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# Niosomes as Nanoparticular Drug Carriers

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**ABSTRACT**

Niosomes are novel drug delivery systems, containing medication which is encapsulated in a vesicle. The vesicle is composed of bilayered non-ionic surface active agents thus it is named as Niosomes. Structurally, they are similar to liposomes, as both are bilayered but in the case of niosomes, it is made up of non-ionic surface active agents rather than phospholipids as seen in the case of liposomes. Niosomes are preferred over liposomes because they exhibit high chemical stability and economy. The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages. This article focuses on the recent advances and approaches in niosomal drug delivery. The niosomal drug delivery system has potential advantages over other delivery systems such as the formulation methods, characterization methods, and the current research in the field of niosomes. Also, niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. Drug delivery potential of niosome can be enhanced by using novel concepts like proniosomes, discomes and aspasome.

## INTRODUCTION

Niosomes are one of the most favorable drug carriers having a bilayered structure and are formed by self-association of nonionic surfactants and cholesterol in an aqueous phase. Niosomes are biodegradable, biocompatible, and non-immunogenic, having long shelf life. They exhibit high stability and enable the delivery of drug at target site in a controlled or sustained manner. In recent years, the potential of niosomes as a drug carrier has been extensively studied. 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. 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 with the description of their use in drug delivery. This review article will provide an overview of the increasing interest on niosomes in the field of drug delivery.

**Advantages of Niosomes**:

- The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages.
- They improve the therapeutic performance of the drug molecules by delayed clearance from the systemic circulation, thereby protecting the drug from biological environment and restricting its effects to target cells.
- Niosomal dispersion in an aqueous phase can be emulsified in a nonaqueous phase to regulate the delivery.
- Rate of drug and administer normal vesicle in external non-aqueous phase.
- They are osmotically active and stable, as well as they increase the stability of entrapped drug.
- Handling and storage of surfactants require no special environmental conditions.
- They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.

- They can be made to reach the site of action by oral and parenteral route.[1]

**Structure and Components of Niosomes**

The main components of niosomes are nonionic surfactants, hydration medium and lipids such as cholesterol. The self-assembly of nonionic surfactants in aqueous media results in closed bilayer structures. A high interfacial tension existing 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 ensures that hydrophilic termini point outwards and are in contact with water. The assembly into closed Bilayer bilayers usually needs some input of energy such as mechanical or heat. Niosomes can be divided into 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.

**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. 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 an important role in the selection of surfactant molecules for niosome preparation.

**Hydrophilic-Lipophilic Balance (HLB).** HLB is a dimensionless parameter, which determines the solubility of the surfactant molecule. The HLB value describes the balance between the hydrophilic portions 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. Hydrophilic surfactants with HLB value ranging from 14 to 17 are not suitable to form a bilayer membrane due to their high aqueous solubility. However, with the addition of an optimum level of cholesterol, niosomes are formed from polysorbate 80 (HLB value = 15) and Tween 20 (HLB value = 16.7). 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. Drug entrapment efficiency of the niosomes is also affected by HLB value of surfactant.

**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: CPP = V $lc$ × $a0$, (1) where V is hydrophobic group volume, $lc$ is the critical hydrophobic group length, and $a0$ is the area of hydrophilic head group. If CPP ≤ 1/3 corresponding, for instance, to a bulky head group, small hydrophobic tail spherical micelles may form. Nonspherical micelles may form if 1/3 ≤ CPP ≤ 1/2, and bilayer vesicles can occur if 1/2 ≤ CPP ≤ 1. Inverted micelles form if CPP ≥ 1 when the surfactant is composed of a voluminous tail and a small hydrophobic tail. CPP could be considered as a tool for realizing, rationalizing, and predicting the self-assembled structure and its morphological transition in amphiphilic solutions.

**Cholesterol**. In the bilayer structure of niosomes, cholesterol forms hydrogen bonds with hydrophilic head of a surfactant. 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. Cholesterol improves the rigidity of vesicles and stabilizes niosomes towards destabilizing efficiency, long time stability, release of payload, and biostability. 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. Drug entrapment efficiency plays an important role in niosomal formulations and it can be altered by varying the content of cholesterol.

**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, stearyl amine and stearylpyridinium 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 [2].

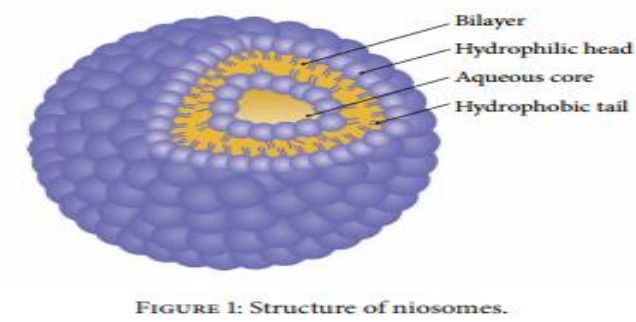


FIGURE 1: Structure of niosomes.

**Figure 1: Structure of niosomes.**

Bilayers usually require some input of energy such as mechanical or heat. Niosomes can be divided into 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.

**COMPARISON OF NIOSOMES AND LIPOSOMES:** Niosomes are now widely studied as an alternative to liposomes, which have certain disadvantages such as –they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they need special storage and handling and purity of natural phospholipids are variable. Niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from double chain phospholipids (neutral or charged). Niosomes behave *in-vivo* like liposomes, extending the circulation of entrapped drug and altering its organ distribution and metabolic stability [3]. Encapsulation of various antineoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects while maintaining, or in some examples, increasing the anti-tumor efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. They can be assumed to target the drug to its desired site of action and to control its release [12].

**Methods of Preparation**

**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 ($Tc$) of the surfactant for specified times with continuous shaking [4] Multilamellar niosomes are formed by this method.

**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. [10]

**Reverse Phase Evaporation Method (REV**): In this method, niosomal ingredients are dissolved in a mixture of ether and chloroform and added to an 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. [5]

**Microfluidization Method** The micro fluidization method is based on submerged jet principle. In this method, the drug and the surfactant fluidized streams interact at ultrahigh velocities, inaccurately defined microchannels 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. [6]

**Supercritical Carbon Dioxide Fluid (scCO2**). Manosroi *et al.* have described the supercritical reverse phase evaporation technique for niosome formation.[7-8] They added Tween 61, cholesterol, glucose, PBS, and ethanol into the view cell and the $CO_2$ gas was introduced into the view cell. After magnetic stirring until equilibrium, the pressure was released and niosomal dispersions were obtained. [8] This method enables one step and increased production.

**Proniosome**. Proniosome technique involves 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 needs to be hydrated before use. 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 provides convenience in dosing, distribution, transportation, and storage showing improved results compared to conventional niosomes. [9]

**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. According to this method, the interior of niosome has a more acidic pH value than the outer medium. The unionized drug which is added passes through the niosome membrane and enters into the niosome. The drug ionizes in an acidic medium and cannot escape from the niosomal bilayer. [10]

**Factors Affecting Niosomes Formulation**

**1. Drug**

Entrapment of drug in niosomes increases vesicle size by interaction of solute with surfactant head groups, increasing the charge and repulsion of the surfactant bilayer, increasing vesicle size. In polyoxyethylene glycol (PEG) coated vesicles; some drugs; are entrapped in the long PEG chains, thus reducing the tendency to increase the size. The hydrophilic lipophilic balance of the drug affects degree entrapment.

**2. Amount and type of surfactant**

The mean size of niosomes increases proportionally with increase in the HLB surfactants like Span 85 (HLB 1.8) to Span20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant. The bilayers of the vesicles are either in the so-called liquid state or in gel state, depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol. In the gel state, alkyl chains are present in an ordered structure, and in the liquid state, the structure of the bilayers is more disordered. The surfactants and lipids are characterized by the gel-liquid phase transition temperature (TC).

Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, TC that eventually provides better entrapment.

**3. Cholesterol content and charge**

Including the cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency. In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, cholesterol decreases the chain order of gel state bilayers. At cholesterol decreases the chain order of gel state bilayers. High cholesterol concentration, the gel state is converted to a liquid-ordered phase. An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material and therefore an increase of the rigidity of the bilayers is achieved. Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater entrapped volume.

**4. Resistance to osmotic stress**

Addition of a hypertonic salt solution to a suspension of niosomes brings reduction in diameter. In hypotonic salt solution, there is initial slow release with slight swelling of vesicles due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress.

**5. Membranes Composition**

The stable niosomes can be prepared with addition of different additives along with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by different additives. In case of polyhedral niosomes formed from C16G2, the shape of these polyhedral niosome remains unaffected by adding low amount of solulan C24 (cholesterol poly-24-oxyethylene ether), which prevents aggregation due to development of stearic hindrance.[24] In contrast, spherical Niosomes are formed by C16G2: cholesterol: solution (49:49:2). The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by C16G2: solution C24 in ration (91:9) having bigger size (8.0} 0.03 mm) than spherical/tubular niosomes formed by C16G2: cholesterol: solution C24 in ratio (49:49:2) (6.6 • } 0.2 mm). Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces the leakage of drug from niosome.

## CHARACTERIZATION OF NIOSOMES

### a. Measurement of Angle of repose

The angle of repose of dry niosomes powder was measured by a funnel method. The niosomes powder was poured measured by a funnel method. The niosomes powder was poured orifice of the funnel is 5 cm above a level black surface. The powder flows down from the funnel to form a cone on the surface and the angle of repose was then calculated by measuring the height of the cone and the diameter of its base.

### b. Scanning electron microscopy

Particle size of niosomes is very important characteristic. The surface morphology roundness, smoothness, and formation by Scanning Electron Microscopy (SEM). Niosomes were sprinkled

onto the double-sided tape that was affixed on aluminum stubs. The aluminum stub was placed in the vacuum chamber of a Netherlands. The samples were observed for morphological characterization using a gaseous secondary electron detector (working pressure: 0.8 torr, acceleration voltage: 30.00 KV) XL 30, (Philips, Netherlands).

### c. Optical Microscopy

The niosomes were mounted on glass slides and viewed under a microscope (Medilux-207RII, Kyowa-Getner, Ambala, India) with a magnification of 1200X for morphological observation after suitable dilution. The photomicrograph of the preparation also obtained from the microscope by using a digital SLR camera.

### d. Measurement of vesicle size

The vesicle dispersions were diluted about 100 times in the same medium used for their preparation. Vesicle size was measured on a particle size analyzer (Laser diffraction particle size analyzer, Sympatec, Germany). The apparatus consists of a He-Ne laser beam of 632.8 nm focused with a minimum power of 5 mW using a Fourier lens [R-5] to a point at the center of multielement detector and a small volume sample holding cell (Su cell). The sample was stirred using a stirrer before determining the vesicle size. Hu C. and Rhodes 7 in 1999

reported that the average particle size of niosomes derived niosomes is approximately 6µm while that of conventional niosomes is about 14µm.

**e. Entrapment efficiency**

Entrapment efficiency of the niosomal dispersion is can be done by separating the unentrapped drug by dialysis centrifugation or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and the drug.

**f. Osmotic shock**

Analyzing the resultant solution by appropriate assay method for the change in the vesicle size can be determined by osmotic studies. Niosomes formulations are incubated with hypotonic, isotonic, hypertonic solutions for 3 hours. Then the changes in the size of vesicles in the formulations are viewed under optical microscopy.

**g. Stability studies**

To determine the stability of Surface characteristics and percentage drug retained in niosomes, the optimized batch was stored in airtight sealed vials at different temperatures and niosomes derived from proniosomes were selected as parameters for evaluation of the stability, since instability of the formulation would reflect in drug leakage and a decrease in the percentage drug retained. The niosomes were sampled at regular intervals of time (0, 1, 2, and 3months ), observed for color change, surface characteristics and tested for the percentage drug retained after being hydrated to form niosomes and analyzed by suitable analytical methods (UV spectroscopy, HPLC methods. [11]

**h. Zeta potential analysis**

Zeta potential analysis is done for determining the colloidal properties of the prepared formulations. The suitably diluted niosomes derived from proniosome dispersion was determined using zeta potential analyzer based on electrophoretic light scattering and laser Doppler velocimetry method (Zeta Plus™, Brookhaven Instrument Corporation, New York, USA). The temperature was set at 25°C. Charge on vesicles and their mean zeta potential values with standard deviation of measurements were obtained directly from the measurement.

***In-vitro* methods for niosomes**

*In vitro* drug release can be done by

- Dialysis tubing

- Reverse dialysis

- Franz diffusion cell

**Dialysis tubing**

Muller *et al*, in 2002 studied *in vitro* drug release could be achieved by using dialysis tubing. The niosomes is placed in achieved by using dialysis tubing. The niosomes is placed in prewashed dialysis tubing which can be hermetically sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and analyzed for drug content using suitable method (U.V. spectroscopy, HPLC *etc*). The maintenance of sink condition is essential.

**Reverse dialysis**

In this technique, a number of small dialysis as containing 1ml of dissolution medium is placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method; however, the rapid release cannot be quantified using this method.

**Franz diffusion cell**

Proniosomes is placed in the donor chamber. *In vitro* diffusion studies can be performed by using a Franz diffusion cell fitted with a cellophane membrane. The proniosomes is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable method (U.V spectroscopy, HPLC, etc) .the maintenance of sink condition is essential.

**APPLICATIONS OF NIOSOMES**

**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.

- **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.

- **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.

- **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. Cantharidin entrapped niosomes were prepared by injection method. Breast cancer cell line MCF-7 tumor-bearing mice. Mice treated with 1.0 mg/kg niosomal cantharidin showed the most. Recently, tamoxifen citrate niosomes were prepared by film hydration technique for localized cancer therapy.

- **Ovarian Cancer:** Uchegbu *et al.* prepared doxorubicin loaded niosomes. The activity of doxorubicin in hexadecyldiglycerol ether (C16G2) 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 IC50 against the resistant cell line when the drug was encapsulated in Span 60 niosomes in comparison to the free drug in solution. [12]

- **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 is 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.[15] 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. [13]

**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, 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. 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. [14-15] Bragagni *et al.* developed brain targeted niosomal formulation using the glucose derivative as a targeting ligand. 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. 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-ethylcarbodiimidehydrochloride) 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.

**Co-Drug Delivery:** In recent years, nanoparticles have emerged as a promising class of carriers in co-delivery of multiple drugs for combination therapy. [16] 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 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. [17] 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.[18] Chemosensitizers, such as Verapamil, Elacridar.

**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. [19] In another study to increase efficacy of the antibiotics and reduce the dose.

**Anti-Inflammatory Drug:** 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]

**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. [20] 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. [21]

**Recent Studies:** Over the past three decades, niosomes have been successfully used as drug carriers to overcome some major biopharmaceutical problems such as insolubility, side effects, and poor chemical stability of drug molecules.

**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. [22] The surfactants which are used for niosomes preparation are biodegradable, biocompatible, and non-immunogenic.[25] 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. [23] 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.

## 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.

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