IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

NIOSOMES: A REVIEW OF THEIR STRUCTURE, TYPES, METHOD OF PREPARATION, CHARACTERIZATION AND APPLICATION

[1]Miss. Apurva Dattatray Chavan, [2]Dr. Rohit R. Shah, [3]Prajakta Ashok Chougule

[1]PG Student (M Pharm), [2]Vice Principal and HOD Pharmaceutics (ABCP, Sangli), [3]PG Student (M Pharm)

[1]Department of Pharmaceutics,

[1]Appasaheb Birnale College of Pharmacy, Sangli, India.

Abstract : Due to its potential for targeted drug delivery to the diseased site while sparing the surrounding healthy tissue, the development of nanocarriers for drug delivery has drawn a lot of attention. When non-ionic surfactant, cholesterol, or other amphiphilic molecules are hydrated, they self-assemble into vesicular nano-carriers called niosomes, which are used in a number of applications as adaptable drug delivery systems. Similar to liposomes, niosomes are capable of delivering medications to the target region, are useful as carriers for both hydrophilic and lipophilic pharmaceuticals, and can be either unilamellar or multilamellar. Niosomes also overcome the main limitations of liposomes by being produced using simple techniques, costing less to produce, and being stable for a long time. This review provides comprehensive summary of formulation components, types of niosomes, effects of components on the formation of niosomes, fabrication and purification methods, physical characterization techniques of niosomes, recent applications in pharmaceutical field.

IndexTerms **- Niosomes, Vesicles, Drug targeting, Nonionic surfactant.**

INTRODUCTION

The sciences of nanomedicine and related subfields, like pharmaceutical nanocarriers, have emerged as new branches of medical science as a result of the rapid and significant advancements in the use of nanotechnology in the treatment and detection of diseases. Materials such as polymers, nanogel, metal oxides, metals, lipid-based carriers (liposomes), and surfactant-based carriers (niosomes) can all be used to create nanostructures. (1)

It might be claimed that the study of delivery of drugs and disease treatment has undergone a revolution as a result of the rapid development of nanotechnology. Numerous nanocarriers (Fig. 1) have been created by shaping nanoparticles into vesicles to safely carry medications and various other therapeutic substances precisely into target locations. Numerous traditional nano DDS, like as liposomes, micelles, and polymer-based nanodevices, are in the last stages of development, and some of them have already received regulatory approval. (2)

The ability to modify molecules and supramolecular structures for advantageous purposes has developed over the last two decades, leading to the creation of creatively engineered nanomaterials appropriate for biopharmaceutical/therapeutic applications. Another significant breakthrough is the increasing integration and functionality of nanocarriers, enabling a variety of applications such as on-demand release, targeting of particular tissue or cell types, in vivo imaging and diagnosis, and photothermal treatment. (2,3)

Niosomes are multilamellar vesicular structures made of nonionic surfactants, much like liposomes, but they lack the phospholipids that make up liposomes. Instead, they are made of non-ionic surfactants. (4) Unfavorable pharmacokinetics and distribution are just two of the difficulties faced by conventional drug delivery systems, which can lead to unintended side effects. Drug efficacy can be reduced by reticuloendothelial system breakdown in blood circulation and insufficient drug absorption at the target site. (2) Due to its chemical stability, biocompatibility, low production costs, minimal toxicity, biodegradability, and ease of handling and storage, niosomes are chosen over alternative bilayer structures. (5) Nanocarriers have been developed in the last few decades, there has been a lot of research into how to solve the problems. Due to the following advantages when compared to traditional drug delivery systems:

1. Niosome serve as a reservoir for drug release that is gradual and controlled.
2. Osmotically active and stable niosomes in addition, when compared to liposomes, the drug's stability over time is substantially higher.
3. They improve medication-taking behavior by delaying drug clearance, protecting the drug from the biological environment, and limiting the drug's impact to the target location. (1)
4. Because the typically employed nonionic surfactants are biocompatible, non-immunogenic, and biodegradable niosomes have minimal toxicity and good compatibility with biological systems. (6)

5. Niosomes boost the oral bioavailability of medications with low absorption and increase the drug's permeability into the skin. (5)
6. The niosomes can entrap a wide range of medicines (hydrophilic and lipophilic) with varying solubilities. (5)
7. Niosomes are successfully used to deliver medications to specific tissues. (4)
8. Considering the functional groups on their hydrophilic heads, niosomes are adaptable and easy to change.
9. Surfactant does not require particular storage or handling conditions.
10. Niosomes are administered in a variety of ways (intravenous, oral, etc.). (1)

Similar to how liposomes are formed, niosomes can be made as unilamellar or multilamellar vesicles. In the 1970s and 1980s, L'Oréal (Clichy, France) researchers first discovered them for use in cosmetic products. Since then, niosomes have undergone in-depth research to determine their potential for use in a variety of industries, including the cosmetic, food sciences, and pharmaceuticals yielding a significant number of papers and patents [2]. Niosomes have the potential to enhance drug delivery through the skin's stratum corneum (SC). (7) There have been some postulated methods to explain their penetration-enhancing effects. (2)

The literature has described topical vaccine delivery employing niosomes as carriers, where the antigen is kept intact in the aqueous core while the niosomal components improve penetration over the skin and trigger an immune response. Because of their low toxicity and penetration-improving properties, niosomes are also being investigated for the delivery of medicines to the eye. (8,9) Niosomes can deliver anti-cancer therapies to specific locations while lowering toxicity, which lessens the negative effects these medications are known to cause. (10) Proniosomes are particularly intriguing for the pulmonary administration of aerosol drugs employing nebulizer devices because they can deposit drug-loaded proniosomes into the deep lung and offer a superior therapeutic response. (5)

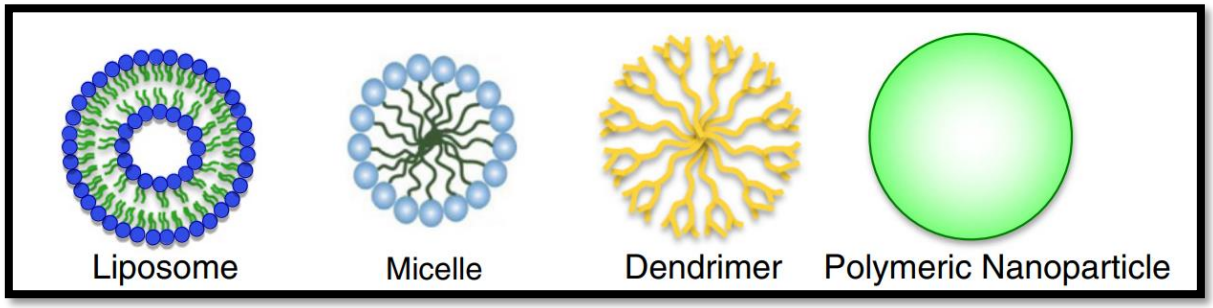

Figure 1. The nanocarriers for drug delivery

❖ STRUCTURE OF NIOSOMES

The bi-layered structure of non-ionic surface-active compounds is called a niosome. Only when surfactants and cholesterol are combined in the right ratio and the temperature is above the gel liquid transition point can these thermodynamically stable bilayered structures develop. (11) The hydrophilic end of nonionic surfactants in niosomes typically faces outward (towards the aqueous phase), while the hydrophobic end typically faces inward to each other to form a closed bilayer structure that encloses solutes in an aqueous solution. In the middle of this two-layered structure lies a hollow area. Niosomes can encapsulate both a hydrophilic and a hydrophobic medication because of their unique geometry. In contrast to hydrophobic drugs, which can partition inside the bilayer structure, hydrophilic drugs can bind to the bilayer surface or the niosomes' central aqueous region for trapping. (Fig. 2) illustrates the two distinct sites for drug trapping and aids in the explanation of the niosome's bilayer structure. (11,12)

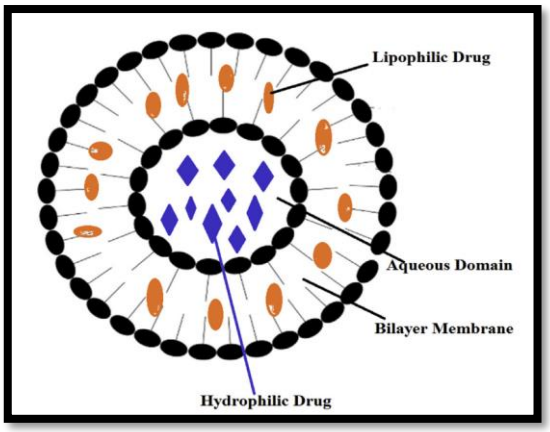

Figure 2. Niosome's bilayer structure showing entrapment of hydrophilic and lipophilic drug

❖ TYPES OF NIOSOMES

These are divided into many groups based on their size or the numbers of lamellar layers. Small unilamellar vesicles (SUV) and large unilamellar vesicles are categorized according to size. Multilamellar vesicles (MLV) and small unilamellar vesicles are classified based on the number of bilayers. (5) The choice of administration method is significantly influenced by the size of niosomes as well. Those up to 10 µm are frequently utilized for nasal, intramuscular, intraperitoneal, and oral administration, whilst submicron size vesicles are excellent for intravenous or transdermal treatments. SUVs range in size from 10 to 100 nm.

They have poor drug loading capability for hydrophilic medicines, lower thermodynamic stability than other forms of niosomes, and a higher propensity to form aggregates. (13) The aqueous core is enclosed by a single bilayer in large unilamellar vesicles (LUVs), which have a diameter of 0.1 to 1 µm. LUV niosomes can encapsulate hydrophilic medicinal molecules due to their vast aqueous compartment. (2) Multiple bilayers surround each of the individual aqueous lipid compartments in multilamellar vesicles (MLV). These vesicles have a diameter that varies from 0.5 to 10 micrometers. Under typical storage circumstances, MLVs are more stable than the other two forms of niosomes and are simple to prepare without the need for complicated methods. Additionally, they are advantageous for loading lipophilic drugs since they have multiple bilayer membranes. (2,13)

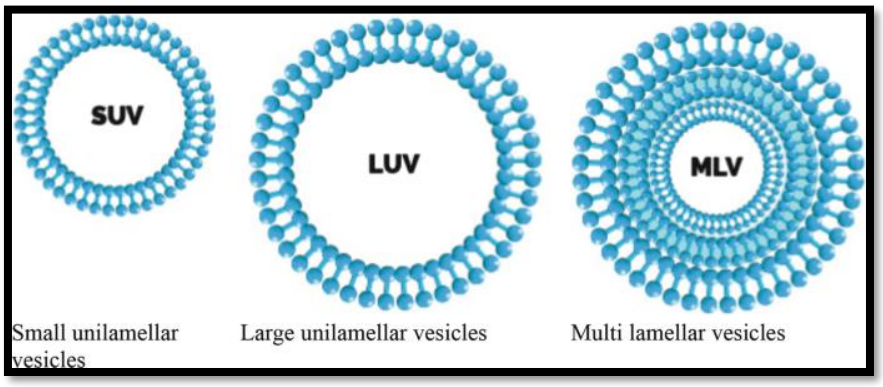

Figure 2. (SUV) (10 to 100 nm), (LUV) (0.1 to 1 µm) and (MLV) (0.5 µm to 10 µm).

Types of specialized niosomes

a. Proniosomes

A fine layer of non-ionic surfactant is coated on a water-soluble carrier to create proniosomes. (2,14,15) To create proniosomes, the water-soluble carriers must be non-toxic, freely flowing, safe and have a high degree of water solubility to facilitate hydration. Proniosomes have been made using lactose monohydrate, maltodextrin, mannitol, glucose monohydrate, sorbitol, and sucrose stearate. (5,14) In comparison to niosomes, proniosomes are available in a dry powder form and provide good stability, a low tendency to form aggregates, and reduced drug leakage. There are several ways to make proniosomes, including the slurry technique, the coacervation phase separation method, and the slow spray coating method. Depending on the manner of manufacturing, they come in two different forms: liquid crystalline proniosomes and dry granular proniosomes. (16,17)

b. Elastic niosomes

Niosomes that are elastic can move through pores that are smaller than they are without losing their structural integrity.These vesicles are made up of surfactants, cholesterol, water, and ethanol. Due to their capacity to pass through tiny pores and hence enhance penetration through the skin barrier, they are frequently utilised in topical or transdermal medication delivery. Due to their capacity to pass through tiny pores and hence enhance penetration through the skin barrier, they are frequently utilised in topical or transdermal medication delivery. In order to administer drugs transdermally, Manosroi and associates created elastic niosomes. Diclofenac Diethylammonium had a deformability index that was almost 14 times greater than that of regular niosomes. (18)

c. Discomes

Niosomes which are large disc like shape are known as discomes. (Fig.4) Uchegbu and colleagues previously used mechanical agitation and sonication to create discomes using hexadecyldiglycerol ether, dicetyl phosphate and cholesterol. In the study, it was discovered that discomes were huge (11–60 m) and that sonication caused them to grow even larger. Discomes are also thermoresponsive; when the temperature rises above 37 °C, their structure becomes disorganized. (19)

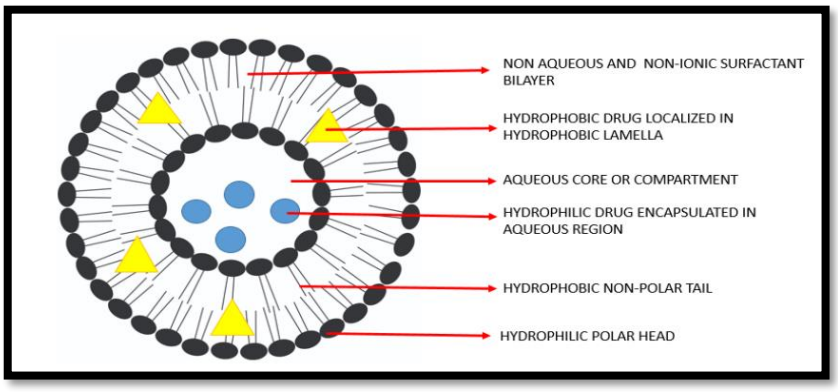

Figure 3. Discomes

d. Bolaniosomes

Bola surfactants are used to create bola niosomes. In the early 1980s, this specific kind of surfactant was discovered in the membrane of an archaebacteria. They have one or two lipophilic linkers in between their two hydrophilic heads. Bola surfactants have a great assembly ability, as evidenced by Zakharova (2010) who found that they had a substantially higher surface tension and lower critical micelle concentration than traditional surfactants. Subsequent studies also revealed that they are tolerable both in vitro and in vivo. (20)

e. Transferosomes

Transfersomes are new deformable vesicular carrier systems made mostly of phospholipids. In an aqueous environment, they self-assemble into a lipid bilayer and close to form a vesicle. (Fig.5) To improve the flexibility and permeability of the lipid bilayer, a softening component is added. It's referred to as an edge activator. An edge activator typically consists of a single chain nonionic surfactant that weakens the lipid bilayer and increases its fluidity and elasticity.Because they contain both hydrophobic and hydrophilic moieties, transfersomes can hold medicinal molecules with a variety of solubilities. Both medications with low and high molecular weights can be transported by them. (21)

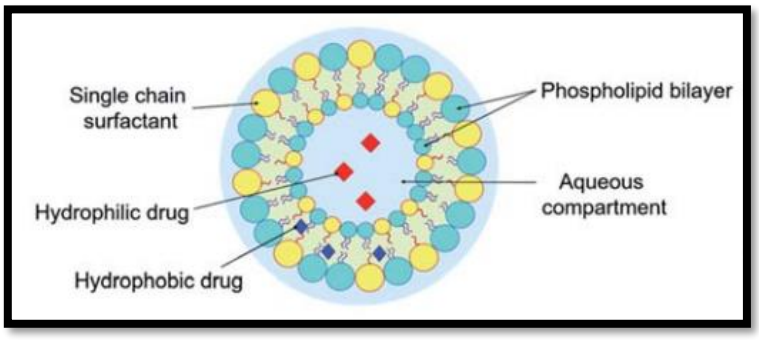

Figure 4. Transferosomes

f. Aspasomes

Ascorbyl palmitate has been investigated as a bilayer-forming agent; it creates vesicles when combined with a lipid (dicetyl phosphate) which is negatively charged, cholesterol, and ascorbylpalmitate. Film hydration technique is used to prepare aspasomes followed by sonication. Aspasomes have been investigated for their potential to improve transdermal penetration across the skin barrier for the delivery of active substances. (22)

g. PEGylated niosomes

Polyethyleneglycol (PEG) modified niosomes have the ability to evade the mononuclear phagocytic system's (MPS) absorption, which prolongs the period that an encapsulated medication is in the bloodstream. (13,23) The hydrophilic PEG chain was further attached with monostearate by He et al. to produce the PEGylated niosomes of paeonol. These molecules are conveniently integrated into the vesicles' lipid core. (24)

❖ FORMULATION COMPONENTS OF NIOSOMES

➢ Surfactants

Surfactants, usually nonionic surfactants, cholesterol, and a charge-inducing substance constitute niosomes. To generate niosomes with the desired properties, it is crucial to comprehend the physicochemical characteristics of these formulation ingredients as well as their impact on niosomes. Non-ionic surfactants are the primary components of niosomes owing to their low toxicity and biocompatibility in comparison to other types of surfactants. Different nonionic surfactants are used in niosome formation such as derivatives of alkyl esters, sorbitan fatty acid esters, and alkyl ethers. (2,13,25) Alkyl esters are a class of non-toxic, non-irritating surfactants that include sorbitan fatty acid esters (Span) and polyoxyethylenesorbitan fatty acid esters (Tween). Alkyl ethers include, for example, brij surfactants. Brij 30 (Polyoxyethylene(4)lauryl ether) is a member of the Brij family having a phase transition temperature of less than 10 °C and the ability to generate large unilamellar vesicles with high drug loading. (26)

Table 1: Surfactants used in formation of niosomes

Sr. No.	Name of the surfactant	Trade name	HLB value
1.	Sorbitan mono laurate	Span 20	8.6
2.	Sorbitan mono palmitate	Span 40	7.6
3.	Sorbitan mono stearate	Span 60	4.7
4.	Sorbitan mono oleate	Span 80	4.3

5.	Sorbitan mono trioleate	Span 85	1.8
6.	Polyoxyethylene sorbitan mono laurate	Tween 20	16.7
7.	Polyoxyethylene Sorbitan Mono palmitate	Tween 40	15.6
8.	polyoxyethylene sorbitan mono stearate	Tween 60	14.9
9.	polyoxyethylene sorbitan mono oleate	Tween 80	15
10.	Polyoxyethylene lauryl ether	Brij 30	9.7
11.	Polyoxyethylene (2) cetyl ether	Brij 52	5
12.	Polyoxyethylene (10) cetyl ether	Brij 56	12.9

➢ **Additive agents**

Different additives have been employed for niosome membrane, with cholesterol being the most prevalent and significant of these substances. (19) By forming a hydrogen bond among its hydroxyl groups and the molecules' alkyl chains, cholesterol interacts with surfactant. (5) By changing the fluidity of chains in bilayers, it raises the transition temperature of vesicles, which can boost stability. Due to cholesterol's ability to diffuse between the bilayer, occupying otherwise empty space and reducing membrane fluidity, it also enhances EE by stabilising the membrane. (13,27-29) Other characteristics of the membrane, such as its permeability and ease of hydration, are influenced by cholesterol. (30,31) The inclusion of cholesterols slows drug release by eliminating the gel to liquid phase transition and enhances drug loading of hydrophilic medicines, both of which can have an impact on drug loading capacity. (32)

Niosomes are given certain charged molecules to increase their stability by supplying electric repulsion to avoid collisions. Dicetyl phosphate (DCP) and phosphotidic acid are two compounds that are negatively charged. Similar to stearyl amine, stearyl pyridinium chloride is a well-known charged compound used in niosomal preparations. (33)

❖ **FACTORS AFFECTING THE PREPARATION OF NIOSOMES**

➢ **Hydrophilic-lipophilic balance (HLB)**

This factor influences the size and quantity of drug loading. Surfactants with an HLB number of 4 to 8 can support vesicle formation. Cholesterol must be added for the development of niosomes since surfactants with HLB values greater than 6 hardly ever produce vesicles. (34)

➢ **CPP**

Polar and non-polar components make up nonionic surfactants. Bilayer vesicles may form instead of micelles depending on the surfactant's HLB, chemical composition, and essential packing parameter (CPP). It is possible to determine the nature of micellar structure created from the CPP value. (2) Spherical micelles are thought to develop when the CPP is less than 0.5, whereas bilayer micelles are thought to form when the CPP is between 0.5 and 1. A CPP greater than 1 indicates the potential for inverted micelle formation. (13)

➢ **Gel liquid transition temperature (Tc)**

It has an impact on EE, membrane permeability, fluidity, and stability. In non-ionic surfactants, Tc and the length of the alkyl chain are associated. The production of "leaky" niosomes is caused by the lower Tc of shorter alkyl chains. Higher Tc surfactants are much more likely to be in an ordered gel phase than those with lower Tc, which lessens bilayer leakage. (14,36)

➢ **Nature of drug**

When it comes to drug trapping in niosomes, the drug's nature is crucial. Numerous factors, including interactions between the drug and the niosome membrane, chemical structure, the drug's hydrophilicity and lipophilicity, and molecular weight influence drug entrapment. For instance, when combined with Tween 60, a water-soluble medication like diclofenac sodium shows the highest loading in niosomes. It's interesting to note that the hydrophobic medication methotrexate had the highest level of entrapment in noisy with Span 60. (1,35,40)

❖ METHOD OF PREPARATION

Different techniques are used to prepare niosomes depending on the sizes and distribution of the vesicles, the number of double layers, the permeability of the vesicle membrane, and the effectiveness of the aqueous phase's entrapment. (37)

➢ **Preparation of Small unilamellar vesicles**

a. Sonication

In a scintillation vial, the mixture of surfactant and cholesterol is combined with the drug-containing aqueous phase. A sonic probe is used to homogenise the mixture for 3 minutes at 60°C. The vesicles are uniformly small and modest in size. (37,38)

b. Microfluidization

A surfactant and drug solution is circulated through an interaction chamber at a rate of 100 ml/min while being compressed. The heat generated during microfluidization is subsequently removed from the solution by running it through a cooling loop, which creates niosomes. (5)

➢ **Preparation of multilamellar vesicles**

a. Hand shaking method (Thin film hydration technique)

In the hand shaking method, a rotary evaporator is used to dissolve the surfactant and cholesterol in a volatile organic solvents like chloroform, diethyl ether, or methanol, leaving a thin coating of the solid mixture deposited on the flask wall. The dried layer is hydrated with an aqueous phase containing the drug while being gently stirred and kept at room temperature. (38)

b. Trans-membrane pH gradient drug uptake process

This process involves dissolving cholesterol and surfactants in an organic solvent. A thin layer is then formed on the wall of the round bottom flask by evaporating this solution under reduced pressure. This film is hydrated using vortex mixing and a citric acid solution with a pH of 4. The resulting vesicles are then subjected to sonication, followed by three cycles of freezing and thawing. After that, a liquid medication solution is added and vortexed. In order to create multilamellar vesicles, the pH of this solution is increased to 7 and heated at 60 °C. (39)

➢ **Preparation of large unilamellar vesicles**

a. Reverse phase evaporation technique (REV)

In this procedure, a solution of ether and chloroform is used to dissolve the cholesterol and surfactant. This is combined with an aqueous phase that contains a drug, and the combined two phases are then sonicated at 4-5°C. A small amount of phosphate buffered saline is added once the clear gel has formed, and then it is further sonicated. Low pressure is used to remove the organic phase at 40 °C. Niosomes are produced by heating the resulting viscous noisome suspension in a water bath at 60°C for 10 minutes before diluting it with phosphate-buffered saline. (37,40)

b. Ether injection method

This procedure involves dissolving the drug and surfactant in diethyl ether, slowly injecting them into an aqueous phase, and then heating them over the boiling point of the organic solvent. (41)

➢ **Miscellaneous**

a. Emulsion method

The emulsion method creates an oil in water emulsion by dissolving surfactant and cholesterol in an organic solvent, which is then added to an aqueous drug solution. The organic solvent is subsequently evaporated in order to produce niosomal suspension in an aqueous medium. (2)

b. Lipid injection method

For this procedure, organic solvents are not required. Surfactant and cholesterol are combined to form a niosomal suspension by being injected into a heated, highly agitated aqueous phase containing drug molecules. (5)

c. Niosomes prepared using micelle solution and enzymes

Enzymes can be used to create niosomes from a mixed micellar solution. For instance, esterases damage the ester bonds in polyethylene stearyl derivatives, resulting in the creation of breakdown products such cholesterol and polyoxyethylene, which, when combined with other lipids like dicetyl phosphate, can create multilamellar niosomes. (25)

d. The bubble method

The bubble method is a simple process that doesn't include any organic solvents. The creation of LUVs is achieved by adding surfactants and cholesterol to a buffer solution at 70 °C, homogenising the dispersion for fifteen seconds with a high shear homogenizer, and then passing nitrogen gas through the mixture. (4)

❖ PURIFICATION

Niosome purification is a crucial step because, despite process improvement for drug loading, full drug molecule encapsulation in niosomes is rarely feasible. When used in in vitro and in vivo investigations, the free drug needs to be taken out to prevent the burst release of niosomes. Dialysis, gel filtration, and centrifugation are purification techniques used to get rid of unentrapped drug molecules. (42)

a. Dialysis

In a dialysis tube, the aqueous niosomal dispersion is dialyzed against phosphate buffer, normal saline, or glucose solution. (43)

b. Gel filteration

By gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or regular saline, the unentrapped drug is eliminated. (44,45)

c. Centrifugation

The supernatant is separated after centrifuging the niosomal solution. To create a niosomal suspension free of any drug that has not been entrapped, the pellet is first washed and then resuspended. (46,47)

❖ CHARACTERIZATION

a. Niosome particle size and size distribution

Microscopy and other methods, like as dynamic light scattering (DLS), can be used to assess the size of niosomes. A different name for DLS is photon correlation spectroscopy. (2) This process requires a tiny amount of sample and is quick and non-destructive. It may be used to measure particles between 3 and 3000 nm in size. This method is based on the idea of little particles scattered in a medium randomly moving. A monodispersed sample is indicated by a polydispersity index (PDI) value less than 0.5, which measures the distribution of niosome size. (25)

b. Zeta potential

The surface charge, commonly referred to as the zeta potential, is crucial information in establishing the physical stability of niosomes. Laser Doppler anemometry can be used to detect the surface potential.and the size of the zeta potential indicates the strength of the electrostatic attraction between two nearby particles. Acceptable stability is defined as a zeta potential of greater than +30 mV or less than 30 mV for niosomes. (3,48,49)

c. Morphology

Niosome morphology is investigated via microscopic methods. For liquid state samples, scanning electron microscopy (SEM) is preferred over electronic microscopic techniques such as transmission electronic microscopy (TEM), negative-staining electronic microscopy (NS-TEM), and freeze-fracture electronic microscopy (FF-TEM). (18,50)

d. Niosome stability

The vesicular system's stability is a problem that affects not only its physical and chemical stability but also its biological stability. The possible usage of the niosomes in vivo and in vitro is determined by this essential parameter. Zeta potential and particle size are typically monitored over time to determine stability, with changes in these two metrics indicatives of potential instability. To evaluate how temperature affects stability, stability is frequently tested for three months in a variety of conditions, such as 4 °C, 25 °C, and 40 °C at 75% relative humidity. (32,42,51,52,53)

e. Bilayer characterization

Niosomes can be found in unilamellar or multilamellar structures, respectively. (13) Nuclear magnetic resonance spectroscopy (NMR), AFM, and small angle X-ray scattering (SAXS) can all be used to count the number of lamellae. Niosomal bilayer thickness can be determined using energy-dispersive X-ray diffraction (EDXD) in conjunction with SAXS. (54)

f. Entrapment efficiency (EE)

The amount of drug molecules successfully trapped inside vesicles, in this case niosomes, is known as EE and can be stated by the following equation:

$$EE = (\text{Amount of drug entrapped} \div \text{Total amount of drug added}) \times 100\%$$

The overall amount of drug refers to the entire amount of drug used in preparation, whereas the amount of drug entrapped refers to the actual amount of drug molecules successfully contained in the vesicles. (2) By means of dialysis, filtration, or centrifugation, the free drug molecules must be separated from the drug that is trapped. For genetic materials, spectrophotometry or gel electrophoresis followed by UV densitometry can be used to measure the EE. (55,56)

g. In vitro drug release

A dialysis membrane is typically used to study the release of medicinal compounds from niosomes. Here, a dialysis bag filled with a purified niosomal solution devoid of free drug is filled, knotted at the ends, and placed in a beaker of phosphate buffered saline (PBS) at a constant temperature of 37 °C while being magnetically stirred. At certain intervals, samples are obtained, and the same volume of new medium is then substituted. After that, these samples are examined with the proper assays to establish the amount of drug released over time. Niosomes' in vitro release behaviour is a fundamental parameter that is influenced by a variety of variables, including hydration volume, membrane composition, and drug concentration. (49,50,57)

❖ APPLICATION

Niosomes are used for a variety of purposes, including drug delivery and cosmetics.

➢ Delivery of proteins and peptides

Because GIT's acidic media and enzymes can degrade proteins and peptides, oral delivery of these medications has long been challenging. However, niosomes shield these medications from the proteolytic enzymes. (58,59) Niosomes of Moghassemi et al.'s preparation of Albumin from bovine serum (BSA). An inverted light microscope was utilised to detect the position of the protein in the vesicle while methyl orange was employed to optimise the formulation for loading and release as a function of cholesterol to span 60 M ratios. To improve the penetration of insulin, trimethyl chitosan-coated niosomes of insulin are also made for oral administration. (60,61)

In one investigation, PEG 6000, Tween 80, and Span 80 were used to create niosomal carriers for haemoglobin (Hb). Their findings demonstrate that this mechanism can stabilise Hb by adsorbing it to the surface of the niosome membrane and allowing it to spread there (Liu et al., 2007) (62). Researchers created a kind of insulin that was contained within niosomes and was stable in bile salt solutions. Because they could successfully delay the release of insulin in both SIF (simulated intestinal fluid) and SGF (simulated gastric fluid), the findings of this study suggested that niosomes may be used as oral carriers of insulin. (63)

In an in-vitro intestinal loop model, Yoshida et al.'s [45] investigation into the oral distribution of 9-desglycinamide, 8-arginine vasopressin trapped in niosomes revealed that the stability of the peptide greatly improved. (64)

➢ Delivery of anticancer drugs

Niosomes can be used to deliver anticancer medications specifically where they are needed. This targeting could be physical (64) (delivery depending on certain environmental parameters like pH or magnetic fields) or active (deposition of niosomes within the tumour due to the distinct features of the tumour cells not present in the normal cells) (65) (active uptake of niosomes by the tumour cell). (67) Either the surface's structural properties can be changed to produce active targeting, or the ligand can be attached to the nisomes. For ligand attachment, either the cholesterol-PEG-ligand conjugation or the terminus of the polyethylene glycol chain can be used to connect the ligand to the niosomes. (68-70)

Paclitaxel niosomes are effectively made for oral administration to increase bioavailability and stability. (71) Lin et al. (72) modified ethanol injection method was used to create PEGylated niosomes of gammogenic acid. These PEGylated niosomes are employed as the delivery system for anticancer therapy and to improve gammogenic acid stability. For the delivery of several drugs, Sharma et al. (73) created a self-degrading niosome. In this study, the anticancer medications curcumin (hydrophobic) and doxorubicin hydrochloride (hydrophilic) were encapsulated in niosomes. They noticed two distinct phases of release: the initial phase saw the release of doxorubicin for the first two days, followed by the release of curcumin for the following seven days. Against HeLa cell lines, an enhanced (synergistic) cytotoxic impact was seen. Alami et al. (81) cationic PEGylated niosomes were produced for the simultaneous delivery of paclitaxel and curcumin. The improved synergistic anticancer effectiveness was reported by these niosomes. The morusin niosome was produced by Agarwal et al. (75) in order to enhance anticancer treatment. He saw that the drug released in a pH-dependent manner. Morusin was released from niosomes less readily at pH 7.4 than it was at pH 4.5. In acidic conditions with a pH of 4.5 after 120 hours, drug release was 58.1%; however, at physiological pH 7.4, only 43.3% of the drug was released. It suggests that high drug release is possible in the acidic environment of cancer cells.

Azmin et al. (35) constructed niosomes containing methotrexate to have a significantly larger AUC (Area under the concentration-time curve) than methotrexate solution. In order to cure skin cancer, Paolino et al. (20) created bola-niosomes, which are carriers for the medicine 5-fluorouracil. When compared to an aqueous solution of the drug, this carrier greatly improved 5-fluorouracil penetration. As an anthracycline antibiotic that is frequently used in combination treatment, doxorubicin has been studied by Rogerson and colleagues for its niosomal delivery in mice with the S-180 tumour. Doxorubicin was given as a bolus injection into mice's tail veins at a dose of 5 mg/kg, and even after just one injection, the drug's concentration in S180 sarcoma had increased. Doxorubicin profiles after free and niosomal drug administration were examined, and it was discovered that levels of niosomal-DOX prepared from surfactant alone were slightly higher than those of free drug administration after the initial peaks (30 min), but only significantly after administration in cholesterol-containing niosomes. Because gradual release from niosomes and circulation are more likely than vesicle entrapment and buildup in the liver, there is an increase in the concentration of drug in the plasma. (76) Through in vitro breast cancer cytotoxicity and in vivo solid antitumor effectiveness, tamoxifen citrate (TMC) niosomes were used to treat localised cancer. Niosomal TMC's tumour size was reduced more in the in vivo testing than it was with the free medication (Shaker et al.). (36) Dodecylglucuronamide surfactant was able to create niosomes with or without cholesterol in one investigation using niosomal formulations based on the medication used to entrap the model drugs doxorubicin and 5-fluorouracil. (77)

➢ Brain Targeting

By creating temozolomide-containing "smart niosomes," De et al. (78) demonstrated improved medication delivery to the brain in glioblastoma patients. A peptide chlorotoxin (36 amino-acid short peptides discovered from the venom of the scorpion Leiurus quinquestriatus) (79) was employed for surface modification to obtain the targeted specificity to gliomas. An antiprotozoal medication called pentamidine also has anti-inflammatory and neuroprotective effects in Alzheimer's patients. (80-82) Its weak blood-brain barrier permeability and strong hepatotoxocity limit its therapeutic usefulness. Pentamidine niosomes with chitosan-glutamate coating were created for intranasal medication delivery to the brain to solve these problems. Bypassing the blood-brain barrier and first-pass hepatic metabolism, intra-nasal administration allows for direct access to the brain. (83-85)

➢ **Drug targeting**

Niosome-mediated targeted drug delivery can be studied in two ways. First, a type of circulating serum factor termed opsonin is involved in the preferential uptake of niosomes by the cells of the Reticulo Endothelial System (RES). Niosomes are advantageous carriers for targeted medication delivery in situations where infectious organisms are present in the organs of RES, as demonstrated by one study that demonstrates Tween 20 niosomes have intrinsic selectivity to macrophages. (86) Second, the medicine can be guided to the intended organs, including the liver and brain. Functionalized niosomes used for dynorphin-B brain targeting were examined by Bragagni et al. In this study, the glucose derivative N-palmitoyl glucosamine was used to functionalize niosomal formulation. When mice were given the optimised niosomal formulation of dynorphin-B via intravenous (IV) administration, the antinociceptive effect was noticeably stronger than when the peptide was supplied via IV in simple solution form at the same concentration. (28) For liver targeting, ribavirin niosomes were made utilising the thin film hydration process using Span 60, DCP, and cholesterol at various molar ratios. The outcomes demonstrated that, in comparison to the other molar ratios, the improved niosomal formulation can greatly boost ribavirin entrapment %. To compare the liver ribavirin concentration, niosomal ribavirin dispersion with an improved formulation and free ribavirin solution were both injected intraperitoneally into two groups of rats. According to the results, ribavirin accumulates in the liver more than six times as much as it does in ribavirin-free solutions. (87) In a different study, Bragagni et al. created a niosomal formulation that was functionalized with the glucose derivative N-palmitoylglucosamine (NPG) to create a brain-targeted delivery system for doxorubicin encapsulation. Their chosen formulation, produced via thin-layer evaporation, contained Span, Solulan, NPG, and cholesterol. Comparative to the commercial formulation, this formulation's intravenous injection to rats led to less drug buildup in the heart. (88)

➢ **Gene delivery**

The properties of the vector have a big impact on how well gene therapy works. Only a few research have concentrated on the use of niosomes as vectors for the transfer of genes, despite the fact that it took them almost three decades to join the pharmaceutical sciences. For the treatment of a number of skin conditions, niosomes have been employed as a cutaneous gene delivery system (Geusens et al.). (89) To function as a vector, niosomes must be charged in their bilayer structure (Huang et al.) (Manosroi et al.). (90,91) Basiri et al. created negatively charged niosomes for the transport of genes. In this study, DNA (PUC18 supercoiled plasmid) complexation was carried out using niosomes. To manufacture niosomes using the film hydration method, various concentrations of Span, Tween, and cholesterol were utilised, either with or without dicetylphosphate (Basiri et al.). (92) In order to assess the effectiveness of transfection in rat retinas to cure inherited retinal illnesses, Puras et al. created a novel niosome formulation based on the 2,3-di(tetradecyloxy)propan-1-amine cationic lipid and mixed it with squalene and polysorbate 80. Since the 2,3-di(tetradecyloxy) propan-1-amine cationic lipid has four domains that control the transfection processes—the polar head, nonpolar hydrophobic chains, linker, and backbone—it gives hope for gene delivery applications. However, it was shown that the linker domain's ether bond is more harmful to cells than its equivalent ester bond. Since it has been noted that the presence of polysorbate 80 reduces the amount of the cationic lipid in the formulation, which increases the tolerance of the cells, the nonionic surfactant polysorbate 80 has been mixed with the cationic lipid to produce niosomes in order to address this issue. The presence of polyethylene glycol (PEG) chains in polysorbate 80's structure improves the transfection effectiveness of liposome formulations and functions as an emulsifier to provide a steric barrier that prevents aggregation. Squalene has been added to the noisome formulation in place of traditional cholesterol to increase the stability and hardness of the vesicles. A terpenoid family member of natural lipids called squalene serves as a metabolic building block for steroid hormones like testosterone. The pCMS-EGFP plasmid was combined with niosomes produced by the solvent emulsification evaporation process to create lipoplexes. This innovative niosomal technology shows a possible method for delivering genetic material to the retina to treat hereditary retinal disorders (Puras et al.). (93)

➢ **Diagnostic imaging**

The nanometric size of the carriers plays a significant role in the early tumour diagnosis. As a diagnostic tool for X-ray imaging, iobitridol is transported by the niosomes. Cholesterol, D-alpha tocopheryl polyethylene glycol 1000 succinate, sorbitan monostearate, polyoxyethylene glycol 4000 stearate, and dicetylphosphate were used to make these niosomes (Muller et al., 2000). (94) The niosomal system significantly improved tumour targeting of an encapsulated paramagnetic agent assessed with MR imaging in a human carcinoma xenograft model, according to Luciani et alevaluation .'s of a magnetic resonance (MR) imaging contrast agent for tumour detection based on combination of polyethyleneglycol (PEG) and glucose conjugates to the surface of niosomes for the targeting of overexpressed glucose receptors (Luciani et al.) (95)

Niosomes may be beneficial for diagnostic imaging of organs like the liver and spleen because they can transport radiopharmaceuticals. Imaging uses DTPA that has been 99mTc labelled. (4,96) Niosomes Iobitridol, a diagnostic drug, is utilised for x-ray imaging. (97) An encapsulated paramagnetic drug has been demonstrated to more effectively target tumours when administered as a conjugated niosomal formulation of gadobenate dimeglumine with [N-palmitoylglucosamine (NPG)], PEG 4400, and both NPG and PEG. (95,98) By including contrast agents or dyes (near-infrared) in the inner aqueous or non-aqueous compartment or by conjugating onto the surface of niosomes, A.Massotti (99) developed unique biconjugate niosomes for imaging. Gd (EDTA) 2 can be utilised as a contrast agent during integration. (100) Optical imaging combined with magnetic resonance imaging is a crucial technique for the diagnosis of malignancies. (101-103) For in-vivo imaging, polyethylene amino groups can be conjugated with near-infrared probes. (103,104)

➢ **Transmucosal drug delivery**

To enhance local and systemic absorption, bioadhesion has been extensively investigated in the creation of pharmaceuticals. In the past ten years, transmucosal medication delivery has impressively accelerated, particularly with the development of nano drug delivery technologies. (105-107) Ocular, nasal, oromucosal (gingival, sublingual, and buccal), gastrointestinal, pulmonary and vaginal sites are among the transmucosal drug delivery pathways. Each site has unique characteristics, and these characteristics must be taken into account while constructing a viable drug delivery system. Because of their advantages, niosomes have been

researched for transmucosal administration of numerous substances through the oral, nasal, and vaginal mucosa. Niosomes are a versatile drug delivery mechanism.

El-Alim and colleagues created benzocaine proniosomal gel formulations employing Span 80, Span 80, Span 85, and mixtures of the three to produce efficient buccal delivery of benzocaine for local anaesthetic. Increases in the ratio of Span 80 or Span 85 were shown to improve EE, and tests on the in vitro release of drugs revealed an initial burst release followed by a delayed release. When tested using a chicken pouch as a model mucosal membrane, formulations made with Span 80 and 85 exhibited superior rates and degrees of benzocaine permeability. Physical stability experiments revealed that after one month of storage at 4–8 °C, more than 90% of the medication was still present. Proniosomes that were loaded with benzocaine had better mucosal membrane permeability and might be used to treat mucosal discomfort. (105)

In order to administer drugs to the brain without crossing the blood-brain barrier, transmucosal administration through the nasal mucosa has been researched. Making advantage of this method will lessen negative effects brought on by systemic circulation, eliminate first pass metabolism, and increase bioavailability. Niosomes smaller than 300 nm can pass through the blood-brain barrier, and because they can transport both hydrophilic and hydrophilic substances, they have been studied for the administration of a variety of active pharmaceutical ingredients. Abdelrahman et al study's produced elastic niosomes called spanlastics for risperidone transport to the brain. These nanoparticles are made of sorbitan and differ from traditional niosomes in that they have an edge activator that makes their membranes more flexible. The spanlastics were made utilising the ethanol injection process, Span 60, and polyvinyl alcohol. The effect of spanlastics to enhance permeability was investigated utilising ex vivo permeation on sheep nasal membrane. When compared to the drug solution, the improved formulation demonstrated noticeably higher transnasal penetration and better distribution to the brain. This may be a promising technology that may efficiently transport drugs from the nose to the brain given the improvement in brain targeting and the percentage of medication delivered through the olfactory route. (106) The specialised epithelial cells take up orally administered antigens. The chosen antigen is subsequently introduced into the local lymphoid tissue, activating particular B lymphocytes at the nascent stage. (108)

A clinical trial was carried out by Priprem and colleagues to look into the pharmacokinetics of a melatonin niosomal oral gel in humans. Niosomal oral gel made with melatonin has been developed to address issues with subpar drug stability and absorption. 14 male participants were chosen for this randomised, double-blind, three-phase crossover design. On the labial mucosa, melatonin oral gel was administered topically at dosages of 2.5, 5 and 10 mg with a seven-day washout between each treatment. Maximum plasma concentration (Cmax), area under the curve (AUC), time to peak concentration (Tmax), and elimination half-life (t1/2) were among the pharmacokinetic characteristics that were identified. The study also assessed potential adverse effects such nauseousness, vomiting, headaches, and irritability. Results showed that when compared to conventional immediate release oral dosage forms, the three different doses of melatonin niosomal oral gel provided dose-proportional pharmacokinetic profiles, prolonged the absorption process, and improved plasma concentration, time to maximum plasma concentration, and half-life. (109)

The aim of the study was to develop and evaluate sublingual fast-dissolving films containing metoprolol tartrate-loaded niosomes. When administered sublingually, the films were used to increase the medicine's bioavailability; however, niosomes allowed for a longer-lasting release of the drug. The size, zeta potential, and degree of entrapment of the niosomes were determined. In order to incorporate the selected niosomal formulation into polymeric films, avicel was utilised as a superdisintegrant while HPMC E15 and methyl cellulose were used as film-forming polymers. In comparison to commercial oral tablets, the sublingual film demonstrated a greater rate of drug absorption and higher drug plasma levels. When compared to oral tablet delivery (39.37%11.4%), the absolute bioavailability of the medication after sublingual administration was shown to be much higher (91.06%13.28%). (A. Allam et al.) (110)

- **Delivery of natural products**

Today, there is a growing interest in research on innovative delivery strategies for natural goods. Here is a quick summary of how the niosome is used to deliver natural ingredients. Turmeric is a from the plant curcuma longa, a hydrophobic polyphenol. It is said to offer a number of pharmacological effects, including anti-inflammatory, antioxidant, and anti-tumor properties. It has been reported that curcumin is particularly effective in treating several cancers, including leukaemia, lymphoma, pancreatic cancer, prostate cancer, colorectal cancer, and breast cancer. Due to curcumin's low aqueous solubility, volatility, rapid metabolic rate, and poor bioavailability, clinical usage of the compound is restricted. (74,111-113) Alemi and others (74) Curcumin and paclitaxel were synthesised as cationic PEGylated niosomes for an improved synergistic anticancer action. Curcumin niosomes were created by Sharma et al. (73) and Naderinezhad et al. (114) using doxorubicin. By combining curcumin and doxorubicin, Naderinezhad et al. (114) sought to determine whether this combination may have a synergistic impact and overcome doxorubicin resistance. Other delivery systems, such as nanoparticles (115), liposomes, lipid nanoparticles, chitosan/poly (butyl cyanoacrylate) nanoparticles, and pH-sensitive prodrug nanoparticles, have also been tested to deliver the combination of curcumin and doxorubicin for the treatment of different cancers.

Other natural compounds, like curcumin, are also administered using a cutting-edge medication delivery technology. Paeonol ethosomes were produced for transdermal administration by Ma et al. (116) Peonies like Paeonia moutan and Radix Cynanchi Paniculati contain péeonol. (117) Paeonol has anti-inflammatory (118), antidiabetic, antiallergic, and antitumor properties. Aqueous solubility (119) and stability are problems with oral administration; transdermal delivery was utilised to solve them. Morusin is a prenylated flavonoid that is naturally found in the roots of the morus alba plant. It has been shown to have antibacterial, antioxidant, anti-inflammatory, and anti-tumor properties. (75,120) In order to bypass the reticuloendothelial system and enter the target cell while also overcoming the issue of poor solubility and stability, Agarwal et al. (75) created morusin-loaded niosomes. To improve the topical permeability, Insan and Jufri [85] created a niosome of green tea extract. Niosomes were also produced for topical application by Pando et al. (122) They contained resveratrol, a naturally occurring polyphenol with anti-tumor, cardioprotective, anti-oxidant, and anti-inflammatory activity, but it has a low water solubility, a short biological half-life,

quick metabolism, and is easily oxidized. (73,123–127) Niosomes of Ginkgo biloba extract were created by Jin et al. (128) to increase oral bioavailability. Morin hydrate, a bioflavonoid having anti-oxidant and anti-cancer properties, was made into niosomes by Waddad et al. (129) These niosomes were designed to be administered intravenously and have demonstrated the potential to pass the blood-brain barrier. Papain elastic niosomes were created by Manosroi et al. (130) and added to a gel to improve transdermal distribution for the treatment of scars. Papain is a protease enzyme that is extracted from Carica papaya latex (131) and used to heal scars, although its high molecular weight makes topical application difficult. (132) Manosroi et al. (130) attempted to improve the transdermal permeability by creating elastic niosomes. To boost the anti-tumor impact, decrease toxicity, and promote overall therapeutic efficacy, Lin et al. (72) produced PEGylated niosomes of gambogenic acid. With the use of span60/tween60 niosomes, Junyaprasert et al. (38) have worked to improve the permeability of ellagic acid. A phytochemical having antioxidant qualities is ellagic acid. It is employed for its ability to lighten skin while having photoprotective benefits (133,134) Its very low solubility in water and many other organic solvents makes formulation design challenging. (135,136) Junyaprasert In 2013, et al. (137) investigated how chemical penetration enhancers affected the permeation of ellagic acid loads.

- **Topical and transdermal delivery**

Localized medication release at the site of action and less adverse effects due to reduced systemic absorption are two benefits of topical drug administration. (7,138) Transdermal drug delivery involves transferring the active substances over the skin for systemic circulation, which provides a number of benefits over other methods of administration. Transdermal distribution is non-invasive since no needle is needed, it prevents acidic and enzymatic breakdown in the gastrointestinal tract, and it removes the possibility of drug-food interactions. It also has a better bioavailability because first-pass hepatic metabolism can be avoided. However, utilisation of the transdermal route is restricted due to the low rate of drug molecule penetration, with the stratum corneum serving as the main barrier for drug absorption through the skin. (122,139) The optimum properties of the drugs for transdermal distribution include low molecular weight (500 Da), lipophilicity, and efficacy at low dosage. Niosomes have been used topically to improve drug delivery to the epidermis and dermis layer, and this has been frequently reported. (140)

Topical vaccines are a fascinating field in cutaneous drug delivery; niosomes have been researched in this area for antigen delivery. The topical vaccine has the benefits of flexibility and safety. The immune system's specialised cells, including Langerhans cells, dendritic cells, and epidermotropic lymphocytes, are distributed throughout the layers of the skin to operate as a barrier against foreign invaders. Infection with hepatitis B is still a serious global health issue. In order to develop a non-invasive topical genetic vaccine against the hepatitis B virus, Vyas and colleagues looked into niosomes. (141,142) Niosomes containing Span 85 and cholesterol were loaded with DNA encoding the hepatitis B surface antigen (HBsAg). By assessing the hepatitis B surface antigen titer and cytokine levels after topical administration of antigen-loaded niosomes to Balb/c mice, the immune-stimulating action was ascertained. Results were compared with intramuscular administration of pure recombinant HBsAg and topical application of bare DNA and liposome-encapsulated DNA. Comparing topical niosomes to intramuscularly injected recombinant antigens, identical quantities of endogenous cytokines and serum antibody titers were produced. (142,143)

- **Applications of niosomes in cosmetics**

A cosmetics firm named L'Oréal (Clichy, France) initially created and patented niosomes in 1975, and goods with the trade name Lancôme (Paris, France) were introduced in 1987. Since then, a wide range of pharmacological uses and a variety of cosmetic products with a range of uses—including anti-aging, skin-whitening, moisturising, and sunscreen—have been created and marketed. (144,145)

Because of their benefits, such as better stability of entrapped active components, enhanced skin penetration, bioavailability, improved surface adherence, and prolonged release qualities, niosomes have received a lot of attention as a carrier system for cosmetic actives. (146) Niosomes' utility in cosmetic formulations has been assessed in comparison to more traditional formulations like emulsions. Because niosomes are less toxic, they can be loaded with active substances that have beneficial effects for skin moisturising and tanning products. (147)

❖ CONCLUSION

Niosomes have undergone substantial research in recent years for a variety of uses, including topical, transdermal, oral, and brain-targeted drug delivery. They can attain higher EE than their analogue system, liposomes, and are simple and inexpensive to prepare. The pharmaceutical and cosmetic sciences sectors have a lot of potential for this adaptable medication delivery technology. Niosomes are promising delivery vehicles, and novel preparation, modification, and formulation techniques have the ability to further unlock their potential by enabling targeted distribution, improved drug entrapment effectiveness, and the development of vesicles with unique shapes.

REFERENCES

1. Khoee S, Yaghoobian M. Niosomes: A novel approach in modern drug delivery systems. InNanostructures for drug delivery 2017 Jan 1 (pp. 207-237). Elsevier.
2. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as an emerging platform for cancer therapy. Nano-Enabled Medical Applications. 2020 Nov 23:61-91.
3. Marianecci C, Di Marzio L, Rinaldi F, Celia C, Paolino D, Alhaique F, Esposito S, Carafa M. Niosomes from 80s to present: the state of the art. Advances in colloid and interface science. 2014 Mar 1;205:187-206.
4. Rajera R, Nagpal K, Singh SK, Mishra DN. Niosomes: a controlled and novel drug delivery system. Biological and Pharmaceutical Bulletin. 2011 Jul 1;34(7):945-53.
5. Chen S, Hanning S, Falconer J, Locke M, Wen J. Recent advances in non-ionic surfactant vesicles (niosomes): Fabrication, characterization, pharmaceutical and cosmetic applications. European Journal of Pharmaceutics and Biopharmaceutics. 2019 Nov 1;144:18-39.
6. Florence AT. Targeted and Controlled Drug Delivery: Novel Carrier Systems-SP Vyas, RK, Khar, CBS Publishers, New Delhi, 2002, ISBN 81-239-0799-0. International Journal of Pharmaceutics. 2003;1(267):157.

7. Alomrani AH, Al-Agamy MH, Badran MM. In vitro skin penetration and antimycotic activity of itraconazole loaded niosomes: Various non-ionic surfactants. Journal of Drug Delivery Science and Technology. 2015 Aug 1;28:37-45.
8. Zeng W, Li Q, Wan T, Liu C, Pan W, Wu Z, Zhang G, Pan J, Qin M, Lin Y, Wu C. Hyaluronic acid-coated niosomes facilitate tacrolimus ocular delivery: Mucoadhesion, precorneal retention, aqueous humor pharmacokinetics, and transcorneal permeability. Colloids and Surfaces B: Biointerfaces. 2016 May 1;141:28-35.
9. Li Q, Li Z, Zeng W, Ge S, Lu H, Wu C, Ge L, Liang D, Xu Y. Proniosome-derived niosomes for tacrolimus topical ocular delivery: in vitro cornea permeation, ocular irritation, and in vivo anti-allograft rejection. European journal of pharmaceutical sciences. 2014 Oct 1;62:115-23.
10. Sharma V, Anandhakumar S, Sasidharan M. Self-degrading niosomes for encapsulation of hydrophilic and hydrophobic drugs: an efficient carrier for cancer multi-drug delivery. Materials Science and Engineering: C. 2015 Nov 1;56:393-400.
11. Bhardwaj P, Tripathi P, Gupta R, Pandey S. Niosomes: A review on niosomal research in the last decade. Journal of Drug Delivery Science and Technology. 2020 Apr 1;56:101581.
12. Abdelkader H, Alani AW, Alany RG. Recent advances in non-ionic surfactant vesicles (niosomes): self-assembly, fabrication, characterization, drug delivery applications and limitations. Drug delivery. 2014 Mar 1;21(2):87-100.
13. Moghassemi S, Hadjizadeh A. Nano-niosomes as nanoscale drug delivery systems: an illustrated review. Journal of controlled release. 2014 Jul 10;185:22-36.
14. Yuksel N, Bayindir ZS, Aksakal E, Ozcelikay AT. In situ niosome forming maltodextrin proniosomes of candesartan cilexetil: In vitro and in vivo evaluations. International journal of biological macromolecules. 2016 Jan 1;82:453-63.
15. Zeng W, Li Q, Wan T, Liu C, Pan W, Wu Z, Zhang G, Pan J, Qin M, Lin Y, Wu C. Hyaluronic acid-coated niosomes facilitate tacrolimus ocular delivery: Mucoadhesion, precorneal retention, aqueous humor pharmacokinetics, and transcorneal permeability. Colloids and Surfaces B: Biointerfaces. 2016 May 1;141:28-35.
16. Mokhtar M, Sammour OA, Hammad MA, Megrab NA. Effect of some formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared from proniosomes. International journal of pharmaceutics. 2008 Sep 1;361(1-2):104-11.
17. Elhissi A, Hidayat K, Phoenix DA, Mwesigwa E, Crean S, Ahmed W, Faheem A, Taylor KM. Air-jet and vibrating-mesh nebulization of niosomes generated using a particulate-based proniosome technology. International Journal of Pharmaceutics. 2013 Feb 28;444(1-2):193-9.
18. Manosroi A, Jantrawut P, Manosroi J. Anti-inflammatory activity of gel containing novel elastic niosomes entrapped with diclofenac diethylammonium. International journal of pharmaceutics. 2008 Aug 6;360(1-2):156-63.
19. Abdelkader H, Ismail S, Kamal A, Alany RG. Design and evaluation of controlled-release niosomes and discomes for naltrexone hydrochloride ocular delivery. Journal of pharmaceutical sciences. 2011 May 1;100(5):1833-46.
20. Paolino D, Cosco D, Muzzalupo R, Trapasso E, Picci N, Fresta M. Innovative bola-surfactant niosomes as topical delivery systems of 5-fluorouracil for the treatment of skin cancer. International journal of Pharmaceutics. 2008 Apr 2;353(1-2):233-42.
21. Saini N, Sodhi RK, Bajaj L, Pandey RS, Jain UK, Katare OP, Madan J. Intravaginal administration of metformin hydrochloride loaded cationic niosomes amalgamated with thermosensitive gel for the treatment of polycystic ovary syndrome: In vitro and in vivo studies. Colloids and Surfaces B: Biointerfaces. 2016 Aug 1;144:161-9.
22. Gopinath D, Ravi D, Rao BR, Apte SS, Renuka D, Rambhau D. Ascorbyl palmitate vesicles (Aspasomes): formation, characterization and applications. International journal of pharmaceutics. 2004 Mar 1;271(1-2):95-113.
23. Laouini A, Jaafar-Maalej C, Sfar S, Charcosset C, Fessi H. Liposome preparation using a hollow fiber membrane contactor—application to spironolactone encapsulation. International journal of pharmaceutics. 2011 Aug 30;415(1-2):53-61.
24. He RX, Ye X, Li R, Chen W, Ge T, Huang TQ, Nie XJ, Chen HJ, Peng DY, Chen WD. PEGylated niosomes-mediated drug delivery systems for Paeonol: preparation, pharmacokinetics studies and synergistic anti-tumor effects with 5-FU. Journal of Liposome Research. 2017 Apr 3;27(2):161-70.
25. Mahale NB, Thakkar PD, Mali RG, Walunj DR, Chaudhari SR. Niosomes: novel sustained release nonionic stable vesicular systems—an overview. Advances in colloid and interface science. 2012 Nov 15;183:46-54.
26. Balakrishnan P, Shanmugam S, Lee WS, Lee WM, Kim JO, Oh DH, Kim DD, Kim JS, Yoo BK, Choi HG, Woo JS. Formulation and in vitro assessment of minoxidil niosomes for enhanced skin delivery. International journal of pharmaceutics. 2009 Jul 30;377(1-2):1-8.
27. Pham TT, Jaafar-Maalej C, Charcosset C, Fessi H. Liposome and niosome preparation using a membrane contactor for scale-up. Colloids and surfaces B: biointerfaces. 2012 Jun 1;94:15-21.
28. Bragagni M, Mennini N, Furlanetto S, Orlandini S, Ghelardini C, Mura P. Development and characterization of functionalized niosomes for brain targeting of dynorphin-B. European Journal of Pharmaceutics and Biopharmaceutics. 2014 May 1;87(1):73-9.
29. Muzzalupo R, Tavano L, La Mesa C. Alkyl glucopyranoside-based niosomes containing methotrexate for pharmaceutical applications: evaluation of physico-chemical and biological properties. International journal of pharmaceutics. 2013 Dec 15;458(1):224-9.
30. Basiri L, Rajabzadeh G, Bostan A. Physicochemical properties and release behavior of Span 60/Tween 60 niosomes as vehicle for α-Tocopherol delivery. LWT. 2017 Oct 1;84:471-8.
31. Tavano L, Rossi CO, Picci N, Muzzalupo R. Spontaneous temperature-sensitive Pluronic® based niosomes: Triggered drug release using mild hyperthermia. International journal of pharmaceutics. 2016 Sep 25;511(2):703-8.
32. Abd-Elbary A, El-Laithy HM, Tadros MI. Sucrose stearate-based proniosome-derived niosomes for the nebulisable delivery of cromolyn sodium. International journal of pharmaceutics. 2008 Jun 5;357(1-2):189-98.
33. Kumavat S, Sharma PK, Koka SS, Sharma R, Gupta A, Darwhekar GN. A Review on Niosomes: Potential Vesicular Drug Delivery System. Journal of Drug Delivery and Therapeutics. 2021 Sep 15;11(5):208-12.
34. Yoshida H, Lehr CM, Kok W, Junginger HE, Verhoef JC, Bouwstra JA. Niosomes for oral delivery of peptide drugs. Journal of controlled release. 1992 Jul 1;21(1-3):145-53.
35. Chandraprakash KS, Udupa N, Devi PU, Pillai GK. Effect of niosome encapsulation of methotrexate, macrophage activation on tissue distribution of methotrexate and tumor size. Drug Delivery. 1993 Jan 1;1(2):133-7.

36. Shaker DS, Shaker MA, Hanafy MS. Cellular uptake, cytotoxicity and in-vivo evaluation of Tamoxifen citrate loaded niosomes. International journal of pharmaceutics. 2015 Sep 30;493(1-2):285-94.
37. Kazi KM, Mandal AS, Biswas N, Guha A, Chatterjee S, Behera M, Kuotsu K. Niosome: a future of targeted drug delivery systems. Journal of advanced pharmaceutical technology & research. 2010 Oct;1(4):374.
38. Baillie AJ, Coombs GH, Dolan TF, Laurie J. Non-ionic surfactant vesicles, niosomes, as a delivery system for the anti-leishmanial drug, sodium stibogluconate. Journal of pharmacy and pharmacology. 1986 Jul;38(7):502-5.
39. Bhaskaran S, Lakshmi PK. Comparative evaluation of niosome formulations prepared by different techniques. Acta Pharmaceutica Sciencia. 2009;51(1).
40. Naresh RR, Pillai GK, Udupa N, Chandrashekar G. Anti-inflammatory activity of niosome encapsulated diclofenac sodium in arthritic rats. Indian Journal of Pharmacology. 1994;26(1):46-8.
41. Devaraj GN, Parakh SR, Devraj R, Apte SS, Rao BR, Rambhau D. Release studies on niosomes containing fatty alcohols as bilayer stabilizers instead of cholesterol. Journal of colloid and interface science. 2002 Jul 15;251(2):360-5.
42. Manconi M, Sinico C, Valenti D, Loy G, Fadda AM. Niosomes as carriers for tretinoin. I. Preparation and properties. International journal of pharmaceutics. 2002 Mar 2;234(1-2):237-48.
43. Chauhan S, Luorence MJ. The preparation of polyoxyethylene containing non-ionic surfactant vesicles. J. Pharm. Pharmacol. 1989;41(6).
44. Yoshioka T, Sternberg B, Florence AT. Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60 and 80) and a sorbitan triester (Span 85). International journal of pharmaceutics. 1994 Apr 25;105(1):1-6.
45. Devi SG, Udupa N. Niosomal sumartriptan succinate for nasal administration. Indian Journal of Pharmaceutical Sciences. 2000;62(6):479.
46. Hu C, Rhodes DG. Proniosomes: a novel drug carrier preparation. International journal of pharmaceutics. 1999 Aug 5;185(1):23-35.
47. Shekade MS. Journal Of Pharmacy And Experimental Medicine.
48. Zubairu Y, Negi LM, Iqbal Z, Talegaonkar S. Design and development of novel bioadhesive niosomal formulation for the transcorneal delivery of anti-infective agent: In-vitro and ex-vivo investigations. asian journal of pharmaceutical sciences. 2015 Jul 1;10(4):322-30.
49. Escudero I, Geanta RM, Ruiz MO, Benito JM. Formulation and characterization of Tween 80/cholestherol niosomes modified with tri-n-octylmethylammonium chloride (TOMAC) for carboxylic acids entrapment. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2014 Nov 5;461:167-77.
50. El-Menshawe SF. A novel approach to topical acetazolamide/PEG 400 ocular niosomes. Journal of drug delivery science and technology. 2012 Jan 1;22(4):295-9.
51. Patel J, Ketkar S, Patil S, Fearnley J, Mahadik KR, Paradkar AR. Potentiating antimicrobial efficacy of propolis through niosomal-based system for administration. Integrative medicine research. 2015 Jun 1;4(2):94-101.
52. Kassem AA, Abd El-Alim SH, Asfour MH. Enhancement of 8-methoxypsoralen topical delivery via nanosized niosomal vesicles: Formulation development, in vitro and in vivo evaluation of skin deposition. International journal of pharmaceutics. 2017 Jan 30;517(1-2):256-68.
53. Manconi M, Valenti D, Sinico C, Lai F, Loy G, Fadda AM. Niosomes as carriers for tretinoin: II. Influence of vesicular incorporation on tretinoin photostability. International Journal of Pharmaceutics. 2003 Jul 24;260(2):261-72.
54. Manosroi A, Chutoprapat R, Abe M, Manosroi J. Characteristics of niosomes prepared by supercritical carbon dioxide (scCO2) fluid. International journal of pharmaceutics. 2008 Mar 20;352(1-2):248-55.
55. Chuah LH, De Silva L, Saravanan M, Fu JY. Preparation and optimization of tocotrienol rich fraction (TRF)-loaded niosomes. Asian J Pharm. 2016 Feb 1;11(1):56-7.
56. Dwivedi A, Mazumder A, Du Plessis L, Du Preez JL, Haynes RK, Du Plessis J. In vitro anti-cancer effects of artemisone nano-vesicular formulations on melanoma cells. Nanomedicine: Nanotechnology, Biology and Medicine. 2015 Nov 1;11(8):2041-50.
57. Hao Y, Zhao F, Li N, Yang Y. Studies on a high encapsulation of colchicine by a niosome system. International journal of pharmaceutics. 2002 Sep 5;244(1-2):73-80.
58. Kumar GP, Rajeshwarrao P. Nonionic surfactant vesicular systems for effective drug delivery—an overview. Acta pharmaceutica sinica B. 2011 Dec 1;1(4):208-19.
59. Sharma D, Ali AA, Aate JR. Niosomes as novel drug delivery system. PharmaTutor. 2018 Mar 1;6(3):58-65.
60. Bini KB, Akhilesh D, Prabhakara P, Kamath JV. Development and characterization of non-ionic surfactant vesicles (niosomes) for oral delivery of lornoxicam. International Journal of Drug Development and Research. 2012;4(3):0-.
61. Moghassemi S, Parnian E, Hakamivala A, Darzianiazizi M, Vardanjani MM, Kashanian S, Larijani B, Omidfar K. Uptake and transport of insulin across intestinal membrane model using trimethyl chitosan coated insulin niosomes. Materials science and engineering: C. 2015 Jan 1;46:333-40.
62. Liu T, Guo R, Hua W, Qiu J. Structure behaviors of hemoglobin in PEG 6000/Tween 80/Span 80/H2O niosome system. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2007 Feb 1;293(1-3):255-61.
63. Pardakhty A, Moazeni E, Varshosaz J, Hajhashemi VA, Najafabadi AR. Pharmacokinetic study of niosome-loaded insulin in diabetic rats. DARU journal of pharmaceutical sciences. 2011;19(6):404.
64. Gregoriadis G. Targeting of drugs: implications in medicine. The Lancet. 1981 Aug 1;318(8240):241-7.
65. Tavano L, Muzzalupo R, Mauro L, Pellegrino M, Andò S, Picci N. Transferrin-conjugated pluronic niosomes as a new drug delivery system for anticancer therapy. Langmuir. 2013 Oct 15;29(41):12638-46.
66. Brewer JM, Alexander J. The adjuvant activity of non-ionic surfactant vesicles (niosomes) on the BALB/c humoral response to bovine serum albumin. Immunology. 1992 Apr;75(4):570.
67. Gharbavi M, Amani J, Kheiri-Manjili H, Danafar H, Sharafi A. Niosome: a promising nanocarrier for natural drug delivery through blood-brain barrier. Advances in pharmacological sciences. 2018 Dec 11;2018.
68. Kim TH, Jo YG, Jiang HH, Lim SM, Youn YS, Lee S, Chen X, Byun Y, Lee KC. PEG-transferrin conjugated TRAIL (TNF-related apoptosis-inducing ligand) for therapeutic tumor targeting. Journal of controlled release. 2012 Sep 10;162(2):422-8.

69. Oswald M, Geissler S, Goepferich A. Targeting the central nervous system (CNS): a review of rabies virus-targeting strategies. Molecular pharmaceutics. 2017 Jul 3;14(7):2177-96.
70. Marqués-Gallego P, de Kroon AI. Ligation strategies for targeting liposomal nanocarriers. BioMed research international. 2014 Jul 14;2014.
71. Bayindir ZS, Yuksel N. Characterization of niosomes prepared with various nonionic surfactants for paclitaxel oral delivery. Journal of pharmaceutical sciences. 2010 Apr 1;99(4):2049-60.
72. Zaidi SA. Molecular imprinted polymers as drug delivery vehicles. Drug delivery. 2016 Sep 1;23(7):2262-71.
73. Sharma V, Anandhakumar S, Sasidharan M. Self-degrading niosomes for encapsulation of hydrophilic and hydrophobic drugs: an efficient carrier for cancer multi-drug delivery. Materials Science and Engineering: C. 2015 Nov 1;56:393-400.
74. Alemi A, Zavar Reza J, Haghiralsadat F, Zarei Jaliani H, Haghi Karamallah M, Hosseini SA, Haghi Karamallah S. Paclitaxel and curcumin coadministration in novel cationic PEGylated niosomal formulations exhibit enhanced synergistic antitumor efficacy. Journal of nanobiotechnology. 2018 Dec;16(1):1-20.
75. Agarwal S, Mohamed MS, Raveendran S, Rochani AK, Maekawa T, Kumar DS. Formulation, characterization and evaluation of morusin loaded niosomes for potentiation of anticancer therapy. RSC advances. 2018;8(57):32621-36.
76. Rogerson AC, Cummings J, Willmott N, Florence AT. The distribution of doxorubicin in mice following administration in niosomes. Journal of pharmacy and pharmacology. 1988 May;40(5):337-42.
77. Tavano L, Aiello R, Ioele G, Picci N, Muzzalupo R. Niosomes from glucuronic acid-based surfactant as new carriers for cancer therapy: preparation, characterization and biological properties. Colloids and Surfaces B: Biointerfaces. 2014 Jun 1;118:7-13.
78. De A, Venkatesh N, Senthil M, Sanapalli BK, Shanmugham R, Karri VV. Smart niosomes of temozolomide for enhancement of brain targeting. Nanobiomedicine. 2018 Oct 10;5:1849543518805355.
79. Mamelak AN, Jacoby DB. Targeted delivery of antitumoral therapy to glioma and other malignancies with synthetic chlorotoxin (TM-601). Expert opinion on drug delivery. 2007 Mar 1;4(2):175-86.
80. Cirillo C, Capoccia E, Iuvone T, Cuomo R, Sarnelli G, Steardo L, Esposito G. S100B inhibitor pentamidine attenuates reactive gliosis and reduces neuronal loss in a mouse model of Alzheimer's disease. BioMed research international. 2015 Oct;2015.
81. Capoccia E, Cirillo C, Marchetto A, Tiberi S, Sawikr Y, Pesce M, D'Alessandro A, Scuderi C, Sarnelli G, Cuomo R, Steardo L. S100B-p53 disengagement by pentamidine promotes apoptosis and inhibits cellular migration via aquaporin-4 and metalloproteinase-2 inhibition in C6 glioma cells. Oncology letters. 2015 Jun 1;9(6):2864-70.
82. Hartman KG, McKnight LE, Liriano MA, Weber DJ. The evolution of S100B inhibitors for the treatment of malignant melanoma. Future medicinal chemistry. 2013 Jan;5(1):97-109.
83. Illum L. Is nose-to-brain transport of drugs in man a reality? Journal of pharmacy and pharmacology. 2004 Jan;56(1):3-17.
84. Mistry A, Stolnik S, Illum L. Nanoparticles for direct nose-to-brain delivery of drugs. International journal of pharmaceutics. 2009 Sep 8;379(1):146-57.
85. Casettari L, Illum L. Chitosan in nasal delivery systems for therapeutic drugs. Journal of Controlled Release. 2014 Sep 28;190:189-200.
86. Agrati C, Marianecci C, Sennato S, Carafa M, Bordoni V, Cimini E, Tempestilli M, Pucillo LP, Turchi F, Martini F, Borioni G. Multicompartment vectors as novel drug delivery systems: selective activation of Tγδ lymphocytes after zoledronic acid delivery. Nanomedicine: Nanotechnology, Biology and Medicine. 2011 Apr 1;7(2):153-61.
87. Hashim F, El-Ridy M, Nasr M, Abdallah Y. Preparation and characterization of niosomes containing ribavirin for liver targeting. Drug delivery. 2010 Jul 1;17(5):282-7.
88. Bragagni M, Mennini N, Ghelardini C, Mura P. Development and characterization of niosomal formulations of doxorubicin aimed at brain targeting. Journal of pharmacy & pharmaceutical sciences. 2012 Feb 10;15(1):184-96.
89. Geusens B, Strobbe T, Bracke S, Dynoodt P, Sanders N, Van Gele M, Lambert J. Lipid-mediated gene delivery to the skin. European Journal of Pharmaceutical Sciences. 2011 Jul 17;43(4):199-211.
90. Huang Y, Rao Y, Chen J, Yang VC, Liang W. Polysorbate cationic synthetic vesicle for gene delivery. Journal of biomedical materials research Part A. 2011 Mar 1;96(3):513-9.
91. Manosroi A, Thathang K, Werner RG, Schubert R, Manosroi J. Stability of luciferase plasmid entrapped in cationic bilayer vesicles. International journal of pharmaceutics. 2008 May 22;356(1-2):291-9.
92. Basiri M, Pardakhty A, Mozafari R, Mottaghi A. Preparation and characterization of negatively-charged niosomes as gene-delivery vectors. Research in Pharmaceutical Sciences. 2012 Sep 1;7(5):365.
93. Puras G, Mashal M, Zárate J, Agirre M, Ojeda E, Grijalvo S, Eritja R, Diaz-Tahoces A, Navarrete GM, Avilés-Trigueros M, Fernández E. A novel cationic niosome formulation for gene delivery to the retina. Journal of Controlled Release. 2014 Jan 28;174:27-36.
94. Muller D, Foulon M, Bonnemain B, Vandamme TF. Niosomes as carriers of radiopaque contrast agents for X-ray imaging. Journal of microencapsulation. 2000 Jan 1;17(2):227-43.
95. Luciani A, Olivier JC, Clement O, Siauve N, Brillet PY, Bessoud B, Gazeau F, Uchegbu IF, Kahn E, Frija G, Cuenod CA. Glucose-receptor MR imaging of tumors: study in mice with PEGylated paramagnetic niosomes. Radiology. 2004 Apr;231(1):135-42.
96. Korkmaz M, Özer AY, Hincal AA. DTPA niosomes in diagnostic imaging. InSynthetic surfactant vesicles 2000 Feb 23 (pp. 263-278). CRC Press.
97. Kaur D, Kumar S. Niosomes: present scenario and future aspects. Journal of drug delivery and therapeutics. 2018 Sep 6;8(5):35-43.
98. Madhav NV, Saini A. Niosomes: a novel drug delivery system. International journal of research in pharmacy and chemistry. 2011;1(3):498-511.
99. Masotti A. Niosomes as candidate bioconjugates for imaging and pH-sensitive drug delivery nanocarriers for rare pediatric tumors. Journal of Drug Delivery Science and Technology. 2013 Jan 1;23(1):22-4.

100. Masotti A, Mangiola A, Sabatino G, Maira G, Denaro L, Conti F, Ortaggi G, Capuani G. Intracerebral Diffusion of Paramagnetic Cationic Liposomes Containing Gd (DTPA) 2-Followed by MRI Spectroscopy: Assessment of Patternc Diffusion and Time Steadiness of a Non-Viral Vector Model. International Journal of Immunopathology and Pharmacology. 2006 Apr;19(2):379-90.
101. Rome C, Couillaud F, Moonen CT. Gene expression and gene therapy imaging. European Radiology. 2007 Feb;17(2):305-19.
102. Shah K, Jacobs A, Breakefield XO, Weissleder R. Molecular imaging of gene therapy for cancer. Gene therapy. 2004 Aug;11(15):1175-87.
103. Masotti A, Vicennati P, Boschi F, Calderan L, Sbarbati A, Ortaggi G. A novel near-infrared indocyanine dye–polyethylenimine conjugate allows DNA delivery imaging in vivo. Bioconjugate chemistry. 2008 May 21;19(5):983-7.
104. Masotti A, Pampaloni F. Polyethylenimine bioconjugates for imaging and DNA delivery in vivo. InBioconjugation Protocols 2011 (pp. 145-165). Humana Press.
105. Abd El-Alim SH, Kassem AA, Basha M. Proniosomes as a novel drug carrier system for buccal delivery of benzocaine. Journal of Drug Delivery Science and Technology. 2014 Jan 1;24(5):452-8.
106. Abdelrahman FE, Elsayed I, Gad MK, Elshafeey AH, Mohamed MI. Response surface optimization, ex vivo and in vivo investigation of nasal spanlastics for bioavailability enhancement and brain targeting of risperidone. International Journal of Pharmaceutics. 2017 Sep 15;530(1-2):1-1.
107. Chattaraj SC, Das SK. Physicochemical characterization of influenza viral vaccine loaded surfactant vesicles. Drug Delivery. 2003 Jan 1;10(2):73-7.
108. Challacombe SJ, Tomasi Jr TB. Systemic tolerance and secretory immunity after oral immunization. The Journal of experimental medicine. 1980 Dec 1;152(6):1459-72.
109. Priprem A, Nukulkit C, Johns NP, Laohasiriwong S, Yimtae K, Soontornpas C. Transmucosal delivery of melatonin-encapsulated niosomes in a mucoadhesive gel. Therapeutic delivery. 2018 May;9(5):343-57.
110. Allam A, Fetih G. Sublingual fast dissolving niosomal films for enhanced bioavailability and prolonged effect of metoprolol tartrate. Drug design, development and therapy. 2016;10:2421.
111. Ferreira N, Gonçalves NP, Saraiva MJ, Almeida MR. Curcumin: A multi-target disease-modifying agent for late-stage transthyretin amyloidosis. Scientific Reports. 2016 May 20;6(1):1-2.
112. Yang X, Li Z, Wang N, Li L, Song L, He T, Sun L, Wang Z, Wu Q, Luo N, Yi C. Curcumin-encapsulated polymeric micelles suppress the development of colon cancer in vitro and in vivo. Scientific reports. 2015 May 18;5(1):1-5.
113. Zaman MS, Chauhan N, Yallapu MM, Gara RK, Maher DM, Kumari S, Sikander M, Khan S, Zafar N, Jaggi M, Chauhan SC. Curcumin nanoformulation for cervical cancer treatment. Scientific reports. 2016 Feb 3;6(1):1-4.
114. Naderinezhad S, Amoabediny G, Haghiralsadat F. Co-delivery of hydrophilic and hydrophobic anticancer drugs using biocompatible pH-sensitive lipid-based nano-carriers for multidrug-resistant cancers. RSC advances. 2017;7(48):30008-19.
115. Misra R, Sahoo SK. Coformulation of doxorubicin and curcumin in poly (D, L-lactide-co-glycolide) nanoparticles suppresses the development of multidrug resistance in K562 cells. Molecular pharmaceutics. 2011 Jun 6;8(3):852-66.
116. Ma H, Guo D, Fan Y, Wang J, Cheng J, Zhang X. Paeonol-loaded ethosomes as transdermal delivery carriers: design, preparation and evaluation. Molecules. 2018 Jul 17;23(7):1756.
117. Xu Y, Zhu JY, Lei ZM, Wan LJ, Zhu XW, Ye F, Tong YY. Anti-proliferative effects of paeonol on human prostate cancer cell lines DU145 and PC-3. Journal of physiology and biochemistry. 2017 May;73(2):157-65.
118. Zong S, Pu Y, Li S, Xu B, Zhang Y, Zhang T, Wang B. Beneficial anti-inflammatory effect of paeonol self-microemulsion-loaded colon-specific capsules on experimental ulcerative colitis rats. Artificial Cells, Nanomedicine, and Biotechnology. 2018 Oct 31;46(sup1):324-35.
119. Zong SY, Pu YQ, Xu BL, Zhang T, Wang B. Study on the physicochemical properties and anti-inflammatory effects of paeonol in rats with TNBS-induced ulcerative colitis. International immunopharmacology. 2017 Jan 1;42:32-8.
120. Li X, Wang H, Liu C, Chen R. Chemical constituents of Acacia catechu. Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese materia medica. 2010 Jun 1;35(11):1425-7.
121. Isnan AP, Jufri M. Formulation of niosomal gel containing green tea extract (Camellia sinensis L. Kuntze) using thin-layer hydration. International Journal of Applied Pharmaceutics. 2017 Oct 1;9:38-43.
122. Pando D, Matos M, Gutiérrez G, Pazos C. Formulation of resveratrol entrapped niosomes for topical use. Colloids and surfaces B: Biointerfaces. 2015 Apr 1;128:398-404.
123. Caddeo C, Manconi M, Fadda AM, Lai F, Lampis S, Diez-Sales O, Sinico C. Nanocarriers for antioxidant resveratrol: formulation approach, vesicle self-assembly and stability evaluation. Colloids and surfaces B: Biointerfaces. 2013 Nov 1;111:327-32.
124. Pando D, Gutiérrez G, Coca J, Pazos C. Preparation and characterization of niosomes containing resveratrol. Journal of Food Engineering. 2013 Jul 1;117(2):227-34.
125. Pando D, Caddeo C, Manconi M, Fadda AM, Pazos C. Nanodesign of olein vesicles for the topical delivery of the antioxidant resveratrol. Journal of Pharmacy and Pharmacology. 2013 Aug;65(8):1158-67.
126. Scognamiglio I, De Stefano D, Campani V, Mayol L, Carnuccio R, Fabbrocini G, Ayala F, La Rotonda MI, De Rosa G. Nanocarriers for topical administration of resveratrol: a comparative study. International journal of pharmaceutics. 2013 Jan 20;440(2):179-87.
127. Matos M, Gutiérrez G, Coca J, Pazos C. Preparation of water-in-oil-in-water (W1/O/W2) double emulsions containing trans-resveratrol. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2014 Feb 1;442:69-79.
128. Jin Y, Wen J, Garg S, Liu D, Zhou Y, Teng L, Zhang W. Development of a novel niosomal system for oral delivery of Ginkgo biloba extract. International journal of nanomedicine. 2013 Jan 24:421-30.
129. Waddad AY, Abbad S, Yu F, Munyendo WL, Wang J, Lv H, Zhou J. Formulation, characterization and pharmacokinetics of Morin hydrate niosomes prepared from various non-ionic surfactants. International journal of pharmaceutics. 2013 Nov 18;456(2):446-58.
130. Manosroi A, Chankhampan C, Manosroi W, Manosroi J. Transdermal absorption enhancement of papain loaded in elastic niosomes incorporated in gel for scar treatment. European journal of pharmaceutical sciences. 2013 Feb 14;48(3):474-83.

131. Ionescu A, Aprodu I, Pascaru G. Effect of papain and bromelin on muscle and collagen proteins in beef meat. The Annals of the University Dunarea de Jos of Galati. Fascicle VI-Food Technology. 2008 Nov 17;32:9-16.
132. Roslan NZ, Aziz AA, Sarmidi MR, Aziz RA. Anti-oxidant coated liposome as the delivery system for papain based natural cosmetics. In2010 International Conference on Enabling Science and Nanotechnology (ESciNano) 2010 Dec 1 (pp. 1-1). IEEE.
133. Seeram NP, Lee R, Heber D. Bioavailability of ellagic acid in human plasma after consumption of ellagitannins from pomegranate (Punica granatum L.) juice. Clinica chimica acta. 2004 Oct 1;348(1-2):63-8.
134. Shimogaki, Tanaka, Tamai, Masuda. In vitro and in vivo evaluation of ellagic acid on melanogenesis inhibition. International journal of cosmetic science. 2000 Aug;22(4):291-303.
135. Bala I, Bhardwaj V, Hariharan S, Kumar MR. Analytical methods for assay of ellagic acid and its solubility studies. Journal of pharmaceutical and biomedical analysis. 2006 Jan 23;40(1):206-10.
136. Junyaprasert VB, Singhsa P, Suksiriworapong J, Chantasart D. Physicochemical properties and skin permeation of Span 60/Tween 60 niosomes of ellagic acid. International journal of pharmaceutics. 2012 Feb 28;423(2):303-11.
137. Junyaprasert V, Singhsa P, Jintapattanakit A, Bhardwaj P, et al. Influence of chemical penetration enhancers on skin permeability of ellagic acid-loaded niosomes, Journal of Drug Delivery Science and Technology 56 (2020) 101581 15, Asian J. Pharm. Sci. 8 (2013) 110–117.
138. Muzzalupo R, Pérez L, Pinazo A, Tavano L. Pharmaceutical versatility of cationic niosomes derived from amino acid-based surfactants: Skin penetration behavior and controlled drug release. International journal of pharmaceutics. 2017 Aug 30;529(1-2):245-52.
139. Abdelbary AA, AbouGhaly MH. Design and optimization of topical methotrexate loaded niosomes for enhanced management of psoriasis: application of Box–Behnken design, in-vitro evaluation and in-vivo skin deposition study. International journal of pharmaceutics. 2015 May 15;485(1-2):235-43.
140. Manosroi A, Khanrin P, Lohcharoenkal W, Werner RG, Götz F, Manosroi W, Manosroi J. Transdermal absorption enhancement through rat skin of gallidermin loaded in niosomes. International Journal of Pharmaceutics. 2010 Jun 15;392(1-2):304-10.
141. Jain S, Singh P, Mishra V, Vyas SP. Mannosylated niosomes as adjuvant–carrier system for oral genetic immunization against Hepatitis B. Immunology letters. 2005 Oct 15;101(1):41-9.
142. Vyas SP, Singh RP, Jain S, Mishra V, Mahor S, Singh P, Gupta PN, Rawat A, Dubey P. Non-ionic surfactant based vesicles (niosomes) for non-invasive topical genetic immunization against hepatitis B. International journal of pharmaceutics. 2005 May 30;296(1-2):80-6.
143. Gupta PN, Mishra V, Rawat A, Dubey P, Mahor S, Jain S, Chatterji DP, Vyas SP. Non-invasive vaccine delivery in transfersomes, niosomes and liposomes: a comparative study. International journal of pharmaceutics. 2005 Apr 11;293(1-2):73-82.
144. Azeem A, Anwer MK, Talegaonkar S. Niosomes in sustained and targeted drug delivery: some recent advances. Journal of drug targeting. 2009 Nov 1;17(9):671-89.
145. Montenegro L. Nanocarriers for skin delivery of cosmetic antioxidants. Journal of pharmacy & pharmacognosy research. 2014;2(4):73-92.
146. Kaul S, Gulati N, Verma D, Mukherjee S, Nagaich U. Role of nanotechnology in cosmeceuticals: a review of recent advances. Journal of pharmaceutics. 2018;2018.
147. Handjani-Vila RM, Ribier A, Rondot B, Vanlerberghie G. Dispersions of lamellar phases of non-ionic lipids in cosmetic products. International journal of cosmetic Science. 1979 Oct 1;1(5):303-14.