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NIOSOMES: PROMISING NOVEL DRUG DELIVERY SYSTEM FOR IMPROVING TARGETING PROPERTIES AND BIOAVAILABILITY OF VARIOUS PHARMACEUTICAL COMPOUNDS

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ABSTRACT

Niosomes acts as a novel drug delivery system, in which the formation of niosomes can take place by using non-ionic surfactants. The particle size of niosomes required must be in the range between 10nm to100nm which is mainly to avoid the fusion and its aggregation. There are many types of niosomes but their types and size mainly depend on the method used for its preparation. There are many factors affecting on the formation of niosomes such as nature of drug, type of surfactants used, cholesterol content and charge, resistance to osmotic stress and temperature of hydration. Various methods are used for separation of un-entrapped drug from final product such as dialysis, gel filtration and centrifugation. There are several routes used for its administration includes oral, parenteral, transdermal, ocular etc. The present article represents the preparation, characterization of niosomes and its effective applications in the drug delivery.

KEYWORDS: Niosomes, Novel Drug Delivery, Surfactants.

INTRODUCTION

Niosomes are non-ionic surfactant vesicles made by hydrating a cholesterol non-ionic surfactant combination. It's a drug carrier that's both amphiphilic and lipophilic. The particle size of niosomes must be in the range of 10 to 100 nanometres (small and microscopic in size). The medicine is encased in biodegradable, biocompatible vesicles in this drug delivery method. The primary goal of this study is to highlight the numerous uses of niosome technology, which is utilized to treat a variety of illnesses. It looks to be a more popular drug delivery method than liposomes since it is more stable and cost-effective. Poul Ehrlich began developing targeted medication delivery in 1909, demonstrating direct effect on a specific and desired location. The capacity of therapeutic medicines to operate directly on desired locations with little or no interaction with non-targeted sites is described as targeted medication delivery. The first non-ionic surfactant was developed and commercialized by the 'L' oreal firm, which specializes in cosmetics. Because of their multi-environmental structure, niosomes can be used as a targeted medication delivery method for a variety of medicines.[1] Niosomes are more stable than liposomes, which are susceptible to degradation and oxidation due to their lipophilic nature. Because of the non-ionic surfactants in niosomal formulations, they last longer in the bloodstream and hence have a more focused impact.[2] Niosomes are fundamentally similar to liposomes, however they have additional benefits. Because niosomes are so tiny (nm), they may readily travel through any transdermal pathway. They have less metabolism and removal via the reticular-endothelium system due to their tiny size.[3] Niosome-containing drugs have greater advantages not only in terms of increasing the stability of unstable drugs, but also in terms of improving the drug's physico-chemical characteristics. It has various charges on its surface, and the varying charges, such as (+), (-), caused flocculation and aggregation, requiring less ionic surfactant to maintain the same charge in the formulation.[4]If the medication becomes unentrapped in a niosomal formulation, the unentrapped drug is separated using a gel filtering and centrifugation technique. The use of a non-ionic surfactant, rather than phospholipid, which is utilized in the creation of liposomes, is one of the best reasons for the formation of niosomes. Phospholipids in liposomes have an ester bond, which causes them to hydrolysis.[5] Niosomes demonstrate the controlled release of a medication into the bloodstream at a specified time and space. Proniosomes are water soluble carrier particles that have been coated with a surfactant, or, to put it another way, the dry version of niosomes. They help with a variety of issues, including physical stability. The systemic non-selective toxicity of anti-cancer drugs is reduced via niosomal preparation. Niosomes carrying medication are taken by lever, and the lysosomal lipase enzyme degrades the niosomes, releasing the drug into the biological fluid. They occur at a much slower rate due to the longer-lasting effect.[6]

Difference between Niosomes and Liposomes[7]

Table 1: Comparison between Niosomes and Liposomes.

Sr.No.	Niosomes	Liposomes
1.	Surfactant	Phospholipid
2.	Size 10-100nm	Size 10-3000nm
3.	Inexpensive	Expensive
4.	Not required special storage condition	Required special storage condition
5.	Less toxic	More toxic
6.	Surfactant-stable	Phospholipid-unstable

Niosomes Have Quiet Characteristics[8-10]

1. Niosomes have the ability to entrap solutes.
2. Niosomes are stable and osmotically active.
3. Niosomes improve the stability of the medication contained in some way.
4. Niosomes release medicine in a regulated manner through their bilayer, which supports the arrival of the encased drug, allowing them to function as a pharmaceutical storehouse in the body.

Structure of Niosomes

The following are the three components used in the production of niosomes.

1. Non-ionic surfactant
2. Cholesterol
3. Charge molecule

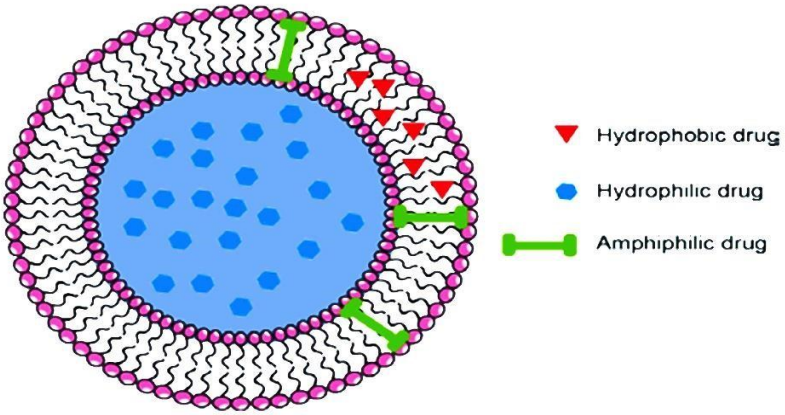

Figure 1: schematic representation of niosomes.

1) Non-ionic Surfactant

Niosomes are a non-ionic surfactant with a circular bilayer structure. Surfactant selection for niosome preparation is based on the HLB scale, with a surfactant value of 4-8.[11] Surfactants with micelle formation capabilities that produces micelles where it rises over the critical micelle concentration. Non-ionic surfactants, on the other hand, can create circular bilayer structures**.**

Examples: Tweens, Spans, Brij[12,13]

The following are examples of non-ionic surfactants.

Table 2: Different types of Non-Ionic Surfactants.

Type	Examples
Ethers	Brij, Decyl glucoside, Octyl glucoside, Lauryl glucoside
Esters	Spans, Glyceryl Laurate, Polysorbates
Fatty alcohols	Cetyl alcohol, Cetostearyl alcohol, Stearyl alcohol
Black copolymers	Poloxamers

2) Cholesterol

Cholesterol is a kind of steroid found in cell membranes. Cholesterol is added to the formulation to provide the vesicle rigidity and shape, however when the concentration of cholesterol is increased in the vesicle, it influences not only the fluidity, but also the drug's penetration and permeability.[14]

3) Charge Molecule

To prevent aggregation, a charge molecule is introduced to the niosomal preparation. If the particles have the same charge in the formulation, repulsion occurs and aggregation does not occur. In the formulation, there is some (+) and (-) charge surfactant. The formation of niosomes is prevented as the concentration of charges rises.

Negative Charge Molecule.

Examples: Diacetyl phosphate, phosphatidic acid, lipoamino acid, dihexadecyl phosphate.

Positive charge molecule.

Examples: Stearyl amine, stearyl pyridinium chloride.[15]

Advantages and Disadvantages of Niosomes

Table 3: Advantages and Disadvantages of Niosomes.

Advantages	Disadvantages
The size, lamellarity, and other properties of the vesicle can be changed based on the demand.	Fusion
The vesicles can function as a depot, allowing the medication to be released slowly and in a regulated manner.	Aggregation
The structure of niosomes allows for the incorporation of hydrophilic, lipophilic, and amphiphilic drug moieties, making them suitable for a wide range of medicines.	Leaking of entrapped drug
Water-based vesicle suspensions have higher patient compliance than oil-based solutions.	Physical instability
They are both osmotically active and osmotically stable.	Encapsulated medicines are hydrolysed, reducing the shelf life of the dispersion.

Types of Niosomes[16]

They can be classified as follows.

- Depending upon number of bilayer present (MLV, SUV)
- Depending upon size (LUV, SUV)
- Depending upon method of preparation (REV, DRV)

a. Small Uni-lamellar vesicle (SUV)
b. Multi-lamellar vesicle (MUV)
c. Large Uni-lamellar vesicle (LUV)

Table 4: Types of Niosomes[17]

Sr.No.	Types of Niosomes	Size	Methods of Preparation
1.	Small Uni-lamellar vesicle	0.025-0.05µm	Sonication method
2.	Multilamellar vesicle	≥0.05µm	Thin film hydration method
3.	Large Uni-lamellar vesicle	≥0.10µm	Ether injection and Reverse Phase Evaporation method

Other types of Niosomes

Niosomes Containing Bola Surfactant

'Bola surfactant containing niosomes' is a mixture of span-80 and cholesterol in a 2:3:1 molar ratio. Bola shapes have lately been utilized in the production of niosomes.

Asposome

Ascorbyl palmitate is used in a new vesicular drug delivery method. Ascorbyl palmitate is an ascorbic acid ester. In vitro tests revealed that asposomes had higher antioxidant activity than free ascorbic acid and that ascorbyl palmitate improves skin penetration. Ascorbyl palmitate is a more stable form of ascorbic acid than ascorbic acid. Asposome is utilized in a variety of cosmetic and medicinal preparations. They improve transdermal penetration.[18-20] Asposomes, aqueous solution hydration, sonication and niosomes.

Hydroxyl Propyl Methyl Cellulose containing Niosomes

The niosomes were mixed into this sort of base, which included 10% glycerin of hydroxy propyl methyl cellulose.[14]

Deformable Niosomes

Non-ionic surfactant +ethanol /and water combine to produce deformable niosomes. They are tiny vesicles that penetrate readily through the stratum corneum, increasing penetrating power.[7]

Discome

During the transition from niosomes to mixed micelles, a disc-shaped or large discoid structure was observed under light microscopy under certain conditions of the phase diagram of a non-ionic surfactant vesicle prepared from a hexadecyl ether: diacetyl phosphate: cholesterol (69:29:2) by sonication method.[21]

Niosomes in Carbopol Gel
Niosomes were made from drug, spans, and cholesterol, and then integrated into a Carbopol934 gel (1 percent w/w) base comprising propylene glycol (10% w/w) and glycerol (30% w/w).

Pro-Niosomes
Surfactant + carrier make up pro-niosomes. The creation of pro-niosomes is the first step in the production of niosomes. They reduce the issue of niosome aggregation, fusion, and leakage.
Carrier + surfactant - pro-niosomes
Pro-niosomes + water – niosomes

Preparation of Pro-Niosomes
1) Slurry Method
Maltodextrin is utilized as a carrier for the preparation in this technique. It took a longer time for it to develop. The ratios of surfactant and carrier were employed separately in this approach. The surfactant solution was applied to the maltodextrin powder in a rotary flash evaporator while it was sucked. Finally, there is a free-flowing dry powder.[22]

2) Coacervation Phase Separation Method
For the preparation of pro-niosomes, this technique is frequently utilized. Add weight amounts of surfactant, medication, and lipid to a wide mouthed glass vial with a capacity of roughly 5ml, as well as 0.5ml of alcohol. After warming, the components were well combined using a cover to prevent solvent evaporation from the vials. Warm the vials in a water bath at 60°-70°F for 5 minutes to ensure adequate surfactant mixing. Then, in heated vials on a water bath, add aqueous phase of 0.1 percent glycerol solution until a clear solution form. The production of pro-niosomes occurs after cooling.

3) Spray Coated Method
Pro-niosomes were created using this approach by spraying surfactant in an organic solvent onto sorbitol powder, and then evaporating the solvent. This step must be done until the surfactant is loaded. Surfactant coated a very thin layer on the carrier in this procedure, and the hydration of the coating resulted in the creation of multi-lamellar vesicles.[22]

Methods of Preparation of Niosomes
Ether Injection Method
In this approach, niosomes are gently introduced into a surfactant solution, which is subsequently dissolved in diethyl ether and poured into warm water at 60º. A 14-gauze needle was used to inject the ether mixture into an aqueous solution. Niosomes were formed by evaporating ether and forming single-layered niosomes.[23,24]

Sonication
To make niosomes, a mixture of drug solution in buffer, surfactant, and cholesterol was sonicated at 60º for 3 minutes with a titanium probe sonicator.[9]

Reverse Phase Evaporation Technique (REV)
Cholesterol and surfactant (1:1) were added to a combination of ether and chloroform in this technique. A drug-containing aqueous phase was added to this, and the two phases were sonicated at 4º-5º. After that, a tiny quantity of phosphate buffer saline was added to the clear gel and sonicated again. The organic phase was extracted at low pressure and at 40º.The viscous niosome solution was then diluted with phosphate-buffer saline and cooked in a water bath at 60°C for 10 minutes to generate niosomes.[25]

Micro Fluidization Method
Two fluidized streams contact at ultra-high velocities within the interaction chamber in this approach. This technique produced niosomes that were more consistent, reproducible, and smaller in size. Two ultra-high-speed jets were present within the interaction chamber during the preparation. Uniform niosomes are produced by impinging a thin layer of liquid into tiny channels.[23]

Trans Membrane pH gradient (inside acidic) drug uptake process or Remote Loading Technique.
A solution of surfactant and cholesterol was dissolved in chloroform in this manner. The solvent was then evaporated at a low pressure to form a thin layer on the round bottom flask's wall. The film was then vortex mixed with citric acid to hydrate it. Then add the aqueous medication solution and vortexes. With 1M disodium phosphate, the pH of the sample was increased to 7.0-7.2. The niosomes were obtained by heating the mixture at 60°C for 10 minutes.[26,27]

Hand Shaking Method
Azmin et al. and Baillie et al. described this method for the production of liposomes in 1985, which was originally disclosed by Bangham and others in 1965.[28] Surfactant and cholesterol were dissolved in solvent in a round bottom flask in this technique. The solvent was evaporated at room temperature (20º) using an evaporator, leaving a thin layer of solid mixture on the flask. The production of multilamellar niosomes can be achieved by rehydrating the dried surfactant film with aqueous phase at 60º with moderate agitation.

Bubble Method
This is a new technique for producing liposomes and niosomes that does not require the use of an organic solvent. This bubbling machine has a circular bottom flask with three necks that is placed in a water bath to keep the temperature constant.[29] The water-cooled reflux and thermometer were placed in the first and second necks, respectively, with the nitrogen supply in the third neck. Surfactant and cholesterol were combined in a pH-7.4 buffer at 70ºC for 15 seconds in a high shear homogenizer, then immediately bubbled at 70ºC with nitrogen gas.[21,30]

Multiple Membrane Extrusion Method

This is the most effective way for regulating the size of niosomes. In this approach, a surfactant, cholesterol, and diacetyl phosphate solution in chloroform was applied to a rotatory flash evaporator for organic solvent evaporation, resulting in a thin layer.[29] It is then filled with the aqueous phase, which contains the drug polycarbonate membrane solution. The resulting suspension was extruded through which up to 8 passages were inserted in succession.[21]

Ethanol Injection Method

In this approach, a surfactant ethanol solution was rapidly injected into excess saline or other aqueous media using a tiny needle. The ethanol was then vaporized, resulting in the formation of a vesicle.[31]

Factors affecting on Niosomes Drug Property

Table 6 shows how the nature of the medication influences the vesicular characteristic. The size of niosomes is influenced by the molecular weight, chemical structure, lipophilicity, hydrophilicity, and HLB value of the drug. The drug's entrapment efficiency is likewise affected by the HLB value. With increased vesicle size, drug trapping in niosomes rises.[1]

Table 5: Nature of Drug affects the vesicle property.

Nature of drug	Stability	Leakage from vesicle	Other property
Hydrophilic	Decrease	Increase	----------
Hydrophobic	Increase	Decrease	Improve transdermal delivery
Amphiphilic	----------	Decrease	Increase encapsulation

Amount and Types of Surfactants

Effect of hydrophilicity and lipophilicity of surfactant on niosomes were shown in Table 6. The size of niosomes vesicle get increases with increasing the HLB value of surfactant such as span 85 (HLB 1.8) to span 20 (HLB 8.6) because increase in lipophilicity of surfactant will decreases the surface free energy.[21]

Table 6: Effect of Hydrophilicity and Lipophilicity of Surfactant on Niosomes[21]

Increase Hydrophilicity of Surfactant	Increase Lipophilicity of Surfactant
Low phase transition (TC)	High phase transition (TC)
Low molecular weight drug more leakage from aqueous compartment	Low molecular weight drug less leakage from aqueous compartment
Stability of niosomal suspension decrease	Stability of niosomal suspension increase

Cholesterol Content and Charge

Cholesterol expands the diameter and enhances the effectiveness of trapping. If there is a higher percentage of cholesterol in the formulation, the stiffness of the vesicle increases, and the release rate of the encapsulate medicine lowers.[5] In a multi-lamellar vesicle, if cholesterol carries any charge, the charge increases the interlamellar distance between consecutive bilayers.[32]

Resistance to Osmotic Stress

When a hypertonic salt solution is added to a niosome suspension, the diameter of the vesicles gets shrinks.[5] When a hypotonic salt solution is introduced to a niosomal suspension, the swelling of the vesicle structure occurs owing to the blockage of eluting fluid from the vesicle, and subsequently the release occurs extremely quickly due to mechanical loosening of the vesicle structure under osmotic stress.[1]

Temperature of Hydration

The form and size of niosomes are influenced by the temperature of hydration.

Methods of Preparations

The size of the vesicle varies depending on the technique of production. As a result, it has an impact on drug entrapment efficiency and release rate from vesicles.

Membrane Composition

The addition of different additives to the combination of surfactant and medication can help to stabilize niosomes. Cholesterol and other additives affect vesicle permeability. Entrapment efficiency is improved when the membrane has a more rigid vesicle shape and helps to decrease drug leakage.

Separation of Un-Entrapped Drug

1. Dialysis
2. Gel filtration or column chromatography
3. Centrifugation

Dialysis

Using the appropriate dissolving media, the aqueous niosomal suspension is dialyzed at room temperature in dialysis tubing, dialysis membrane, or cellulose bag. After removing the sample from the medium at a

sufficient time interval, it was centrifuged and tested for drug content using Ultra Violet Visible spectroscopy or High-Performance Liquid Chromatography (HPLC).[1]

Merits
1. Inexpensive and easy to performed.
2. Suitable for highly viscous system.
3. Many time dilutions of niosomal suspension take place.

Reverse dialysis
Reverse dialysis is a technique that is similar to dialysis but works in the other direction. The dialysis media, such as phosphate buffer saline, distilled water, or glucose solution, is placed in a cellulose bag or tubing made of dialysis membrane and suspended in a beaker containing niosomal suspension from which unentrapped drug is desired to be removed, and then stirred at room temperature with a magnetic stirrer. Then separate the drug that hasn't been ensnared.[33]

Merits
1. It is simple and affordable to do.

Demerits
1. It's a long and tedious procedure.
2. The possibility of niosomal suspension dilution.[21]

Gel filtration or column chromatography
The unentrapped drug in niosomal solution may be eluted and evaluated using appropriate analytical techniques using a sephadex-G-50 column and a suitable mobile phase (phosphate buffer or normal saline).

Merits
1.1. It is a pretty fast procedure.

Demerits
1. The column must be pre-treated with an empty niosome.
2. It is incompatible with very viscous and big particle sizes (>10-20m).
3. Gel is expensive if it is not re-used.[21]

Centrifugation
The supernatant of the niosomal suspension is separated after centrifugation. To achieve a niosomal suspension devoid of unentrapped medication, the particle is washed and then resuspended.[34]

Merits
1. This is a low-cost instrument.
2. It is a fairly quick procedure.

Demerits
1. It is possible that the delicate system will be destroyed.
2. Vesicles with a diameter of less than a micron fail to sediment.

The above-mentioned new breakthrough is ultra-centrifugation, in which unentrapped medication is separated at a high speed of 150000g for 1-1.5 hours.

Merits
1. All type of particles gets sediment.

Demerits
1. Particle aggregation can occur at times.
2. Extensive centrifugation was required.
3. It is quite costly.[21]

Characterization of Niosomes[16,29]

Size, Shape and Morphology
Freeze fracture microscopy was utilized to observe and establish the structure of surfactant-based vesicles, while photon correlation spectroscopy was employed to estimate the vesicles' mean diameter. Electron microscopy is used to study the morphology of vesicles, whereas a laser beam is used to assess the size distribution, mean surface diameter, and mass distribution of niosomes.

Polydispersibility Index
Particle size distribution is another name for PDI. When a sample has a wide size distribution, the poly dispersed value rises over 0.7. Photon correlation spectroscopic analysis may also be used to determine the PDI of niosomes. During the formulation of niosomes, the maker must strive for the lowest PDI value possible.

Entrapment efficiency
The unentrapped medication is separated by dialysis centrifugation and gel filtering once the niosomal dispersion is prepared. Complete vesicle disruption with 5 percent n-propanol or 0.1 percent Triton X-100 was used to evaluate if the medication was still entrapped in niosomes, and the resulting solution was assessed using the following equation.
% Entrapment efficiency =Amount entrapped/ Total amount × 100 or (W-w/W) × 100.

Vesicle diameter
Light microscopy and freeze fracture electron microscopy can be used to measure the diameter of niosomes. The increase in vesicle width during freeze thawing of niosomes (by holding vesicles suspension at 20ºC for 24 hours and then heating to ambient temperature) might be due to vesicle fusion during the cycle.

Niosomal drug loading efficiency
The niosomal aqueous solution was ultra-centrifuged, the supernatant was collected, and the sediment was washed twice with distilled water to remove the adsorbed drug in order to assess drug loading and encapsulation efficiency. The following formula was used to determine the medication loading.
% Drug loading = Amount of drug in niosomes / Amount of niosomes recovered × 100 or

(Qn / Wn) × 100.

Zeta potential

The charge of niosomes is determined using the zeta potential. In general, charged niosomes are more resistant to aggregation and fusion than uncharged niosomes.[35] Alternative techniques for determining the charge of the vesicle include micro electrophoresis, dynamic light scattering, and pH-sensitive fluorophores.

Routes of Administrations:

Various routes for administration of niosomes are as follows.

Table 7: Example of Drugs administered through various routes[36]

Route of Administration	Examples of Drug
Intravenous route	Doxorubicin, Comptothecin, insulin, Zidovudine, Cisplatin, Rifampicin
Nasal route	Sumatriptan, influenza viral vaccines
Inhalation route	All trans-retinoic acids
Ocular route	Timolol maleate, cyclopentolate
Transdermal route	Piroxicam, Oestradiol, Nimesulide

Marketed Formulations of Niosomes

Table 8: Marketed Formulations of Niosomes.

Sr.No.	Brand	Name of the Product
1.	Orlane Lipcolor and Lipstick	Lip Gloss
2.	Britney Spears–Curious	Curious coffret: Edp Spray 100ml +Dualended Perfume and Pink Lipgloss+ Body Souffle 100ml
3.	Loris Azzaro-Chrome	Chrome Eau De Toilette Spray 200ml
4.	Lancome– Foundation and Complexation	Flash Retouch Brush on Concealer

Applications of Niosomes Transdermal delivery systems

The sluggish penetration of transdermal medication delivery systems into the skin is a drawback. To address this issue, niosomes and pro-niosomal preparations have been proposed as a method of increasing medication penetration in the skin, as well as effectiveness and bioavailability. Consider the evaluation of simvastatin niosomes for transdermal medication administration in children.

Dyslipidemia is a condition in which the body's cholesterol and fat levels are abnormally high. In adults, dyslipidemia raises the risk of cardiovascular disease. Obesity, a poor diet, and a lack of exercise are all common causes among adults. The study offered transdermal gels containing niosomes simvastatin as a potential transdermal medication delivery for pediatric usage in order to lower lipid levels. Not only does niosomes simvastatin have the potential to enhance bioavailability and hypolipidemic effect, but it's also a suitable pediatric formulation for hyperlipidemic youngsters.

Specifications

Parameters	Description
Microscopic analysis	Transmission electron microscopy and scanning electron microscopy are used to examine the surface characteristics of simvastatin niosomes.
Drug entrapment efficacy	HP1200 UV detector with wavelength 238nm, HP1200 auto sampler, and quaternary HP1200 pump were utilised in a Hewlett-Packard HPLC system.
Vesicular size analysis	The Zetasizer 3000 with avalanche photodiode and detector was used to determine it.
Surface charge analysis	The zeta sizer was used to quantify surface charge characteristics such as zeta potential, net charge, conductivity, and electrophoretic activity of the niosome system.
In vivo hypolipidemic activity	Simvastatin niosomes' hypolipidemic action was tested in male Sprague–Dewey rats weighing 200–300 gm. The animals were fasted overnight before the trials, and blood samples were taken by retro orbital puncture to measure the starting serum cholesterol. Levels of TG and lipids Following the injection of niosomes containing simvastatin. Initial values are used to evaluate its biochemical parameters.
Bioavailability studies	Bioavailability experiments in rats were conducted to see if transdermal niosome formulations might improve the pharmacokinetic characteristics of simvastatin.

The findings revealed that simvastatin niosomal gel improves substantial biological activities and is a promising preparation for transdermal medication administration in children.[37,38]

Ocular drug delivery systems

One of the most intriguing issues facing pharmaceutical scientists is ophthalmic medication delivery. In today's world, traditional ocular dosage forms such as solutions, suspensions, and ointments are employed. Because to low absorption, tear generation, ocular epithelial impermeability, and temporary residence duration, such dose formulations are ineffective in glaucoma. Niosomes outperformed most ophthalmic drug delivery methods in terms of making close contact with the corneal and conjunctival surfaces, resulting in increased ocular medication absorption. For instance, research and development of a timolol maleate niosomes formulation for glaucoma therapy.

Glaucoma is a kind of blindness defined by damage to the optic nerve caused by high intraocular pressure, optic nerve ischemia, and the activation of oxidative stress-related factors. To address the issue, niosomes gel formulations of timolol maleate were developed to extend the time of release and enhance drug bioavailability from an ocular dose form.

Specifications

Parameters	Description
Entrapment efficacy	The results revealed that formulations containing span 60 had the highest entrapment efficacy compared to formulations containing span 40, whereas formulations containing span 20 had the lowest entrapment efficacy.
Drug release from noisome	A simple dialysis technique was used to assess the in vitro release of timolol maleate from various formulations. The rate of release of TM niosome preparation was found to be lower for span 40 and 60 than for span 20.
Particle size and zeta potential	The Zetasizer NS3000 was used to measure particle size via light scattering based on laser diffraction. Using a combination of laser dropper velocimetry and phase analysis light scattering by Zetasizer, the zeta potential was calculated. The results revealed that when the HLB values of surfactants grow, the zeta values of the vesicles decrease and become negative.
Microscopic examination	Under an optical microscope, transmission electron microscopy, and differential scanning colorimetric analysis, the produced vesicles were examined.
Antiglaucoma action by measurement of IOP	When TM niosome ocular gel was administered to the control eye, there was no impact on IOP. However, the niosomal gel had a longer lasting effect than the marketed formulation.

The results revealed that niosomal formulations provided more consistent and regulated medication release than non-niosomal formulations.[39]

Chemotherapy

Cancer has spread over the world and is now a leading cause of death. Traditional cancer treatments including surgery and chemotherapy have been proven to have some disadvantages and risks in certain forms of cancer. Colloidal Nano carriers produced from cholesterol and non-ionic surfactants are known as niosomes. For instance, carum-loaded niosomes were tested on breast cancer cells.

Thymoquinone is a phytochemical substance discovered in carom cells that has several medical uses. Two distinct TQ and carom formulations were encapsulated into niosomes, and their characteristics were examined.

Specifications

GC-MS analysis	Iran provided the carvil plant. The medication was dried and crushed before being extracted with an ethanolic solution using a soxhlet device. The mass spectrum produced from the sample was compared to the instrument's database. When compared to normal TQ, the quantity of TQ in carum had the most anticancer effect against MCF -7.
Morphological analysis	SEM and DLS analyses were used to determine the formulation's stability and mono-dispersibility. Carum and TQ loaded molecules have a spherical form without aggregation, according to SEM. DLS was performed on blank niosomes that were not loaded with carum or TQ.
In- vitro cytotoxic study	With a blank niosome formulation, the in vitro cytotoxic impact of niosome formulations was evaluated using tetrazolium salt on MCF cell survival.
Migration assay	The ability of cancer cells to migrate is one of their most significant features, since it promotes cancer spread. TQ, nio/TQ, and TQ niosomes stop MCF 7 cells from migrating.

Antitumor action of loaded niosomes	Different niosomal preparations were tested for anticancer activity on MCF7 cell lines for 24 hours at 2 Um doses. TQ encapsulated in niosome has more anticancer activity than free TQ, according to the findings.

The findings revealed that encapsulating low soluble phytochemicals like TQ and carum into niosomes can boost their efficacy and therefore be used as a chemotherapeutic treatment against breast cancer. In comparison to free TQ, both loaded formulations allow regulated release.[40]

Pulmonary Drug Delivery Systems

According to Terzano et al, beclomethasone dipropioate in the form of niosome-based polysorbate 20 was used to treat chronic obstructive pulmonary disease. Niosomes were shown to offer prolonged and targeted drug delivery, enhanced mucus infusion, and increased therapeutic impact, according to the researchers.

For example, encapsulating ethambutol HCl in niosomes to increase its efficacy and safety. Tuberculosis is a worldwide illness. New instances have recently emerged, and many individuals have died as a result of tuberculosis. To address this issue, niosomes are prepared by encapsulating ethambutol HCL in order to improve therapeutic efficacy and safety.

Specifications

Entrapment efficacy	Ethambutol HCL entrapment efficacy varies from 12 to 25%.
Zeta potential	The stability of neutral and negatively charged preparations was estimated using zeta potential values.
In vitro drug release	The drug release in vitro was biphasic.
Lung targeting	In vitro targeting is improved by encapsulation of niosome.
Biological evaluation	The biological assessment indicated that niosome ethambutol HCL outperforms the free drug.

The findings revealed that encapsulating drugs in niosomes leads in regulated drug release. For a longer length of time, a Niosomes formulation directs more medicines to the lungs of mice. In comparison to free medication, encapsulated niosomes prepared for TB therapy offers greater effectiveness and safety.[41]

In immune system

Niosomes are used as adjuvants in vaccines to study the nature of immune responses elicited by antigens, for example, niosome formulation modulates the Th1 /Th2 bias immune response in mice and also provides protection against anthrax spore challenge due to their immune system selection, low toxicity, and greater stability. Anthrax is caused by the bacteria Bacillus anthrasis. Protective Antigen is a key immunogen found in all authorized vaccinations that aids in the neutralization of anthrax antibodies. Vaccination with AL hydrogel adsorbed cell free culture filtrate of BA strain and alum precipitated culture supernatant of BA strain is the currently available preventive method.

Specifications

Particle characterization	Niosome formulations were found to be spherical in shape after particle characterisation using TEM and atomic force microscopy.
Entrapment efficacy	To assess entrapment effectiveness, the encapsulated protein from the niosome preparation was extracted by ultracentrifugation. The entrapment effectiveness values for PA and D4 were determined to be 58.5% and 44.75 percent, respectively.
In vitro drug release	The micro–BCA method was used to determine the amount of protein released. In-vitro release assays revealed a burst of antigen from the niosome within 24 hours, followed by a 144hour progressive release.
Confocal microscopy	In comparison to antigen alone, the niosome increased antigen macrophage absorption.
Immunological studies	Both PA and D4 encapsulated niosomes evoked IgG titers in immunological tests.
Antibody isotyping and cytokine profile	In mice, NISV + PA and NISV + D4 enhance both Th1 and Th2 responses, implying a mixed Th1/Th2 response. Anti inflammatory activity is strong in both NISV +PA and NSIV + PB formulations.

The PA and D4 Encapsulated NISV formulation increased both Th1 and Th2 immune responses and was proven to be more effective in preventing Anthrax.[42]

Therapeutic applications of Niosomes

Applications	Surfactants	Method	Drugs
Treatment of HIV AIDS	Span 80	Ether injection method	Lamivudine
Vaccine and antigen therapy	Span 20 and span 60	Lipid layer hydration method	Newcastle disease vaccine.
Cancer chemotherapy Protein delivery	Span 60 Bola surfactant	Lipid layer hydration Lipid layer hydration	Cisplatin 5 flurouracil
	Brij 92	Lipid layer hydration	Insulin
Pulmonary delivery	Span 60 Tween 40	Lipid layer hydration Lipid layer hydration	Rifampicin Ciprofloxacin

RESULTS

Because non-ionic surfactant is more stable and non-toxic in nature, niosomes do not require the same specific storage and handling conditions as liposomes. Niosomes have an extremely tiny vesicle size as compared to other vesicle sizes, such as liposomes. There are several commercially available niosome formulations. To prevent niosome aggregation and fusion, a charge component must be included in the formulation. The production of niosomes begins with the creation of pro-niosomes, which is followed by the hydration of pro-niosomes.

CONCLUSION

One of the greatest instances of remarkable progress in drug delivery technologies and nanotechnology is the niosomal drug delivery system. There is a lot of potential for encapsulating toxic anti-cancer drugs, anti-infective drugs, anti-AIDS drugs, anti inflammatory drugs, anti-viral drugs, and other drugs in niosomes and using them as promising drug carriers to improve bioavailability and targeting while lowering toxicity and side effects. Niosomes play a critical part in a variety of drug delivery methods, including targeted, topical, ophthalmic, and parenteral. Niosomes will be extremely beneficial to the pharmaceutical industry in the future.

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Abbreviations
CMC: Critical Micelle Concentration
HLB: Hydrophilic Lipophilic Balance
MLV: Multi-Lamellar Vesicle
SUV: Small Uni-lamellar Vesicle
LUV: Large Uni-lamellar Vesicle
REV: Reverse phase evaporation technique
TC: Gel phase transition temperature
HPLC: High performance Liquid chromatography
PDI: Poly Disperse Index
REV: Reverse Phase Evaporation Technique

REFERENCES

1. Chandu VP, Arunachalam A, Jeganath S, Yamini K, Tharangini K, Chaitanya G. Niosome: A Novel Drug Delivery System. Int. J. Novel Trends Pharm. Sci, 2012; 2(1): 27-30.
2. Ahuja N, Saini V, Bishnoi VK, Garg A, Hisoria M, Sharma J. Formulation and evaluation of lansoprazole niosome. Rasayan J Chem, 2008; 1(3): 561-3.
3. Makeshwar KB, Wasankar SR. Niosome: A Novel Drug Delivery System. Asian J Pharm Res, 2013; 3(1): 16-20.
4. Salih OS, Samein LH, Ali WK. Formulation and in-vitro evolution of rosuvastatin calcium niosome. Int J Pharm Sci, 2013; 5(4): 525-35.
5. Tangri P, Khurana S. Niosome: Formulation and Evaluation. Int J Biopharmaceutics, 2011; 2(1): 47-52.
6. Udupa N, Chandra prakash KS, Umadevi P, Pillai GK. Formulation and evaluation of methotrexate niosome. Drug Dev Ind Pharm, 1993; 19(11): 1331-2.
7. Sanklecha VM, Pande VV, Pawar SS, Pagar OB, Jadhav AC. Review on Niosomes. Austin J Pharmacology and Pharmaceutics, 2018; 3(2): 2-4.
8. Makeshwar K, Wasankar S. Niosomes: a novel drug delivery system. Asian J. Pharm. Res, 2013; 3: 16-20.
9. Sankhyan A, Pawar P. Recent Trends in Niosome as Vesicular Drug Delivery System. J. Appl. Pharm. Sci, 2012; 2: 20-32.
10. Gurjar P. Niosome: A Promising Pharmaceutical Drug Delivery. Int. J. Pharm Anal, 2014; 2: 425-431.
11. Shakya V, Bansal BK. Niosome: A Novel Trend in drug Delivery. International J Research and Development in Pharmacy and Life Sciences, 2014; 3(4): 1037-8.
12. Jain AP, Sharma P, Pandey P. Niosomes a novel approach for drug delivery system: A overview. Asian J. Pharm. Sci. Res, 2013; 3(5): 18-30.
13. Yoshioka T, Stermberg B. Florence A.T. Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60,80) and a sorbitan triester (Span 85). Int. J Pharm, 1994; 105: 1-6.
14. Rajera R, Nagpal K, Singh SK, Mishra DN. Niosome: A Controlled and Novel Drug Delivery

System. Biological and Pharmaceutical Bulletin, 2011; 34(7): 945-51.
15. Gayatri DS, Venkatesh P, Udupa N. Niosomal sumatriptan succinate for nasal administration. Int J Pharm Sci, 2000; 62(6): 479-81.
16. Gadhiya P, Shukla S, Modi D, Bharadia P. A Review- Niosomes in Targeted Drug Delivery. International J for Pharmaceutical Research Scholars, 2012; 2: 61.
17. Sudheer P, Kaushik K. Review on niosomes: a novel approach for drug targeting. Journal of Pharmaceutical Research, 2015; 114(1): 20-25.
18. Djerassi D. The role of the corrective Vitamins A, B5 and C in the new, high performance cosmetics. Drug Cosmetic Ind, 1997; 160(6): 60-2.
19. Han S. Structure of Ascorbyl Palmitate Bilayers (Asposomes) from Molecular Dynamics Simulation. Bull Korean Chem Soc, 2018; 11229-49.
20. Yadav P, Lariya N. Asposome: A novel carrier for drug delivery system. Journal of Pharma Research, 2016; 5(10): 220-3.
21. Rane S, Inamdar Y, Rane B, Ashish J. Niosomes: A Non-Ionic Surfactant Based Vesicles as a Carriers for Drug Delivery. International J Pharmaceutical Sciences Review and Research, 2018; 51(1): 198-213.
22. Indira U, Uma Shankar MS. A Review: Pro-niosome as a drug carrier. International J Pharmaceutical Science and Research, 2012; 3(12): 4617-20.
23. Rogerson A, Cummings J, Willmott N, Florence AT. The Distribution of Doxorubicin in Mice, Following Administration in Niosomes. J Pharm, Pharmacol, 40(5): 337-42.
24. Mayer LD, Bally MB, Hope MJ, Cullis PR. Uptake of Antineoplastic Agents into Large Unilamellar Vesicles in Response to A Membrane Potential. BiochemBiophys Acta, 1985; 816(2): 294-302.
25. Raja Naresh RA, Chandrashekhar G, Pillai GK, Udupa N. Anti-inflammatory activity of Niosome encapsulated diclofenac sodium with Tween-85 in Arthitic rats. Ind J Pharmacol, 1994; 46-48.
26. Yeo PL, Lim CL, Chye SM, Kiong LAP, Koh RY. Niosomes: A review of their structure, properties, methods of preparation and medical applications. Asian Biomed, 2017; 11(4): 303.
27. Biju SS, Talegaonkar S, Misra PR, Khar RK. Vesicular systems: An overview. Indian J Pharm Sci, 2006; 68(2): 141-53.
28. Khandare JN, Madhavi G, Tamhankar BM. Niosomes Novel Drug Delivery System. The Eastern Pharmacist, 1994; 37: 61-4.
29. Pawar SD, Pawar RG, Kodag PP, Waghmare AS. Niosome: A Unique Drug Delivery System. International J Biology, Pharmacy, Allied Science, 2012; 3(1): 409-12.
30. Ijeoma FU, Suresh PV. Non-ionic surfactant-based vesicles (niosomes) in drug delivery. Int J Pharm, 1998; 172(1-2): 33-70.
31. Gurjar P, Naik N, Chouksey S. Niosome: A Promising Pharmaceutical Drug Delivery. Int. J. Pharm Anal, 2(5): 425-431.
32. Alsarra A, Bosela A, Ahmed SM, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur J Pharm and Biopharm, 2004; 2(1): 1-6.
33. Blazek-Walsh AI, Rhodes DG. SEM imaging predicts quality of niosomes from maltodextrin-based Proniosomes. Pharm Res, 2001; 18(5): 656-61.
34. Akhilesh D, Kamath JV. Review on span-60 based non-ionic surfactant vesicles as novel drug delivery. International J research pharmaceutical and biomedical sciences, 2012; 3(1): 6-12.
35. Uchegbu IF, Vyas S.P. Non-ionic surfactant-based vesicles(niosomes) in drug delivery. International J Pharmaceutics, 1979; 172(1-2): 33-70.
36. Sharma DE, Ali AA, Aate JR. Niosome as Novel Drug Delivery System. Pharma Tutor, 2008; 6: 58-64.
37. Ahmed s. zidan, Khalad M. Hosny, Osama A. A. Ahmed, Usma A. Fahmy. Assessment of simvastatin niosomes for pediatric transdermal drug delivery, Drug Delivery, 2016; (23.5): 1536 -1541.
38. Durga Bhavani G and Veera Lakshmi P. Recent advances of non-ionic surfactants based nano vesicles (niosomes and pro-niosomes); a brief review of these in enhancing transdermal delivery of drug. Future J Pharmaceutical Sciences, 2020; 14 - 15.
39. Afaf A. Ramdan, Shereen A. Eladaway, Amal Saber Mohammed Abu El –Enin, Zeinab M. Hussein. Development and investigation of timolol maleate niosomal formulations for treatment of glaucoma. Journal of Pharmaceutical Investigation, 2019; 50(4): 1-12.
40. Mahamood Barani, Mohmmad Mirzaei, Masoud Torkzadeh Mahaniand Mahboubeh Adeli Sardou. Evaluation of carum loaded niosomes on breast cancer cells; physicochemical properties, in-vitro toxicity, flow cytometric, DNA Fragmentation and Cell Migration Assay. Scientific Reports, 2019; 1-8.
41. Mahmoud Gharbavi, Jafar Amani, Hamidrez Kheiri Manjili, Hossein Danafarand Ali Sharafi. Niosome: A promising Nanocarrier for Natural Drug Delivery through Blood Brain Barrier. Advances in Pharmacological Sciences, 2018; 03: 01-15.
42. Himanshu Gogoi, Rajesh Mani, Rakesh Bhatnagar. A niosome formulation modulates Th1 /Th2 bias immune response in mice and also provides protection against anthrax spore challenge. Int J Nanomedicine, 2018; 13: 7427-7440.