepared using Span 80 efficiently. When the niosomal DADS was administered to *C. albicans* infected animals, it cleared the fungal burden and increased the animals' survival rate; and the effect was better than the drug in free from [97]. Fluconazole (FLZ), which is commonly available as 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 oral form, high dose is usually required to reach the therapeutic concentration. Hence, topical formulation of the drug is developed recently. For example, FLZ-loaded niosomal gels were formulated as a topical ocular drug delivery system for corneal fungal infections. FLZ was incorporated into poloxamer or chitosan niosomal gel and the anti-fungal effects of the two gels were compared. FLZ in poloxamer gel showed better effect than the chitosan gel [98]. In another study, miconazole loaded in proniosomal vesicles was proven to be effective against *Trichophyton rubrum* in the treatment of tinea infections [99].

Nisin is an antimicrobial agent used in food and pharmaceutical applications [100]. However, its effectiveness is limited due to its inaccessibility to an inner membrane of bacteria. Hence, ethylenediaminetetraacetic acid (EDTA) is used to improve the efficacy of nisin [101-103]. Niosomes encapsulating both nisin and EDTA were evaluated for their antibacterial activity in a study. The encapsulated form of nisin and EDTA showed better and longer-lasting effect in inhibiting *Staphylococcus aureus* as compared to their free forms [104]. Gallidermin (Gdm), an antibiotic that has similar effects as erythromycin or fusidin, is effective against endocarditis, abscesses, skin infections and human acne disease [105]. When Gdm is loaded in anionic niosomes and incorporated in gel, it accumulated in skin with no risk of systemic effect and displayed better anti-bacterial effects, particularly against *Propionibacterium acnes* and *S. aureus* [106]. Propolis has broad-spectrum antimicrobial properties [107-114]. 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 propolis constituents across the cell wall [115].

Gatifloxacin is widely used for ocular infections. Patients are required to apply the medicine several times in a day and this is greatly inconvenience for the patients. Hence, Zubairu *et al.* (2015) designed and formulated a novel delivery system of the drug that could help in reducing the dosing frequency. A chitosan-coated niosomal formulation of gatifloxain developed by the researchers showed a longer retention time on eyes, suggesting the potential use of the drug in the form of transcorneal delivery [116]. Another group of scientists developed chitosan gel-embedded moxifloxacin niosomes; and the drug formulation was used for topical microbial infections [117].

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## CONCLUSION

Niosome, the nonionic surfactant vesicular system is a novel and efficient approach for drug delivery system. With the incorporation of appropriate non-ionic surfactant and cholesterol in the vesicular membrane, wide range of drugs can be entrapped into niosomes, making it a novel delivery system. In addition, niosome possesses higher stability and reduces toxic effect with sustained release of entrapped drug. Furthermore, no special condition is required for handling and storage of noisome, in comparison with other drug delivery systems. Proper modification of noisome, such as proniosome, enables it to be used in special route of administration. In short, niosomes are very effective tool for drug delivery of numerous diseases. They have the potential to provide better treatment than conventional drug delivery systems.

## REFERENCES

[1] TM Allen. *Drugs*, **1998**, 56(5), 747-756.
[2] K Strebhardt; A Ullrich. *Nat. Rev. Cancer*, **2008**, 8(6), 473-480.
[3] X Chen; W Huang; BC Wong; L Yin; YF Wong; M Xu; Z Yang, *Int. J. Nanomedicine*, **2012**, 7, 1139-1148.
[4] PN Shek; ZE Suntres; JI Brooks. *J. Drug Target.*, **1994**, 2(5), 431-442.
[5] G Parthasarathi; N Udupa; P Umadevi; G Pillai. *J. Drug Target.*, **1994**, 2(2), 178-182.
[6] E Moazeni; K Gilani; F Sotoudegan; A Pardakhty; AR Najafabadi; R Ghalandari; MR Fazeli; H Jamalifar. "*J. Microencapsul.*, **2010**, 27(7), 618-627.
[7] GP Kumarn; P Rajeshwarrao. *Acta Pharm. Sin. B*, **2011**, 1(4), 208-219.
[8] I F Uchegbu; SP Vyas. *Int. J. Pharm.*, **1998**, 172(1-2), pp. 33-70.
[9] M Rangasamy; B Ayyasamy; S Raju; S Gummadevelly; S Shaik, *J. Pharm. Res.*, **2008**, 1(2), 163-166.
[10] S Bhaskaran; PK Lakshmi. *Acta Pharma. Sci.*, **2009**, 51(1), 27-32.
[11] LM Negi; AK Garg; M Chauhan. *Pharma Times*, **2009**, 41(9), 11-14.
[12] V Sankar; K Ruckmani; S Jailani; KS Ganesan; S Sharavanan. *Pharmacologyonline*, **2009**, 2, 926-932.
[13] IF Uchegbu; AT Florenc. *Adv. Colloid Interface Sci.*, **1995**, 58(1), 1-55.
[14] JA Bouwstra; DA Van Hal; HEJ Hofland. *Colloids Surf. A Physicochem. Eng. Asp.*, **1997**, 123-124, 71-80.
[15] AJ Baillie; AT Florence; LR Hume; GT Muirhead; A Rogerson. *J. Pharm. Pharmacol.*, **1985**, 37(12), 863-868.
[16] G Tiwari; R Tiwari; B Sriwastawa; L Bhati; S Pandey; P Pandey; SK Bannerjee. *Int. J. Pharma. Investig.*, **2012**, 2(1), 2-11.
[17] D Thacharodi; KP Rap. *Biomaterials*, **1995**, 16(2), 145-148.
[18] R Krishna; JK Pandit. *J. Pharm. Pharmacol.*, **1996**, 48(4), 367-370.
[19] M Bhat; DS Shenoy; N Udupa; CR Srinivas. *Indian Drugs*, **1995**, 32(5), 211-214.
[20] K Diljyot. *Int. J. Pharm. Phytopharm. Res.*, **2012**, 2(1), 53-59.
[21] M Malhotra; NK Jain. *Indian Drugs*, **1994**, 31(3), 81-86.
[22] HS Giddi; MA Arunagirinathan; JR Bellare. *Indian J. Exp. Biol.*, **2007**, 45(2), 133-159.
[23] SS Biju; S Talegaonkar; PR Mishra; RK Khar. *Indian J. Pharm. Sci.*, **2006**, 68(2), 141-153.
[24] P Bandyopadhyay; M Johnson. *Colloids Surf. B Biointerfaces*, **2007**, 58(1), 68-71.
[25] W Shan; H Liu; J Shi; L Yang; N Hu. *Biophy. Chem.*, **2008**, 134(1-2), 101-109.
[26] A Gandhi; SO Sen; A Paul. *Asian J. Pharm. Life Sci.*, **2012**, 2(2), 339-353.
[27] KM Kazi; AS Mandal; N Biswas; A Guha; S Chatterjee; M Behera; K Kuotsu. *J. Adv. Pharm. Technol. Res.*, **2010**, 1(4), 374-380.
[28] NO Sahin. Nanomaterials and Nanosystems for Biomedical Applications, Springer, Netherlands, **2007**, 67-81.
[29] RK Keservani; AK Sharma; M Ayaz; RK Kesharwani. *Int. J. Res. Controlled Release*, **2011**, 1(1), 1-8.
[30] JN. Khandare; G Madhavi; BM Tamhankar. *The East Pharmacist*, **1994**, 37, 61-64.
[31] SC Jayaraman; C Ramachandran; N Weiner. *J. Pharm. Sci.*, **1996**, 85(10), 1082-1084.
[32] RA Naresh; G Chandrashekhar; GK Pillai; N Udupa. *Indian J. Pharmacol.*, **1994**, 26(1), 46-48.
[33] S Chauhan; MJ Luorence. *J. Pharm. Pharmacol.*, **1989**, 41(Suppl), 6 pages.
[34] LD Mayer; MB Bally; MJ Hope; PR Cullis. *Biochim. Biophys. Acta*, **1985**, 816(2), 294-302.
[35] AK Verma; JC Bindal. *Indian J. Novel Drug Deliv.*, **2011**, 3(4), 238-246.
[36] D Aggarwal; A Garg; IP Kaur. *J. Pharm. Pharmacol.*, **2004**, 56(12), 1509-1517.
[37] Y Hao; F Zhao; N Li; Y Yang; K Li. *Int. J. Pharm.*, **2002**, 244(1-2), 73-80.
[38] A Sankhyan; P Pawar. *J. Applied Pham. Sci.*, **2012**, 2(6), 20-32.
[39] N Udupa. Controlled and Novel Drug Delivery, CBS Publishers and Distributors, New Delhi, **2002**.
[40] A Rogerson. *J. Microencapsul.*, **1987**, 4(4), 321-328.
[41] R Muzzalupo; L Tavano; F Lai; N Picci. *Colloids Surf. B Biointerfaces*, **2014**, 123, 207-212.
[42] P Arunothayanun; MS Bernard; DQ Craig; IF Uchegbu; AT Florence. *Int. J. Pharm.*, **2000**, 201(1), 7-14.
[43] S Biswal; PN Murthy; J Sahu; P Sahoo; F Amir. *Int. J. Pharm. Sci. Nanotech.*, **2008**, 1(4), 1-8.
[44] C Hu; DG Rhodes. *Int. J. Pharm.*, **1999**, 185(1), 23-25.

REJECTED

[45] AB Solanki; JR Parikh; RH Parikh. *AAPS Pham. Sci. Tech.*, **2007**, 8(4), 43.
[46] MM Ahmed Ibrahim; OA Sammour; MA Hammad; NA Megrab. *AAPS Pham. Sci. Tech.*, **2008**, 9(3), 782-790.
[47] BS Reddy; JSC Padman; V Santosh. *Int. J. Pharm. Sci. Res.*, **2012**, 4, 1560-1568.
[48] JA Zasadzinski; B Wong; N Forbes; B Gary; G Wu. *Curr. Opin. Colloid Interface Sci.*, **2011**, 16(3), 203-214.
[49] J W Yoo; N Doshi; S Mitragotri. *Adv. Drug Deliv. Rev.*, **2011**, 63(14-15), 1247-1256.
[50] S Chakraborty; D Shukla; B Mishra; S Singh. *Eur. J. Pharm. Biopharm.*, **2009**, 73(1), 1-15.
[51] R Rajera; K Nagpal; SK Singh; DN Mishra. *Phamaceutical Society of Japan*, **2011**, 34(7), 945-953.
[52] RZ Mujoriyaa; K DHamandeb; RB Bodlac. *Int. J. Appl. Pharm.*, **2011**, 3(3), 1-7.
[53] S Medda; S Mukhopadhyay; MK Basu. *J. Antimicrob. Chemother.*, **1999**, 44(6), 791-794.
[54] K Ruckmani; V Sankar. *AAPS Pham. Sci. Tech.*, **2010**, 11(3), 1119-1127.
[55] KD Kieburtz; M Seidlin; JS Lambert; R Dolin; R Reichman; F Valentine. *J. Acquir. Immune Defic. Syndr.*, **1992**, 5(1), 60-64.
[56] D Gopinath; SR Parakh; R Devraj; SS Apte; RB Rao; D Rambhau. *J. Colloid Interface Sci.*, **2002**, 251(2), 360-365.
[57] J Cummings; JF Staurt; KC Calman. *J. Chromatogr. B Biomed. Sci. Appl.*, **1984**, 311, 125-133.
[58] KS Chandraprakash; N Udupa; P Umadevi; GK Pillai. *Indian J. Pharm. Sci.*, **1992**, 54(5), 197-200.
[59] D Paolino; D Cosco; R Muzzalupo; E Trapasso; N Picci; M Fresta. *Int. J. Pharm.*, **2008**, 353(1-2), 233-242.
[60] G Parthasarathi; N Udupa; P Umadevi; GK Pillai. *J. Drug Target.*, **1994**, 2(2), 173-182.
[61] K Nesaretnam; N Guthrie; AF Chambers; KK Carroll. *Lipids*, **1992**, 30(12), 1139-1145.
[62] JY Fua; DMY Tan; HM Er; YS Chen; K Nesaretnam. *Asian J. Pharm. Sci.*, **2016**, 11(1), 79-80.
[63] NG Vallianou; A Evangelopoulos; N Schizas; C Kazazis. *Anticancer Res.*, **2015**, 35(2), 645-651.
[64] Y Xu; WR Chen; JK Tsosie; X Xie; P Li; J Wan; C He; M Chen. *J. Nanomater.*, **2016**, 2016(6365295), 9 pages.
[65] V Sharma; S Anandhakumar; M Sasidharan. *Mater. Sci. Eng. C*, **2015**, 56, 393-400.
[66] Antimalaria Coordinating Research Group. *Chin. Med. J.*, **1979**, 92(12), 811-816.
[67] HJ Woerdenbag; TA Moskal; N Pras. *J. Nat. Prod.*, **1993**, 56(6), 849-856.
[68] P Reungpatthanaphong; S Mankhetkorn. *Biol. Pharm. Bull.*, **2002**, 25(12), 1555-1561.
[69] T Efferth; A Saverbrey; A Olbrich. *Mol. Pharmacol.*, **2003**, 64(2), 382–394.
[70] MP Crespo-Ortiz; MQ Wei. *J. Biomed. Biotechnol.*, **2012**, 2012(247597), 18 pages.
[71] M Ashton; D. Nguyen; VH Nguyen; T Gordi; NH Trinh; XH Dinh; TN Nguyen; DC Le. *Clin. Pharmacol. Ther.*, **1998**, 63(4), 482-493.
[72] Q Li; PJ Weina; WK Milhous. *Curr. Drug Ther.*, **2007**, 2(3), 210-223.
[73] A Dwivedi; A Mazumder; L du Plessis; JL du Preez; RK Haynes; J du Plessis. *Nanomedicine*, **2015**, 11(8), 2041-2050.
[74] MP Cole; CT Jones; ID Todd. *Br. J. Cancer*, **1971**, 25(2), 270-275.
[75] DS Shaker; MA Shaker; MS Hanafy. *Int. J. Pharm.*, **2015**, 493(1-2), 285-294.
[76] D Tila; SN Yazdani-Arazi; S Ghanbarzadeh; S Arami; Z Pourmoazzen. **2015**, *EXCLI J.*, 14, 21-32.
[77] S Shilpa; BP Srinivasan; M Chauhan. *Int. J. Drug Deliv.*, **2011**, 3(1), 14-24.
[78] C Terzano; L Allegra; F Alhaique; C Marianecci; M Carafa. "*Eur. J. Pharm. Biopharm.*, **2005**, 59(1), 57-62.
[79] G Singh; H Dwivedi; SK Saraf; SA Saraf. *Trop. J. Pharm. Res.*, **2011**, 10(2), 203-210.
[80] CP Jain; SP Vyas; VK Dixit. *Indian J. Pharm. Sci.*, **2006**, 68(5), 575-578.
[81] K Kaur; A Gupta; RK Narang; RSR Murthy. *J. Adv. Pharm. Tech Res.*, **2010**, 1(2), 145-163.
[82] AR Mullaicharam; RSR Murthy. *J. Drug Deliv. Sci. Tech.*, **2006**, 16(2), 109-113.
[83] A Manosroi; P Jantrawuta; J Manosroi. *Int. J. Pharm.*, **2008**, 360(1-2), 156-163.
[84] RMG Vankadari; M Nappinnai; J Suribabu; K Srikanth. *Res. J. Pharm. Biol. Chem. Sci.*, **2010**, 1(2), 308-316.
[85] D Fathalla; A Abdel-Mageed; F Abdel-Hamid; M Ahmed. *Int. J. Pharm. Sci. Res.*, **2014**, 1(105), 11 pages.
[86] D Kumbhar; P Wavikar; P Vavia. "*AAPS Pham. Sci. Tech.*, **2013**, 14(3), 1072-1082.
[87] S Kamboj; V Saini; S Bala; G Sharma. *Int. J. Med. Health Biomed. Bioeng. Pharm. Eng.*, **2013**, 7(12), 877-881.
[88] UA Shinde; SS Kanojiya. *J. Pharm.*, **2014**, 2014(382959), 9 pages.
[89] T Fukai; K Satoh; T Nomura; H Sakagami. *Fitoterapia*, **2003**, 74(7-8), 624-629.
[90] K Morteza-Semnani; M Saeedi; B Shahnavaz. *J. Cosmetic Sci.*, **2003**, 54(6), 551-558.
[91] D Paolino; G Lucania; D Mardente; F Alhaique; M Fresta. *J. Control. Release*, **2005**, 106(1-2), 99-110.
[92] S Matsui; H Matsumoto; Y Sonoda; K Ando; E Aizu-Yokota; T Sato; T Kasahara. *Int. Immunopharm.*, **2004**, 4(13), 1633-1644.
[93] T Genovese; M Menegazzi; E Mazzon; C Crisafulli; R Di Paola; M Dal Bosco; Z Zou; H Suzuki; S Cuzzocrea. *Shock*, **2009**, 31(4), 367-375.
[94] C Marianecci; F Rinaldi; M Mastriota; S Pieretti; E Trapasso; D Paolino; M Carafa. *J. Control. Release*, **2012**, 164(1), 17-25.
[95] A Priprem; K Janpim; S Nualkaew; P Mahakunakorn. *AAPS Pham. Sci. Tech.*, **2016**, 17(3), 631-639.
[96] VD Wagh; OJ Deshmukh. *Int. Sch. Res. Notices*, **2012**, 2012(653465), 7 pages.

REJECTED

[97] M Alam; S Zubair; M Farazuddin; E Ahmad; A Khan; Q Zia; A Malik; O Mohammad. *Nanomed. Nanotech. Biol. Med.*, **2013**, 9(2), 247-256.
[98] G Fetih. *J. Drug Deliv. Sci. Tech.*, **2016**, 35, 8-15.
[99] A Gupta; HK Kar. *Asian Pac. J. Trop. Dis.*, **2015**, 5(9), 707-710.
[100] LJ de Arauz; AF Jozala; PG Mazzola; TCV Penna. *Trends Food Sci. Techn.*, **2009**, 20(3-4), 146-154.
[101] IS Boziaris; MR Adams. *Int. J. Food Microbiol.*, **1999**, 53(2-3), 105-113.
[102] E Parente; MA Giglio; A Ricciardi; F Clementi. *Int. J. Food Microbiol.*, **1998**, 40(1-2), 65-75.
[103] KA Stevens, BW Sheldon, NA Klapes, TR Klaenhammer. *Appl. Env. Microbiol.*, **1991**, 57(12), 3613-3615.
[104] P Kopermsub; V Mayen; C Warin. *Food Res. Int.*, **2011**, 44(2), 605-612.
[105] R Kellner; G Jung; T Hörner; H Zähner; N Schnell; KD Entian; F Götz. *Eur. J. Biochem.*, **1988**, 177(1), 53-59.
[106] A Manosroi; P Khanrin; W Lohcharoenkal; RG Werner; F Götz; W Manosroi; J Manosroi. *Int. J. Pharm.*, **2010**, 392(1-2), 304-310.
[107] G Burdock. "*Food Chem. Toxicol.*, **1998**, 36(4), 347-363.
[108] AG Hegazi; FK Abd El Hady. *Z. Naturforsch. C*, **2002**, 57(3-4), 395-402.
[109] A Kujumgiev; I Tsvetkova; Y Serkedjieva; V Bankova; R Christov; S Popov. *J. Ethnopharm.*, **1999**, 64(3), 235-240.
[110] YK Park; MH Koo; JA Abreu; M Ikegaki; JA Cury; PL Rosalen. *Curr. Microbiol.*, **1998**, 36(1), 24-28.
[111] N Kalogeropoulos; SJ Konteles; E Troullidou; I Mourtzinos; VT Karathanos. *Food Chem.*, **2009**, 116(2), 452-461.
[112] O Mirzoeva; R Grishanin; P Calder. *Microbiol. Res.*, **1997**, 152(3), 239-246.
[113] MM Rahman; A Richardson; M Sofian-Azirun. *Afr. J. Microbiol. Res.*, **2010**, 4(18), 1872-1878.
[114] YB Ghasem; A Ownagh; M Hasanloei. *Pak. J. Biol. Sci.*, **2007**, 10(8), 1343-1345.
[115] J Patel; S Ketkar; S Patil; J Fearnley; KR Mahadik; AR Paradkar. *Integr. Med. Res.*, **2015**, 4(2), 94-101.
[116] Y Zubairu; LM Negi; Z Iqbal; S Talegaonkar. *Asian J. Pharm. Sci.*, **2015**, 10(4), 322-330.
[117] S Sohrabi; A Haeri; A Mahboubi; A Mortazavi; S Dadashzadeh. *Int. J. Biol. Macromol.*, **2016**, 85, 625-633.

RETRACTED