Review Article

Niosome as a Novel Pharmaceutical Drug Delivery: A Brief Review Highlighting Formulation, Types, Composition and Application

Mahesh Gajanan Umbarkar

Department of Pharmaceutics, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur, Maharashtra, INDIA.

ABSTRACT

Aim: Formation of niosome by using non-ionic surfactant. The particle size of niosome must be required in the range in between 10 nm -100 nm. This is just due to avoid the aggregation of niosome and show proper result. **Materials and Methods:** There are many types of niosome, their types and size depend on which method used for preparation. In this article we covered method of preparation of pro-niosome and niosome. Many factors are affecting formation of niosome such as drugs, its chemical and physical property, amount and type of surfactant, cholesterol content and its charge, resistance to osmatic stress as well as membrane composition. Various method is used for separation of un-entrapped drug from final product such as dialysis, gel filtration and centrifugation. There are several routes used for administration of niosome such as oral, parenteral, transdermal and ocular etc. **Results:** The evaluation and characterization of niosome done by many methods such as entrapment efficacy, vesicle diameter, *in-vitro* release and loading efficiency. Niosome have many pharmaceutical and non-pharmaceutical applications; which having marketed product of niosome are available in market are explain in this article. **Conclusion:** Niosome formation methods are completely based on liposome methods of preparation. Niosome are having more storage capacity than liposome i.e. niosome are more advance than liposome. The cost of preparation of niosome is also less than liposome. Many pharmaceutical formulations of niosome are now available in market.

Key words: Niosome, Pro-niosome, Non-ionic surfactant, Preparation, Application.

INTRODUCTION

In 1909, Poul Ehrlich, started the development of targeted drug delivery. The targeted drug delivery shows its action direct on the targeted or desirable site. Targeted drug delivery can be defined as the ability of therapeutic agent show its action direct on desirable site with little or no interaction with any other non-targeting sites. The niosome are made up of non-ionic surfactant which contain cholesterol and some quantity of ionic surfactant such as diacetyl phosphate used for stability purpose. The first product of non-ionic surfactant was prepared and marketed by L'Oréal Company which used for cosmetical application. Various type of drug can be delivered in targeted site by incorporating niosome, due to their multi-environmental structure.[1] Niosome may be uni-lamellar or multi-lamellar vesicle is made up of non-ionic surfactant, cholesterol and ionic surfactant used to reduce aggregation of formulation. The hydrophilic, lipophilic and amphiphilic drug can be incorporate in bilayer structural vesicle of niosome. Niosome shows more stability than liposome because liposome can be degraded and oxidized due to their specific lipophilic nature. Niosomal formulation live prolonged in blood circulation due to their non-ionic surfactant and hence their target action is more.[2] The niosome are small and microscopic in size. The size of niosome are in nanometric scale which ranges about 20nm-100 nm. Niosome

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Correspondence:
Mr. Mahesh Gajanan Umbarkar
RC Patel Institute of Pharmaceutical Education and Research, Shirpur, Maharashtra, INDIA.
Phone no: +91-9767662125
Email id: mgumbarkar2000@gmail.com

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are structurally same as liposome but consist more advantage than liposome. Their size is in nanometres i.e. very small due to their small size they easily pass through any transdermal routes of administration. Due to its nanometric size niosome shows less metabolism and elimination by reticular-endothelium system.[3] Drug containing niosomal vesicle shows many advantages not only it increases the stability of unstable drug but also improves physicochemical property of drug. Many times, niosome contain different charge on their surface due to that different charge like (+) and (-), which shows flocculation or aggregation, to reduce ionic surfactant added in it for maintaining same charge in formulation.[4] Generally, Span-60 is non-ionic surfactant is used formulation of niosome.[5] Niosome are does not required any special condition for preparation and storage conditions like liposome.[6] The method of preparation of niosome completely based on method of preparation of liposome. Many times, during niosomal formulation drug is unentrapped, this unentrapped drug is separated by gel filtration or centrifugation method. Several pharmacological agents potentially capable to entrapped in niosome for treatment of many disease. One of the best reasons for formulation of niosome is its non-ionic surfactant show more stability than phospholipid is used in preparation of liposome. In liposomal phospholipid contain ester bond and due to this bond, phospholipid undergoes hydrolysis.[7] Niosome shows the controlled release of drug in blood circulation at pre-determine time and for pre-determine rate. Pro-niosome are water soluble carrier particle these are coated with surfactant or in another way we can said that dry form of niosome are also called as pro-niosome. The pro-niosome reduces the many problem of such as its physical stability. Pro-niosome are also another drug delivery formulation, these show good transdermal penetration property because it contains surfactant, surfactant is act as penetration enhancer and it also non-toxic, biodegradable and they can be entrapped both hydrophilic and lipophilic drug in it.[8]

The niosomal formulation decreases the systemic non-selective toxicity of anti-cancer drug. Live show metabolism of many drug , where niosome containing drug also taken by liver and the enzyme lysosomal lipase, it shows degradation of niosome and the drug are entrapped in niosome is release into blood circulation, but degradation and breakdown of niosome in liver take place very slowly due to that it show more sustained effect.[9] Cholesterol are the important in structure of niosome it give rigidity to vesicle but when cholesterol added more quantity in vesicle then it not only it affects the fluidity but also penetration and permeability of drug.[10] Niosomal formulation is administered by several route such as transdermal, parenteral, oral, ocular and subcutaneous route.[11] In targeted drug delivery several carriers are used such as immunoglobulin, plasma protein, microsphere, synthetic polymers, sometimes erythrocytes and liposome but among all of these liposome and niosome are well documented as drug delivery system.[12,19]

DEFINITION

Niosomes are nanometric size vesicle which is made up of surfactant (non-ionic) and cholesterol. The niosome are more stable than liposome due to their structural components. Thus, they are less toxic and more stable than liposome because it contains non-ionic surfactant. The particle size of niosome ranges in between 20 nm -100 nm.[1]

STRUCTURE AND COMPOSITION OF NIOSOME

The selection of surfactant for preparation of niosome mainly depend on the HLB value of surfactant. Vesicle forming ability of surfactant are completely based on hydrophilic-lipophilic balance of surfactant. For proper and compatible vesicle formation of niosome the HLB value of surfactant must be in between 4 to 8.[13]

The niosome are circular bilayer structure of non-ionic surfactant, surfactant which must having ability to form micelle. When surfactant concentration are goes above the critical micelle concentration (CMC) then it forms micelles in formation, but non-ionic surfactant has ability to form circular bilayer structure instead of micelles. The cholesterol also added in formulation to give rigidity to vesicle and ionic surfactant reduces aggregation.[1] The structure of niosome may be uni-lamellar or multi-lamellar depending on which method used for preparation of niosome. There are all types of drug can be incorporate in structure of niosome such as hydrophilic, lipophilic and amphiphilic drugs. The location of all types of drug in niosome structure are show in Figure 1.[3,92]

The niosome mainly made up of following components-

Non-ionic surfactant

Niosome is bilayer structure of surfactant in which polar head of surfactant towards the aqueous phase and non-polar tail toward each other. There are several types of non-ionic surfactant use in formulation of niosome are mentation in Table 1.

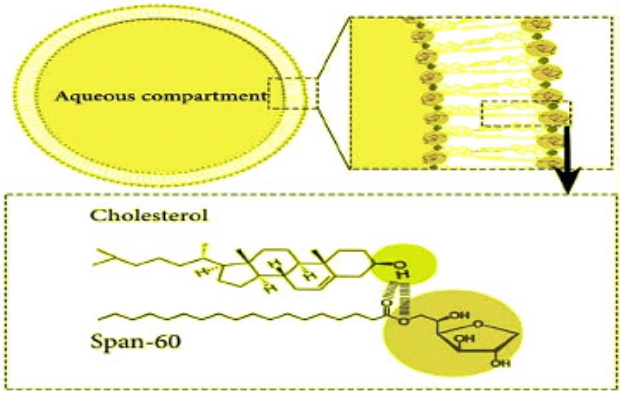


Figure 1: Structure of Niosome.

Alkyl ether

The L'Oréal cosmetic preparation described that some of the below non-ionic surfactant used for the formulation of niosome.

1.1.1) Surfactant-I: This surfactant is having molecular weight about 473 Daltons. Surfactant-I is 16 carbon containing monoalkyl glycerol unit.

1.1.2) Surfactant-II: Molecular weight of surfactant-II is 972. This is a diglycerol ether with average of the seven-glycerol unit.

1.1.3) Surfactant-III: (Molecular weight-393) is ester linked surfactant.

Alkyl ester

The Sorbitan ester are the surfactant, come under the category of alkyl ester surfactant. The Sorbitan surfactant is mostly used for the preparation of niosome. Poly-oxyethylene Sorbitan monolaurate is surfactant which form the niosomal vesicle but the vesicle made up of this surfactant are less soluble than other types of surfactant vesicle. For encapsulation of diclofenac sodium in niosomal vesicle the polysorbate-60 (polyoxyethylene) were used. Polyoxyethylene-10-stearyl ether: glyceryl laurate: cholesterol (27:15:57) this mixture is used for formation of niosome in which cyclosporin-A is used for transdermal delivery. The methotrexate niosome are made by using this surfactant.[89]

Amino acid and fatty acid compound

There are many types of amino acid and fatty acid used for preparation of niosome.

Alkyl amide

Glycosides and glactosides are the alkyl amide used for formulation of niosome.

Cholesterol

Cholesterol is steroid is present in cell membrane and this is very important component for rigidity, fluidity and permeability. Cholesterol are steroid and its important component during preparation of niosome. Cholesterol is added in niosome but in very less quantity because in large quantity of Cholesterol affects the penetration or permeability of niosomal vesicle. It increases permeability, rigidity, encapsulation efficacy and also it shows very easily rehydration of frees dried niosome and their toxicity.[10]

Charge molecule

Some charge molecule is added in niosomal formulation to avoid aggregation of niosome. If same charge present in formulation then repulsion of particle takes place and aggregation not take place. Some of positive and negative charge ionic surfactant added in niosomal formulation. Negative charge molecules-Diacetyl phosphate, phosphatidic acid, lipoamino acid, dihexadecyl phosphate.[92] Positive charge molecule-Stearyl amine, stearyl pyridinium chloride. The charge molecule is also required in optimum concentration, if charge molecule added in more concentration then formation of niosome does not take place. About 2.5-5 mole percentage concentration of charge molecule required for preparation of niosome.[7]

ADVANTAGE OF NIOSOME[1,3]

1. Niosome formulation inexpensive on economical as compared to other formulation. All ingredients which are required for formulation of niosome are inexpensive and easily available.
2. They improve therapeutic targeted performance of drug by delaying clearance of drug from circulation.
3. Niosome formulation are very less toxic due to their ingredient use for preparation. Also, non-ionic surfactant is the main constituent of niosome and toxicity of non-ionic surfactant are very less.
4. The structure of niosome show all types of nature such as hydrophilic, lipophilic and amphiphilic, so they can used in variety of drug.
5. Many factors in the body such as enzyme, pH and other are affect the chemical and physical property of drug, to avoid this niosome formulation are preferred
6. Surfactant are biodegradable, biocompatible and non-immunogenic so usually non-allergic.
7. The niosome are nano range particle so they can be easily penetrating into skin and enhance skin penetration of drug also niosome formulation have very less toxic effect due to that they can administer in various routes such as for topical, oral, parenteral and ocular.

8. The drug present in niosome are protected from biological environment due to that degradation of drug are take place very less and also avoid first pass metabolism hence oral bioavailability of drug increase.
9. Handling and storage of surfactant does not require any special condition so reduces the cost of preparation.
10. Niosome are osmotically stable and active.
11. They show slow or controlled release drug delivery.
12. The characteristic of niosome such as size, shape is completely depending on the ingredient and their quantity use in formulation of niosome. For example, if concentration of cholesterol increases then rigidity of vesicle also increases. Also, by increasing the drug concentration in formulation affect the vesicle size.
13. Water base suspension of niosome vesicle show more patient compliance than oil-based system.
14. Niosome are used in many preparations such as pharmaceutical and cosmetic preparation.

DISADVANTAGE OF NIOSOME[1,3]

1. The niosome formulation are physically unstable.
2. In niosome formulation sometimes different charge present on surface of niosome vesicles due to that opposite charge come to near and fusion of niosome vesicle occur.
3. Many times, niosome shows aggregation if standard method of preparations not followed.
4. Hydrolysis of entrapped drug take place sometimes.
5. In some cases, found insufficient drug loading.
6. Formulation of niosome is time consuming process.

DIFFERENCE BETWEEN LIPOSOME AND NIOSOME[15]

The difference between Niosome and Liposome are shown in Table 2.

TYPES OF NIOSOME

Types of Niosome are shown in Figure 2.

Niosome are classified on the basis of number of bilayer present such as (MLV, SUV) or on the basis of size (LUV, SUV) or on the basis of method of preparation (REV, DRV). The above types of niosome are as follow-

i) Small Uni-lamellar vesicle (SUV)

ii) Multi-lamellar Vesicle (MUV)

iii) Large Uni-lamellar Vesicle (LUV)

Small Uni-lamellar vesicle (SUV)

The small uni-lamellar vesicle are obtained from large uni-lamellar vesicle (LUV) by sonication method and French press extrusion electrostatic stabilization. Small Uni-lamellar vesicle having size range about 0.025-0.05μm or 25-50nm.

Table 1: Types of surfactant used in niosome preparation and their example.[14]

Non-ionic surfactants	Examples of surfactant	Reference
Alkyl esters: (i) Sorbitan fatty acid esters (Spans)	Span 20, Span 40, Span 60, Span 80, Span 65, Span 85	14,5,21,22,23,24.
(ii) Polyoxyethylene Sorbitan fatty acid esters (Tweens)	Tween 20, Tween 40, Tween 60, Tween 80, Tween 65, Tween 85	31,32,33.
Alkyl ethers: (i) Alkyl glycerol ethers	Hexadecyl diglycerol ether	5,14,25
(ii) Polyoxyethylene glycol alkyl ethers (Brij)	Brij30, Brij52, Brij72, Brij76, Brij78	35,36.
Crown ethers	Bola	26,27
Alkyl amides: (i) Glycosides	C-glycoside derivative surfactant	28
(ii) Alkyl polyglucoside	Octyl-decyl polyglucoside	37
Fatty alcohols or fatty acids: (i) Fatty alcohols	Stearyl alcohol, acetyl alcohol, myristyl alcohol	34
(ii) Fatty acids	Stearic acid, Palmitic acid, myristic acid.	34
Block copolymer: (i) Pluronic	Pluronic L64, Pluronic 105.	38,39
Lipidic components: Cholesterol		30
l-α-Soya phosphatidyl choline		40
Charged molecule: Negative charge	Diacetyl phosphate, phosphatidic acid, lipoamino acid, dihexadecyl phosphate	41,42
Positive charge	Stearyl amine, stearyl pyridinium chloride.	29

Multi-lamellar Vesicle (MUV)

The formation of SUV, MLV and LUV are depending on which method used for preparation of niosome.

MLV contain number of bilayers surrounding to aqueous lipid compartment separately. The average size of MLV is about 0.5-10 μm in diameter.[90] MLV niosome are mostly used for incorporation of drug. The MLV is very simple for preparation and it more stable for long period of time. This vesicle more suitable for lipidic drug compound. This types of niosome mainly prepared by thin film hydration method.[16]

Large Uni-lamellar Vesicle (LUV)

The LUV are having uni-lamellar vesicle it contains single bilayer membrane but it having large diameter. Aqueous and lipidic content of this vesicle is more so that it has more size.[16] The entrapment quantity of drug in this vesicle is more as compare to other types. Average size of Large uni-lamellar vesicle is 100nm.[3] These vesicles generally prepared by ether injection method and reverse phase evaporation method. LUV are having more advantage than MLV such as high encapsulation of water-soluble drug, reproducible drug release rates and economy of lipid.[13,90]

Niosome containing bola surfactant

The vesicle containing omega-hexadecyl-bis-(1-aza-18 crown-6) (bola surfactant): Span-80: Cholesterol in 2:3:1 molar ratio is called bola surfactant containing niosome. Bola forms have recently been used as component for the preparation of niosome.

Aspasome

It is a new vesicular drug delivery system and it made up of ascorbyl palmitate. The ascorbyl palmitate (AP) is ester of ascorbic acid, Palmitic acid and is amphiphilic in nature and studies delineating their surface-active property. Ascorbyl palmitate has ability to suppress pigmentation of skin and decomposition of melanin.[81] Characterization of aspasome carried out for vesicular shape, vesicular size, zeta potential, stability, entrapment efficiency, *in vitro* skin penetration and *in vivo* animal model to determine its whitening activity.[82]

In cosmetic and dermatological preparation ascorbic acid and its derivatives are widely used. It also improves the elasticity of the skin by promoting formation of collagen. Ascorbyl palmitate is more stable than ascorbic acid and lipophilicity of ascorbyl palmitate is beneficial for its skin penetration.[83] Due to bioactivity of ascorbyl moiety, aspasome are used in many cosmetic and pharmaceutical application.[84] Ascorbyl palmitate obtained from palm oil and corn dextrose fermentation. It is highly bioavailable and fat soluble.[85,86]

Aspasome are combination of acorbyl palmitate, highly charge lipid diacetyl phosphate and cholesterol lead to formation of vesicle. Niosome are also formed from aspasome by hydration of aspasome then sonicate it and formation of niosome take place. The aspasome are also used for treatment of reactive oxygen diseases, hence it used as antioxidant. Aspasome also increase the transdermal penetration of drug.[87,88]

Aspasome → hydration by aqueous solution → sonication → Niosomes

Hydroxy propyl methyl cellulose containing niosome

Firstly, prepared base containing 10% glycerine at hydroxy propyl methyl cellulose and the niosome were incorporate in it.[10]

Deformable niosome

Deformable niosome are combination of non-ionic surfactant + ethanol and water. These are small vesicle and easily pass through pore of stratum cornium and increase the penetration power.[15]

Polyhedral niosome

The polyhedral niosome made up of combination of hexadecyl diglycerol ether (C_{16} G_2): Cholesterol: Polyoxyethylene 24 cholesteryl ether (solulan C_{24}). The finally disc like, spherical, tubular and polyhedral shape like vesicle form. The formation of polyhedral niosome completely depend on molar ratio of above component. Generally deformable niosome are used for transdermal route.[15]

Discome

The several types of "some' are available in Table 3.

The disc shape or large discoid structure were observed during niosome to mixed micelles transition under light microscope existing under certain condition of phase diagram of non-ionic surfactant vesicle prepared

Table 2: Niosome Vs Liposome.

Sr.No.	Niosome	Liposome
1.	Surfactant	Phospholipid
2.	Size-10nm-100nm.	Size-10-3000nm
3.	Inexpensive	Expensive
4.	Not required special storage condition.	Required special storage condition.
5.	Surfactant more stable	Phospholipid unstable
6.	Less toxic	More toxic
7.	Cholesterol present.	Not contain cholesterol
8.	Non-ionic surfactants are uncharged	Phospholipids may have neutral charged.

from a hexadecyl ether: diacetyl phosphate: cholesterol (69:29:2) by mechanical disruption and then sonicate then incubate with various proportion of solulan C_{24} at 74°C and finally water soluble solute entrapped in it effectively.[16]

Pro-niosome

The pro-niosome made up of surfactant and carrier. Pro-niosome are initial stage of niosome formation. They are decrease the aggregation, fusion and leaking problem associated with niosome.

Carrier + Surfactant = Pro-niosome

Pro-niosome + Water = Niosome.

PREPERATION OF PRO-NIOSOME

Drugs incorporated into pro-niosome are shown in Table 4.

Proniosomes are prepared by three methods

1. Slurry method
2. Coacervation Phase Separation Method
3. Spray coated method

Slurry method

In this method maltodextrin is used as carrier for preparation of pro-niosome. In slurry method more time required for formation of pro-niosome. In this method ratio of surfactant and carrier independently used. In rotary flash evaporator the surfactant solution added in maltodextrin powder under vacuumed. Finally, free flowing dry powder occurs.[8]

Coacervation phase separation method

This method is widely used for preparation of pro-niosome. Take a wide mouthed glass vial having capacity about 5ml and add weight amount of surfactant, drug and lipid in it, also add 0.5ml of alcohol. After warming all ingredient mixed it well by using glass rod. The open end of vial is close by using lid to stop the evaporation of solvent from vials. Vials warm in water bath at 60-70°C for 5 min for proper mixing of surfactant. Then add aqueous phase of 0.1% glycerol solution in warm vials on water bath till clear solution was form. After cooling formation of pro-niosome take place.

Spray coated method

In this method pro-niosome is formed by spraying surfactant in organic solvent onto the sorbitol powder. After evaporation of solvent pro-niosome formed. This process must be repeated until surfactant has been load. In this process surfactant coated very thin layer on carrier and on hydration of coating formation of multi-lamellar vesicle form.[8]

FORMATION OF NIOSOME FROM PRO-NIOSOME

Preparation of Niosome and Pro-niosome as shown in Figure 3.

The niosome can be prepared from pro-niosome by adding aqueous phase such as water in pro-niosome to form niosome. The formation of pro-niosome and niosome shown in Figure 2. For formation of niosome from pro-niosome required brief agitation at temperature greater than mean transition phase temperature of surfactant.

$$T > Tm$$

Where,

T = Temperature

Tm = mean phase transition temperature [1]

PREPERATION METHOD OF NIOSOME

Advantages and Disadvantages of preparation methods of niosome are explain in Table 5.

The method for preparation of niosome are choose according to use of niosome. The preparation method influence size, bilayer, size distribution, entrapment efficiency and permeability of vesicle.[1]

Ether injection method

This method was described by Baillie and others in 1985; previously described by Deamer and Bangham in 1976 for the preparation of liposomes.

Preparation steps

Surfactant is dissolved in diethyl ether → Then injected in warm water maintained at 60°C through a 14-gauze

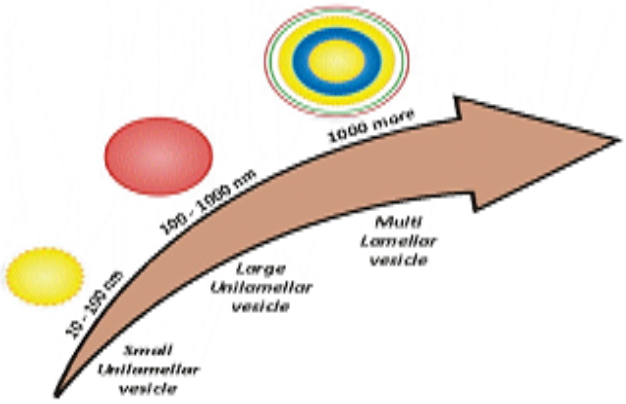


Figure 2: Types of Niosome.

Table 3: Different type of "some" used as drug delivery.

Types of "some"	Description	Benefits and potential uses	References
Virosomes	Liposomes prepared using natural or synthetic phospholipids, viral spike proteins and viral envelope proteins.	Used as influenza vaccines	43
Vesosomes	Lipid bilayer within a bilayer i.e. nested lipid bilayers, with an aqueous core	The facility of multiple compartments lends improved protection to the internal contents.	44
Ufasomes	Unsaturated fatty acid vesicles; developed to enhance the penetration of a drug through the stratum corneum layer of skin	Increased stability, better entrapment efficiency and cheaper than liposomes counterparts.	45
Transferosomes	Deformable, stress responsive, complex vesicles consisting of an aqueous core enveloped by a lipid bilayer.	Increased permeability over niosomes and liposomes. Amphiphilic in nature, entrap both high and low molecular weight drugs, protect drug from enzymatic and metabolic degradation and can penetrate narrow pores of skin. Transferosome loading of meloxicam, ibuprofen etc. have been investigated.	46-47
Sphingosomes	Similar to liposomes, instead are composed of sphingolipids.	More resistant to hydrolysis, reduced toxicity, can be administered via SC, IV, IA, IM, oral and TD routes.	48
Photosomes	Liposomes encapsulated with photolyase. Photolyase DNA repair enzyme obtained from bacteria.	Capable of repairing ultraviolet B induced pyrimidine dimers in eukaryotic cells. Could be used in sunscreens.	49
Niosomes	Non-ionic surfactants vesicles (either uni- or multi-lamellar) produced by addition of non-ionic surfactant to cholesterol.	More stable, easier handling, flexible design in comparison to liposomes. Osmotically active, increase bioavailability and can entrap drugs with a wide range of solubility. Niosome loading of voriconazole, acyclovir etc. have been investigated.	50-52
Layerosomes	Liposomes containing several layers; these layers consist of biocompatible electrolytes in order to increase structure stability.	Potential for oral administration or incorporation in biomaterials.	53
Hemosomes	These are haemoglobin containing liposomes, prepared by combining haemoglobin with polymer-forming lipids.	Used as a high capacity oxygen carrying system.	54
Genosomes	Large molecular complexes used for the transfer of genes. Cationic liquids are best suited due to their increased biodegradability and stability in the blood	Non-viral transfer of genes to specific cells.	55
Ethosomes	Soft and malleable vesicles, composed of phospholipids, ethanol and water, ethanol helps increase permeation through skin layers.	Used to enable drugs to reach deep skin tissue and the systemic circulation.	56
Erythrosomes	An erythrocyte cytoskeleton coated with a lipid bilayer.	Potential encapsulation systems for macromolecular drugs	57
Enzymosomes	They are liposomes with enzymes covalently associated to the surface.	Potential for targeted delivery to tumour cells	58
Emulsosomes	They are nano lipid particles that consist of a lipid assembly with a polar core.	Used for administration of sparingly water-soluble drugs via the parenteral route.	59-60
Discosomes	Niosomes that have been coupled with a non-ionic surfactant, Solulan C24 (a lanolin derivative).	Potential for use as ophthalmic drug carriers.	61
Cubosomes	Particles formed by the high energy dispersion of bulk cubic phase liquids. These cubic phases consist of two hydrophilic regions divided by a lipid bilayer.	Provide a means of targeted and controlled release of therapeutic compounds. Easily prepared, biodegradable and bio adhesive. Hydrophilic, hydrophobic and amphiphilic drugs can be loaded.	62-63
Cryptosomes	They are lipid vesicles that have surface coats comprising of phosphatidylcholine and polyoxyethylene derivative of phosphatidylethanolamine.	The modified surface coat serves to reduce macromolecular adsorption on the vesicle surface thereby, increasing the circulation time in the body	64

Colloidosomes	They are hollow microcapsules comprising of either coagulated or fused particles at the interface of the emulsion droplets. Size ranges between several microns to about 5 nm	Easily constructed, flexible, controlled permeability, significant mechanical strength.	65,66
Archaeosomes	Liposomes made from naturally occurring archaebacteria membrane lipids.	Stable under varying conditions of temperature, pH, oxidative conditions, pressure etc.	67
Aquasomes	Self-assembled spherical particles ranging between 60-300 nm in size. They consist of a solid phase nanocrystalline core coated by an oligomeric film to which biochemically active compounds are adsorbed.	Preserves the conformation and stability of the bioactive constituents. Insulin, antigen, gene and drug delivery; oxygen carrier; for the oral delivery of an acid labile enzyme	68,69

Figure 3: Preparation of Pro-niosome and Niosome.

needle → Ether is evaporate and form single layered niosome.

Sonication Method

In 1986, this method was described by Baillie *et al.* previously it described by Huang in 1969 for the preparation of liposomes.

Preparation steps

Drug in buffer + surfactant or cholesterol in 10 ml Using titanium probe above mixture sonicate for 3 min at 60°C to form niosome.

Reverse Phase Evaporation Technique (REV)

Raja Naresh have reported the preparation of Diclofenac Sodium niosome using Tween 85 by this method.

Preparation steps

Cholesterol + surfactant (1:1) dissolved in ether + chloroform → Sonicated at 5°C and again sonicated after adding PBS → Aqueous phase containing drug is added to above mixture Viscous niosome suspension is diluted with PBS → Removed the organic phase at 40°C at low pressure → Heated on a water bath for 60°C for 10 min to form niosome.[95]

Micro fluidization Method

This is the recent technique use for preparation of uni-lamellar vesicle. In this method within the interaction chamber two fluidized streams interact at ultra-high velocities. This method shows greater uniformity, better reproducibility and smaller size of niosome.

Preparation steps

Inside interaction chamber two ultra-high-speed jet present → Impingement of thin layer of Liquid in micro channels → Yield of uniform Niosome.[94]

Trans membranes PH gradient (inside acidic) Drug Uptake Process: or Remote Loading Technique

Preparation steps

Surfactant + cholesterol in chloroform → Evaporation of solvent under reduce pressure Thin film is deposited on the walls of RBF → Hydrated with citric acid by vortex mixing 3 cycles of freezing and thawing then sonication → Add solution of aqueous drug and vertexing → Raised PH to 7.0-7.2 by 1M disodium phosphate → RBF as bubbling unit with three necks in water bath Reflux, thermometer and nitrogen supply by three necks Cholesterol + surfactant dispersed in buffer pH 7.4 at 70°C → Above dispersion is homogenized for 15 sec and then bubbled with nitrogen gas at 70°C → To form Niosome.[18,95]

Multiple membrane extrusion method

This is the best method for controlling size of niosome. In this method mixture of surfactant, cholesterol and diacetyl phosphate in chloroform and these all add in rotary flash evaporator for evaporation of organic solvent and forms thin layer.[90] The aqueous phase

containing drug polycarbonate membrane solution add in it. The resultant suspension extruded through which are placed in series for up to 8 passage.[16]

Hand shaking method (Thin film hydration technique)

This method was described by Azmin *et al.* and Baillie *et al.* in 1985; previously described by Bangham and others in 1965 for the preparation of liposomes.[93]

Preparation steps

Surfactant + cholesterol + solvent ⟶ Remove organic solvent at Room temperature ⟶ Thin layer formed on the Walls of flask ⟶ Film can be rehydrated to form multilamellar Niosomes.

Bubble method

This is the novel method used for preparation of liposome and niosome without use of organic solvent. This bubbling unit contain round bottomed flask with three neck and it position in water bath to maintain the temperature.[90] The water-cooled reflux and thermometer are positioned in first and second neck and supply of nitrogen in third neck. The surfactant and cholesterol mixed together in buffer having PH-7.4 at 70°C for 15 sec in high shear homogenizer and immediately bubbled at 70°C by using nitrogen gas.[16,96]

FACTOR AFFECTING ON NIOSOME

Many factors which are affecting on physical and chemical property of niosome and also affect the formation of vesicle.

Drug property

Nature of drug affect the vesicular property are mentioned in Table 6.

Molecular weight, chemical structure, lipophilicity, hydrophilicity as well as HLB value of drug influence the size of niosome. The HLB value also affect the entrapment efficiency of drug. Drug entrapment in niosome increase with increasing size of vesicle.[1] When drug entrapment in niosome then interaction of solute charge and head group of surfactants take place due to that repulsion, size of vesicle increase. Some drug

Table 4: Drugs Incorporated into Pro-niosome.

Sr.No.	Drugs	Surfactant used	Use	References
1.	Piroxicam	Span 60	Anti-inflammatory	70
2.	Piroxicam	Span 20, 60, 80 and Tween 80	Anti-inflammatory	80
3.	Levonorgestrel	Span 20, 40, 60, 80	Contraceptive agent	79
4.	Ketorolac	Span 60	Anti-inflammatory	78
5.	Ibuprofen	Span 60	Anti-inflammatory	77
6.	Ethinylestradiol and levonorgestrel	Span 20, 40, 60 and 80	Contraception and hormone replacement therapy	76
7.	Frusemide	Span 40	Antihypertensive	75
8.	Flurbiprofen	Span 20, 40, 60, 80	Anti-inflammatory	73
9.	Estadiol	Span 40, Span 60, Span 85 and 17β-estradiol	Hormonal insufficiencies	74
10.	Cromolyn sodium	Sucrose stearates	Anti-asthmatic and anti-allergic	73
11.	Chlorpheniramine maleate	Span 40	Anti-allergic	72
12.	Captopril	Span 20, 40, 60, 80 and sorbitol	Hypertension	71
13.	Aceclofenac	Span 60	Arthritis, ankylosing spondylitis	70

added in polyethylene glycol coated vesicle thus reduce the tendency of increasing size of vesicle.[7]

Temperature of hydration

Temperature present during hydration of pro-niosome are influence the size and shape of niosome. Polyhedral vesicle of $C_{16}G_2$: Solulan C_{24} (91:9) is based at 25°C but this polyhedral vesicle converted into spherical vesicle at 45°C and on cooling it forms 55-49°C gives cluster of smaller spherical niosome.[5]

Resistance to osmatic stress

When hypertonic salt solution adds in suspension of niosome then diameter of vesicle decreases.[7] If hypotonic salt solution added in niosomal suspension, then initially slow release take place with swelling of vesicle structure due to inhibition of eluting fluid from vesicle and finally release occur very fast due to mechanical loosing of vesicle structure under osmatic stress.[1]

Amount and type of surfactant

Effect of Hydrophilicity and lipophilicity of surfactant on niosome as shown in Table 7.

The size of niosome vesicle 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 with decrease in surface free energy. The visible bilayer is present in either liquid state or gel state and are depends on type of surfactant and lipid, temperature and other component like as cholesterol. In liquid state the structure of bilayer is no present in well manner but in gel phase alkyl chain are present in proper way.[97] Lipid and surfactant are identified by gel-liquid phase transition temperature (TC). The entrapment efficiency is also depending on phase transition temperature of

Table 5: Advantage and disadvantage of preparation method of niosome.

Method	Advantage	Disadvantage
Ether injection	i) The captured volume per mole of lipid remains high.	i) Ether is free form of peroxide so chances of oxidative degradation. ii) Careful control needed for introduction of the lipid solution, related to mechanically operated pump. iii) Low encapsulation efficiency but the captured volume per mole of lipid remains high. iv) Very slow process. v) Small amount of ether is present in vesicle suspension and it's very difficult to remove all organic solvent because it not possible to complete evaporation of all organic solvent.
Sonication- a) Probe sonication b Bath sonication	i) Rapid size reduction. i) Accurate regulation of temperature	i) Shedding metal particle from probe tip, heat production and aerosol generation. ----------
Micro-fluidization Method	i) It shows better reproducibility. More uniformity, smaller size ii) Best aqueous phase encapsulation, production rate is very high.	i) In chamber high pressure present that can causes degradation of lipid.
Bubble Method	i) Preparation of niosome without use of organic solvent	----------
Multiple Membrane Extrusion Method	i) Best method for controlling the size of niosome ii) Production of niosome is easy, batch-to-batch reproducibility. iii) This method Reducing polydispersity.	i) Many times, clogging of extrusion membrane occur due to the large-scale production. ii) High product loss. iii) It takes more time.
Hand shaking method (thin film hydration technique)	i) Very Simple and reproducible method. ii) Encapsulation efficiency of lipid soluble drug is very high (up to 100 %).	i) Encapsulation efficiency of water-soluble drug might be low. ii) In this process non-homogeneous vesicle form and so size reduction process required. iii) Time consuming method.

surfactant. For example, span-60 having more TC, shows more entrapment. The HLB value of surfactant between 14 to 17 is not suitable for preparation of niosome.[1,7]

Structure of surfactant

The shape and size of niosome vesicle are depends on Critical Packing Parameter (CPP), according to CPP we can predict the geometry of niosome vesicle.[10]

Critical Packing Parameter (CPP)= v / lc. a_0

Where,

v= hydrophobic group volume,

lc= the critical hydrophobic group length,

a_0= the area of hydrophilic head group

CPP is helpful in predicting the structure of niosome vesicles in following way;

Spherical micelles formed if CPP less than 1/2

Bilayer micelles are formed if CPP between 0.5 to 1

Inverted micelles are formed if CPP more than 1.

Method of preparation

The method of preparation also influences the property of niosome. It observed that acyclovir niosome prepared by hand shaking method having size about 2.7μm and same acyclovir niosome prepared by ether injection method the vesicle size observed 1.5 μm.[10] The small size vesicle can be obtained by reverse phase evaporation method.[12] The niosome having smaller size and more stability can be prepared by micro-fluidization method. The transmembrane PH gradient uptake process show more entrapment efficiency and good retention of drug.[15]

Membrane composition

The niosome can be prepared by addition of surfactant, drug and other additives. Niosome have number of permeability, stability and morphological property, these all property can be change by adding different additives. $C_{16}G_2$ form a polyhedral niosome and are unaffected by adding low concentration of solulan C_{24} (cholesterol poly-24-oxyethylene ether) these are avoiding the aggregation of niosome which occurs due to stearic unhyndrance. The combination of ratio of $C_{16}G_2$:

Table 6: Nature of drug affect the vesicle property.

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

Table 7: Effect of hydrophilicity and lipophilicity of surfactant on niosome.[16]

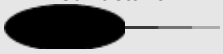
Increase hydrophilicity of surfactant 	Increase lipophilicity of surfactant 
Low phase Transition (TC)	High phase transition (TC)
Low molecular weight drug more leakage from aqueous compartment.	Low molecular weight drug less leakage from aqueous compartment.
Stability of niosomal suspension decrease.	Stability of niosomal suspension increase with more encapsulation.
Transdermal delivery of hydrophobic drug improves.	Toxicity decreases.

Table 8: Evaluation parameter and their methods.[5,7,20]

Evaluation parameter	Evaluation method
In-vitro release study	Dialysis membrane
Permeation study	Franz diffusion cell
Size distribution, polydispersity index	Dynamic light scattering particle size analyser
Morphology	SEM, TEM, freeze fracture technique
Entrapment efficacy	Centrifugation, dialysis, gel chromatography
Turbidity	UV-Visible diode array spectrophotometer
Thermal analysis	DSC
Membrane thickness	X-ray scattering analysis
Viscosity	Ostwald viscometer

Table 9: Example of drug that administered through various routes.[1,5]

Route of administration	Examples of drug
Nasal route	Sumatriptan, influenza viral vaccines
Intravenous route	Doxorubicin, comptothecin, insulin, zidovudine, cisplatin, rifampicin
Ocular route	Timolol maleate, cyclopentolate
Inhalation	All trans-retinoic acids
Transdermal route	Piroxicam, oestradiol, Nimesulide

cholesterol: solution (49:49:2) form spherical niosome. The niosome size affected by membrane composition. Polyhedral niosome form by $C_{16}G_2$: solution C_{24}(91:9) are having large size (8.0 ± 0.03 mm) then spherical niosome form from $C_{16}G_2$: cholesterol: solution (49:49:2) and having size about (6.6± 0.2 mm).[1,7]

Cholesterol content and charge

Cholesterol increase the diameter and entrapment efficiency. If more concentration of cholesterol added in formulation then increase the rigidity of vesicle and decrease the release rate of encapsulate drug.[7] The action of cholesterol is taking place in two way

Table 10: Detail study of drug with their application and method use for formulation of niosome.

Application	Components	Method used	Drug used
To reduce toxicity	Span 20, Span 40, Span 60, cholesterol	Thin film hydration method	Cefpodoxime Proxertil
To increase entrapment efficiency	Span 60, Cholesterol, DCP	Thin film hydration method	Ketoprofen
For enhancement of therapeutic index	Span and Tween (20 and/or 60), Cholesterol	Reverse phase evaporation method	a-Lipoic acid
For liver targeting	Span 60, Cholesterol, DCP	Thin film hydration method	Ribavirin
For sustained antiplatelet effect	Cholesterol, Tween 60, Stearyl amine	Lipid hydration method	Indomethacin
To increase immune response and immunological selectivity	Dimethyl dioctadecyl ammo nium bromide (DDA) and a, a -trehalose-6,6 -di behenate (TDB), 1-Monopalmitoyl glycerol (MP), Cholesterol	Dehydration–rehydration method	Ag85B-ESAT-6, MSP1 or GLURP
As a drug delivery carrier	a, w-Hexadecyl-bis-(1-aza)18- crown-6(bola), Span 80, Cholesterol	Thin layer evaporation technique	5-Fluorouracil (5-FU)
To increase bioavailability	Cholesterol, Sorbitan monostearate (span 60), (DCP)	Film hydration method	Acyclovir
For brain targeting	N-Palmitoyl glucosamine (NPG), Span 60, Cholesterol, Solulan C24	Probe sonication method	Vasoactive Intestinal Peptide
To prolong the release time	Sorbitan esters	Reverse phase evaporation method	Rifampicin
For drug targeting	monostearate (Span 60), Cholesterol, Glycol chitosan Sorbitan monostearate (span 60)	Reverse phase evaporation method	Methotrexate
In leishmaniasis	Span 40, Cholesterol, DCP	Solvent evaporation method	14-deoxy-11-oxoandograph-olide
For anti-inflammatory effect	Cholesterol (CH), Diacetyl phosphate (DCP) and Surfactants (Tween 85, Pluronic F108)	Reverse phase evaporation method	Diclofenac sodium
In anticancer therapy	Span 60, Cholesterol, DCP	Lipid layer hydration method	Bleomycin
In localized psoriasis	Chitosan	Lipid layer hydration method	Methotrexate
In oral delivery of peptide drug	Brij 52, Brij72, Brij92, Brij76, Brij97, Brij58, Brij35, DCP, Cholesterol	Film hydration method	Insulin
In diagnostic imaging	N-Palmitoyl-glucosamine (NPG), Polyethylene glycol (PEG)-4400	Ether injection method	Gadobenate
In transdermal drug delivery system	a, w-Hexadecyl-bis-(1-aza)18-crown-6(bola), Span 80, Cholesterol Brij 96, Cholesterol	Film hydration method	Ammonium glycyrrhinate
In ophthalmic drug delivery system	Span 20, Span 60, Cholesterol	Reverse phase evaporation method, Thin layer hydration method	Acetazolamide
For lung targeting	Span 85, Cholesterol	Hand shaking method, Ether injection method	Rifampicin
In thromboembolic disease	Hexadecyl polyglycerol, DCP, Cholesterol	Film method	Urokinase

such as i) cholesterol increase the lipid state bilayer order and ii) cholesterol decrease the gel state bilayer order. If cholesterol in high concentration then gel-state transformed into liquid order state. If cholesterol contain any charge due to that charge increase the inter-lamellar distance between successive bilayer in multi-lamellar vesicle (MLV).[98]

CMC (Critical micelle concentration)

The surfactant has ability to reduce the surface tension between two phases. If the concentration of surfactant is not going above to critic micelle concentration then formation of niosome are not takes place. Some surfactant is showing the micelle formation when concentration of surfactant goes above CMC, but some surfactant is showing the formation of circular bilayer structure and that are niosome.[16]

SEPERATION OF UN-ENTRAPPED DRUG

Dialysis

At room temperature the aqueous niosomal suspension is dialyzed in dialysis tubing, dialysis membrane or cellulose bag by using proper dissolution medium. The sample withdrawn from the medium at suitable time interval then centrifuge the sample and analysed for drug content in uv-spectroscopy or HPLC.[1]

Merits:

i) Inexpensive and easy to performed.

ii) Suitable for highly viscous system

iii) Many time dilutions of niosomal suspension take place.

Reverse dialysis is also method and are similar but opposite to dialysis. The dialysis media such as phosphate buffer saline, distilled water or glucose solution is filled in cellulose bag or tubing made up of dialysis membrane and this suspended in beaker containing niosomal suspension from which unentrapped drug want to remove and then at room temperature, stirred it by using magnetic stirrer and separate unentrapped drug.[91]

Merits-

i) Easy to performed and inexpensive.

Demerits-

i) Tedious and extremely slow process.

ii) Chances of dilution of niosomal suspension.[16]

Gel filtration or Column chromatography

By using sephadex-G-50 column and suitable mobile phase (phosphate buffer or normal saline) the unentrapped drug in niosomal suspension can be eluted and analysed it using suitable analytical technique.[1]

Merits-

i) It is a Very quick

Demerits-

i) Pre-treatment of the column with empty niosome required.

ii) Gel are costly when it not re-used.

iii) It not suitable for highly viscous and large particle (>10 – 20 μm).[16]

Centrifugation

By using cooling centrifugation separation of unentrapped drug take place with rotary speed under 7000g for 30 min at temperature 4°C. If depends on molecular weight of component. In result two layer occur one is supernatant liquid and second is niosomal pallets. The supernatant withdraws and niosomal pallets wash with distilled water or phosphate buffer to remove the unentrapped drug. This niosomal pallet suspension again centrifuge and complete removal of unentrapped drug take place.[91]

Merits-

i) It is a Very fast process.

ii) This is inexpensive instrument.

Demerits-

i) Sub-micron size vesicle fails to sediment.

ii) May leads to destruction of fragile system.

The new advancement take place in above method is ultra-centrifugation in which separation of unentrapped drug take place with high speed about 150000 g for 1-1.5 hr.

Merits-

i) All types of particle sediment

Demerits-

i) It is a Very expensive

ii) some time show aggregation of particle'

iii) Required long time centrifugation.[16]

CHARACTERIZATION OF NIOSOME

Characterization of Niosome as shown in Table 8.

Zeta Potential

The zeta potential means the charge which are present on the surface of niosome. The many time charge is present on the surface of niosome. This charge is come due to the component or ingredient which was used during the manufacturing.[101] Some charge is must be required on surface of all niosome present in formulation, due to some charge all niosome particle repeal to each other and coagulation of particle are avoided. The zeta potential of niosome was taken in zeta sizer instrument having Malvern software. The analysis of sample was carried

out at 25°C with the angle of detection 90°. The ideal zeta potential value must be required in range between +30 to -30mV. This range prevent the aggregation of niosomal particle.[99]

PDI

PDI is also called "particle size distribution". If the sample having very broad size distribution then poly dispersed value goes to more than 0.7. The PDI of niosome is also obtained by photon Correlation spectroscopic analysis. During formulation of niosome the effort of manufacturer is must be to achieve lowest PDI value.

Particle size

The particle size of niosome is generally taken by zeta sizer instrument. This instrument containing Malvern PCS software. Before taking the result of sample solution the sample must be diluted with distilled water. The distilled water not interferes with result. Then after dilution the result were taken. The particle size must be required in nano range. This software was taken the average particle size of niosome. The particle size of sample solution was determined by using light scattering technique and by transmission electron microscope. If the particle size of niosome increases then decrease the uptake and bioavailability of drug. The analysis of particle size was carried out for 60s at 165°C scattering angle of detection. The particle size is most important, the particle size of niosome in nano range are having more effective drug delivery as compare to micron range. The one advantage of large particle size niosome is having more area to fill more drug but it has very slow release pattern. Various method is used for administration of particle size of niosome such as SEM, TEM, XRD, AFM, Dynamic light scattering (DLS).[90]

Entrapment Efficiency

For determination of drug entrapment, the amount of drug present in the clear supernatant after centrifugation was determined (w) by UV spectrophotometer at 254 nm. A standard calibration curve of drug was plotted for this purpose. The amount of drug in supernatant was then subtracted from the total amount of drug added during the preparation (W). Effectively, (W-w) will give the amount of drug entrapped in the niosome.[99]

$$\%\text{Drug Entrapment} = (W\text{-}w/W) \times 100$$

Loading Efficiency

Drug content in the preparation was determine by extracting drug from the niosome with 0.1M hydrochloric acid. In this method niosome (50mg) were stirred in 50ml hydrochloric acid until dissolved. It was filtered by Millipore filter paper and drug content was determine, after suitable dilution. At 254nm by UV spectroscopy. The loading efficiency (L) of the niosome was calculated according to following formula.

$$L\ (\%) = (Qn / Wn) \times 100$$

Were, Qn is the amount of drug present in niosome and Wn is weight of niosome.[100,101]

In vitro drug release

The niosome is present in aqueous suspension they separated by using ultracentrifugation. Then 2 mg of niosome is taken and dispersed in 10ml 7.4-phosphate buffer. After this 10ml solution place in dialysis membrane bag. Then make 900ml 7.4 phosphate buffer and add it in dissolution apparatus beaker. Make the temperature 37°C. For the dissolution the USP paddle is used. At appropriate time intervals 1mL of the release medium is removed and 1mL fresh 7.4 phosphate buffer solution is added in to the system. The amount of drug in the release medium was estimated by UV Spectrophotometer at 275 nm.[20]

ROUTES OF ADMINISTRATION

Various routes for administration of niosome are explained in Table 9.

APPLICATION

The niosome used for several applications are mentioned in Table 10.

1. It is used in ophthalmic drug delivery.
2. It is used as for drug Targeting.
3. Niosomal targeting system can be used as diagnostic agents.
4. Niosome have been used for studying the nature of the immune response provoked by antigens.
5. Transdermal Drug Delivery Systems Utilizing Niosome.
6. It is used as targeted and selective anti-neoplastic treatment i.e. Cancer Disease
7. It is used in study Immune Response.
8. It is used as Leishmaniasis (Dermal and Mucocutaneous infections) e.g. Sodium stibogluconate.
9. Niosome can be used as a carrier like haemoglobin.
10. It is used act as drug delivery of Peptide Drugs.
11. It shows sustained drug release.
12. Niosome have ability to show localized Drug Action.
13. It also used in gene delivery.[1,3,5,10,17]

MARKETED PRODUCT

The Lancôme has used for variety of anti-aging product which are based on niosomal formulation. The L'Oréal is conducting the research on anti-aging cosmetic formulation. Lancôme is niosomal preparation present in market.[1]

MATERIALS AND METHODS

The non-ionic surfactant are the main component of niosome. There are several ingredients are use for the preparation of niosome such as ionic surfactant or other charge compound which shows the repulsion of niosome molecule and avoid aggregation of niosome. Cholesterol are also added in niosome to maintain rigidity of vesicle. There are several methods used for preparation of niosome such as Ether injection method, Sonication Method, Reverse Phase Evaporation Technique, Micro fluidization Method, Trans membranes PH gradient (inside acidic) Drug Uptake Process: or Remote Loading Technique, Multiple membrane extrusion method, Hand shaking method (thin film hydration technique), Bubble method.

RESULTS AND DISCUSSION

Non-ionic surfactant is more stable and non-toxic in nature, due to non-ionic surfactant the niosome does not required special handling and storage condition as liposome. Niosome vesicle are very small in size as compare to another vesicle such as liposome, microsphere. Many marketed formulations of niosome are available. To avoid the aggregation of niosome charge compound must added in formulation. The pro-niosome is initial step of niosome after hydration of pro-niosome, formation of niosome take place.

CONCLUSION

The niosome having similar structure like liposome but they have more advantage than liposome. Niosome can entrapped many types of drug due to their multi-environmental structure. Niosome as a drug delivery system is a great evaluation in DDS. There is lots of drug can be encapsulated into niosome such as toxic anti-cancer drug, anti-AIDS drug any many more. Niosomal increase the bioavailability of drug and also helpful to reduce its toxicity. Due to its smaller size it by pass or less metabolised by reticular-endothelial system (RES). No special condition required for handling and storage of niosome.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ABBREVIATIONS

CMC: Critical Micelle Concentration; **MW:** Molecular Weight; **SUV:** Small Uni-lamellar Vesicle; **MLV:** Multi-Lamellar Vesicle; **LUV:** Large Unilamellar Vesicle; **REV:** Reverse phase evaporation technique; **Tm:** Mean phase transition temperature; **HLB:** Hydrophilic Lipophilic Balance; **Tc:** Gel phase transition temperature; **CPP:** Critical Packaging Parameter; **HPLC:** High Performance Liquid Chromatography; **PDI:** Poly Disperse Index; **SEM:** Scanning Electron Microscopy; **TEM:** Transmission Electron Microscopy; **XRD:** X-Ray Diffraction; **AFM:** Atomic Force Microscopy; **DLS:** Dynamic Light Scattering; **USP:** United State Pharmacopoeia; **DSC:** Differential Scattering Calorimetry; **DCP:** Di-Cetyl Phosphate; **NPG:** N-Palmitoyl Glucosamine; **DDA:** Dimethyl Dioctadecyl Ammonium bromide; **PEG:** Poly Ethylene Glycol; **DDS:** Drug Delivery System; **RES:** Reticule-Endothelial System.

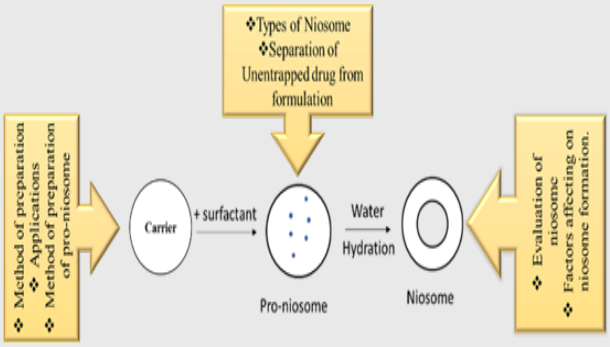
REFERENCES

1. Chandu VP, Arunachalam A, Jeganath S, Yamini K, Tharangini K, Chaitanya G, *et al.* Niosome: A Novel Drug Delivery System. International Journal of Novel Trends in Pharmaceutical Sciences. 2012;2(1):27-30.
2. Ahuja N, Saini V, Bishnoi VK, Garg A, Hisoria M, Sharma J, *et al.* 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. International Journal of Pharmacy and Pharmaceutical Sciences. 2013;5(4):525-35.
5. Sharma DE, Ali AA, Aate JR. Niosome as Novel Drug Delivery System. Pharma Tutor. 2008;6:58-64.
6. Sakthivel M, Kannan K, Manavalan R, Senthamarai R. Formulation and *in vivo* Evaluation of Niosome containing Oxcarbazepine. Journal of Pharmaceutical Science and Research. 2013;5(1):6.
7. Tangri P, Khurana S. Niosome: Formulation and evaluation. International Journal of Biopharmaceutics. 2011;2(1):47-52.
8. Indira U, Uma Shankar MS. Proniosome as a drug carrier: A Review. International Journal of Pharmaceutical Science and Research. 2012;3(12):4617-20.

9. Udupa N, Chandraprakash KS, Umadevi P, Pillai GK. Formulation and evaluation of methotrexate niosome. Drug Development and Industrial Pharmacy. 1993;19(11):1331-2.
10. 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.
11. Madhavi M, Meher CP, Pochaiah B, Rao AM. Formulation and Evaluation Metformin Based Niosome. International Journal of Pharma Research and Review. 2013;2(1):1.
12. Pandya KD, Patel SS, Seth AK, Shah CN, Aundhia CJ, Shah NV, *et al.* NIOSOME: AN Unique Drug Delivery System. Pharma Science Monitor. 2018;7(3):85-92.
13. Shakya V, Bansal BK. Niosome: A Novel Trend in drug Delivery. International Journal of Research and Development in Pharmacy and Life Sciences. 2014;3(4):1037-8.
14. Seleci DA, Seleci M, Walter JG, Stahl F, Scheper T. Niosome as Nanoparticular Drug Carriers: Fundamentals and Recent Applications. Hindawi Publishing Corporation Journal of Nanomaterials. 2016;13:2.
15. Sanklecha VM, Pande VV, Pawar SS, Pagar OB, Jadhav AC. Review on Niosomes. Austin Pharmacology and Pharmaceutics. 2018;3(2):2-4.
16. Rane S, Inamdar Y, Rane B, Ashish J. Niosomes: A Non-Ionic Surfactant Based Vesicles as a Carriers for Drug Delivery. International Journal of Pharmaceutical Sciences Review and Research. 2018;51(1):198-213.
17. Sankhyan A, Pawar P. Recent Trends in Niosome as Vesicular Drug Delivery System. Journal of Applied Pharmaceutical Science. 2012;02(06):28-30.
18. 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.
19. Okore VC, Attama AA, Ofokansi KC, Esimone CO, Onuigbo EB. Formulation and Evaluation of Niosomes. Indian Journal of Pharmaceutical Sciences. 2011;73(3):323-5.
20. Agrawal S, Londhe V, Gaud R. Niosomes: Layered Delivery System for Drug Targeting. International Journal of Scientific Research. 2014;3(1):416.
21. Yoshioka T, Sternberg B, Florence AT. Preparation and properties of vesicles (niosome) of sorbitan monoesters (Span 20, 40, 60 and 80) and a sorbitan triester (Span 85). International Journal of Pharmaceutics. 1994;105(1):1-6.
22. Okore VC, Attama AA, Ofokansi KC, Esimone CO, Onuigbo EB. Formulation and evaluation of niosome. Indian Journal of Pharmaceutical Sciences. 2011;73(3):323-8.
23. Akhilesh D, Bini KB, Kamath JV. Review on span-60 based non-ionic surfactant vesicles (niosome) as novel drug delivery. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2012;3:6-12.
24. Jain CP, Vyas SP. Preparation and characterization of niosome containing rifampicin for lung targeting. Journal of Microencapsulation. 1995;12(4):401-7.
25. Arunothayanun P, Bernard MS, Craig DQM, Uchegbu IF, Florence AT. The effect of processing variables on the physical characteristics of non-ionic surfactant vesicles (niosome) formed from a hexadecyl diglycerol ether. International Journal of Pharmaceutics. 2000;201(1):7-14.
26. Paolino D, Cosco D, Muzzalupo R, Trapasso E, Picci N, Fresta M, *et al*. Innovative bola-surfactant niosomes as topical delivery systems of 5-fluorouracil for the treatment of skin cancer. International Journal of Pharmaceutics. 2008;353(1-2):233-42.
27. Paolino D, Muzzalupo R, Ricciardi A, Celia C, Picci N, Fresta M*, et al. In vitro* and *in vivo* evaluation of Bola-surfactant containing niosomes for transdermal delivery. Biomedical Microdevices. 2007;9(4):421-33.
28. Imran M, Shah MR, Ullah F. Glycoside-based niosomal nanocarrier for enhanced *in-vivo* performance of Cefixime. International Journal of Pharmaceutics. 2016;505(1-2):122-32.
29. Junyaprasert VB, Teeranachaideekul V, Supaperm T. Effect of charged and non-ionic membrane additives on physicochemical properties and stability of niosomes. AAPS Pharm Sci Tech. 2008;9(3):851-9.
30. Bragagni M, Mennini N, Furlanetto S, Orlandini S, Ghelardini C, Mura P, *et al.* Development and characterization of functionalized niosomes for brain targeting of dynorphin-B. European Journal of Pharmaceutics and Biopharmaceutics. 2014;87(1):73-9.
31. Marianecci C, Rinaldi F, Mastriota M. Anti-inflammatory activity of novel ammonium glycyrrhizinate/niosomes delivery system: Human and murine models. Journal of Controlled Release. 2012;164(1):17-25.
32. Mandal S, Banerjee C, Ghosh S, Kuchlyan J, Sarkar N. Modulation of the photophysical properties of curcumin in non-ionic surfactant (Tween-20) forming micelles and niosomes: A comparative study of different microenvironments. The Journal of Physical Chemistry B. 2013;117(23):6957-68.
33. DiMarzio L, Marianecci C, Petrone M, Rinaldi F, Carafa M. Novel pH-sensitive non-ionic surfactant vesicles: Comparison between Tween 21 and Tween 20. Colloids and Surfaces B: Bio Interfaces. 2011;82(1):18-24.
34. Bandyopadhyay P, Johnson M. Fatty alcohols or fatty acids as niosomal hybrid carrier: Effect on vesicle size, encapsulation efficiency and *in vitro* dye release. Colloids and Surfaces B: Bio Interfaces. 2007;58(1):68-71.
35. Pardakhty A, Varshosaz J, Rouholamini A. *In vitro* study of polyoxyethylene alkyl ether niosomes for delivery of insulin. International Journal of Pharmaceutics. 2007;328(2):130-41.
36. Bayindir ZS, Yuksel N. Characterization of niosomes prepared with various non-ionic surfactants for paclitaxel oral delivery. Journal of Pharmaceutical Sciences. 2010;99(4):2049-60.
37. Manconi M, Sinico C, Valenti D, Lai F, Fadda AM. Niosomes as carriers for tretinoin: III. A study into the *in vitro* cutaneous delivery of vesicle-incorporated tretinoin. International Journal of Pharmaceutics. 2006;311(1-2):11-9.
38. Tavano L, Muzzalupo R, Mauro L, Pellegrino M, Ando S, Picci N, *et al.* Transferrin-conjugated Pluronic niosomes as a new drug delivery system for anticancer therapy. Langmuir. 2013;29(41):12638-46.
39. Muzzalupo R, Tavano L, Cassano R, Trombino S, Ferrarelli T, Picci N, *et al.* A new approach for the evaluation of niosomes as effective transdermal drug delivery systems. European Journal of Pharmaceutics and Biopharmaceutics. 2011;79(1):28-35.
40. Vyas SP, Singh RP, Jain S. Non-ionic surfactant-based vesicles (niosomes) for non-invasive topical genetic immunization against hepatitis B. International Journal of Pharmaceutics. 2005;296(1-2):80-6.
41. Sankhyan A, Pawar P. Recent trends in niosome as vesicular drug delivery system. Journal of Applied Pharmaceutical Science. 2012;2(6):20-32.
42. Junyaprasert VB, Teeranachaideekul V, Supaperm T. Effect of charged and non-ionic membrane additives on physicochemical properties and stability of niosomes. AAPS Pharm Sci Tech. 2008;9(3):851-9.
43. Schwendener RA. Liposomes as vaccine delivery systems: A review of the recent advances Therapeutic advances in vaccines. 2014;2(6):159-82.
44. Walker SA, Kennedy MT, Zasadzinski JA. Encapsulation of bilayer vesicles by self-assembly Nature. 1997;387(6628):61-4.
45. Rajkamal M, Arwind S, Sandeep A. Exploring potential of ufasomes as topical/transdermal delivery systems: Reviewing decade of research. American Journal of Phar Tech Research. 2012;4:126-37.
46. Irfan M, Verma S, Ram A. Preparation and characterization of ibuprofen loaded transferosome as a novel carrier for transdermal drug delivery system. Asian Journal of Pharmaceutical and Clinical Research. 2012;5(3):162-5.
47. Duangjit S, Opanasopit P, Rojanarata T, Ngawhirunpat T. Evaluation of meloxicam-loaded cationic transfersomes as transdermal drug delivery carriers. AAPS Pharm Sci Tech. 2013;14(1):133-40.
48. Gavali S, Pacharane S, Jadhav K, Kadam V. Clinical P transfersome: A new technique for transdermal drug delivery. International Journal of Research in Pharmacy and Chemistry. 2011;1(3):735-40.
49. Saraf S, Gupta D, Kaur C, Saraf S. Sphingosomes a novel approach to vesicular drug delivery. Int J Cur Sci Res. 2011;1(2):63-8.
50. Decome L, DeMéo M, Geffard A, Doucet O, Duménil G, Botta A. Evaluation of photolyase (Photosome) repair activity in human keratinocytes after a single dose of ultraviolet B irradiation using the comet assay. Journal of Photochemistry and Photobiology B: Biology. 2005;79(2):101-8.
51. Kumar A, Pal J, Jaiswal A, Singh V. Review on niosomes as novel drug delivery system. International Research Journal of Pharmacy. 2011;2(5):61-5.
52. Allam A, Gamal SEL, Naggar V. Formulation and evaluation of acyclovir niosomes for ophthalmic use. Asian Journal of Pharmaceutical and Biological Research. 2011;1(1):28-40.
53. Parthibarajan R, Kumar S, Gowri SN, Balakishan L, Srinivas B, Bhagya LV, *et al.* Design and evaulation of voriconazole niosomes. International Journal of Pharmacy and Pharmaceutical Sciences. 2013;5(3):604-11.

54. Ciobanu M, Heurtault B, Schultz P, Ruhlmann C, Muller CD, Frisch B. Layersome: Development and optimization of stable liposomes as drug delivery system. International Journal of Pharmaceutics. 2007;344(1-2):154-7.
55. Hayward JA, Levine DM, Neufeld L, Simon SR, Johnston DS, Chapman D. Polymerized liposomes as stable oxygen-carriers. FEBS Letters. 1985;187(2):261-6.
56. Gao X, Huang L. Cationic liposome-mediated gene transfer. Gene Therapy. 1995;2(10):710-22.
57. Gangwar S, Singh S, Garg G. Ethosomes: A novel tool for drug delivery through the skin. Journal of Pharmacy Research. 2010;3(4):688-91.
58. Cuppoletti J, Mayhew E, Zobel CR, Jung CY. Erythrosomes: Large proteoliposomes derived from crosslinked human erythrocyte cytoskeletons and exogenous lipid. Proceedings of the National Academy of Sciences. 1981;78(5):2786-90.
59. Vingerhoeds MH, Haisma HJ, Muijen MV, DeRijt RBV, Crommelin DJ, Storm G. A new application for liposomes in cancer therapy: Immunoliposomes bearing enzymes (immuno-enzymosomes) for site-specific activation of prodrugs. FEBS Letters. 1993;336(3):485-90.
60. Kretschmar M, Amselem S, Zawoznik E, Mosbach K, Dietz A, Hof H, *et al*. Efficient treatment of murine systemic infection with *Candida albicans* using amphotericin B incorporated in nanosize range particles (emulsomes). Mycoses. 2001;44(7-8):281-6.
61. Gill B, Singh J, Sharma V, Hari KS. Emulsomes: An emerging vesicular drug delivery system. Asian Journal of Pharmaceutics. 2012;6(2):87.
62. Prashar D, Sharma D. Cubosomes: A sustained drug delivery carrier. Asian Journal of Research in Pharmaceutical Sciences. 2011;1(3):59-2.
63. Jain S, Jain V, Mahajan SC. Lipid Based Vesicular Drug Delivery Systems. Advances in Pharmaceutics. 2014;(7):1-12.
64. Blume G, Cevc G. Molecular mechanism of the lipid vesicle longevity *in vivo*. Biochimica et Biophysica Acta. 1993;1146(2):157-68.
65. Saraf S, Rathi R, Kaur C. Colloidosomes an advanced vesicular system in drug delivery. Asian Journal of Scientific Research. 2011;4(1):1-15.
66. Lee D, Weitz DA. Double Emulsion-Templated Nanoparticle Colloidosomes with Selective Permeability. Advanced Materials. 2008;20(18):3498-503.
67. Benvegnu T, Lemiègre L, Cammas-Marion S. New generation of liposomes called archaeosomes based on natural or synthetic archaeal lipids as innovative formulations for drug delivery. Recent Patents on Drug Delivery and Formulation. 2009;3(3):206-20.
68. Jain SS, Jagtap PS, Dand NM, Jadhav KR, Kadam VJ. Aquasomes: A novel drug carrier. Journal of Applied Pharmaceutical Science. 2012;02(01):184-92.
69. Patel J, Patel K, Patel H, Patel B, Patel P. Aquasomes: A self-assembling nanobiopharmaceutical carrier system for bio-active molecules: A review. International Journal for Pharmaceutical Research Scholars. 2012;1(1):11-21.
70. Solanki AB, Parikha J, Parikh R. Preparation, characterization, optimization and stability studies of aceclofenac proniosomes. Iranian J Pharm Res. 2008;7(4):237-46.
71. Gupta A, Prajapati SK, Balamurugan M, Singh M, Bhatia D. Design and development of a proniosomal transdermal drug delivery system for captopril. Tropical J Pharm Res. 2007;6(2):687-93.
72. Varshosaz J, Pardakhty A, Mohsen S, Baharanchi H. Sorbitan monopalmitate-based proniosomes for transdermal delivery of chlorpheniramine maleate. Drug Dev. 2005;12(2):75-82.
73. Mokhtar M, Sammour OA, Hammad MA, Megrab NA. Effect of some formulation parameters on flurbiprofen encapsulation and release rates of niosomes prepared from proniosomes. Int J Pharm. 2008;361(1-2):104-11.
74. Fang JY, Hong CT, Chiu WT, Wang YY. Effect of liposomes and niosomes on skin permeation of enoxacin. Int J Pharm. 2001;219(1-2):61-72.
75. Azeem A, Jain N, Iqbal Z, Ahmad FJ, Aqil M, Talegaonkar S. Feasibility of proniosomes based transdermal delivery of frusemide: Formulation optimization and pharmacotechnical evaluation. Pharm Dev Technol. 2008;13(2):155-63.
76. Kumar SK, Jain SK, Pancholi SS, Agarwal S, Saraf DK, Agarwal GP. Provesicular transdermal drug delivery system of ethinylestradiol and levonorgestrel for contraception and hormone replacement therapy. Indian J Pharm Sci. 2003;65(6):620-7.
77. Hu C, Rhodes DG. Proniosomes: A novel drug carrier preparation. Int J Pharm. 1999;185(1):23-35.
78. Alsarra IA, Bosela AA, Ahmed SM, Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur J Pharm Biopharm. 2005;59(3):485-90.
79. Vora B, Khopade AJ, Jain NK. Proniosome based transdermal delivery of levonorgestrel for effective contraception. J Control Release. 1998;54(2):149-65.
80. Alsarra IA. Evaluation of proniosomes as an alternative strategy to optimize piroxicam transdermal delivery. J Microencapsulation. 2008;11:1-7.
81. Gopinatha D, Ravi D, Rao BR, Apte SS, Renuka D, Rambhau D. Ascorbyl palmitate vesicles (Aspasomes): formation, characterization and applications. International Journal of Pharmaceutics. 2004;271(1-2):95-13.
82. Silva GM, Maja CPM. Ascorbic acid and its derivatives in cosmetic formulations. Cosmet Toil. 2000;115(6):59-62.
83. Darr D, Combs S, Dunston S, Manning T, Pinell S. Tropical Vitamin C protects porcine skin from ultraviolet radiation-induced damage. Br J Derm. 1992;127(3):247-53.
84. Djerassi D. The role of the corrective Vitamins A, B5 and C in the new, high performance cosmetics. Drug Cosmet Ind. 1997;160(6):60-2.
85. Fox C. Advances in the cosmetic science and technology of bioactive materials. Cosmet Toil. 1997;112(7):67-84.
86. Spicilin P, Gasperlin M, Kmetec V. Stability of ascorbyl palmitate in topical microemulsion. Int J Pharm. 2001;222(2):271-9.
87. Han S. Structure of Ascorbyl Palmitate Bilayers (Aspasomes) from Molecular Dynamics Simulation. Bull Korean Chem Soc. 2018;1:1229-49.
88. Yadav P, Lariya N. Aspasome: A novel carrier for drug delivery system. Journal of Pharma Research. 2016;5(10):220-3.
89. Gadhiya P, Shukla S, Modi D, Bharadia P. A Review- Niosomes in Targeted Drug Delivery. International Journal for Pharmaceutical Research Scholars. 2012;2:60.
90. Pawar SD, Pawar RG, Kodag PP, Waghmare AS. Niosome: An Unique Drug Delivery System. International Journal of Biology, Pharmacy and Allied Sciences. 2012;3(1):409-12.
91. Blazek-Walsh AI, Rhodes DG. SEM imaging predicts quality of niosomes from maltodextrin-based Proniosomes. Pharm Res. 2001;18(5):656-61.
92. Gayatri DS, Venkatesh P, Udupa N. Niosomal sumatriptan succinate for nasal administration. Int J Pharm Sci. 2000;62(6):479-81.
93. Khandare JN, Madhavi G, Tamhankar BM. Niosomes Novel Drug Delivery System. The Eastern Pharmacist. 1994;37:61-4.
94. Rogerson A, Cummings J, Willmott N, Florence AT. The distribution of doxorubicin in mice following administration in niosomes. J Pharm Pharmacol. 1988;40(5):337-42.
95. Biju SS, Talegaonkar S, Misra PR, Khar RK. Vesicular systems: An overview. Indian J Pharm Sci. 2006;68(2):141-53.
96. Ijeoma FU, Suresh PV. Non-ionic surfactant-based vesicles (niosomes) in drug delivery. Int J Pharm. 1998;172(1-2):33-70.
97. Malhotra M, Jain NK. Niosomes as Drug Carriers. Indian Drugs. 1994;31(3):881-66.
98. 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.
99. Smulders S, Kaiser JP, Zuin S, Landuyt KLV, Golanski L, *et al*. Contamination of nanoparticles by endotoxin: Evaluation of different test methods. Particle and Fibre Toxicology. 2012;9(41):2-11.
100. Selvaraj S, Niraimathi V. Formulation and *in vivo* Evaluation of Acyclovir Loaded Chitosan Nanoparticles for Ocular Delivery. International Journal of Pharmaceutical Sciences and Drug Research. 2016;5(4):619-29.
101. Selvaraj S, Niraimathiand V, Nappinnai M. Formulation and evaluation of acyclovir loaded chitosan nanoparticles. International Journal of Pharmacy and Analytical Research. 2017;9(3):118-25.

PICTORIAL ABSTRACT



SUMMARY

Niosome is novel formulation for treatment of various disease mainly for treatment of cancer and various topical diseases. It has more advantage than conventional dosage form and also liposome. Due to size in nanometric range it does not show faster metabolism and it increase bioavailability. Many marketed preparations of niosome available in pharmaceutical market. Niosome are shows the best targeted action. Stability of niosome is more than liposome due to their non-ionic surfactant as main component.

About Authors

Mr. Mahesh Gajanan Umbarkar, B. Pharmacy pass out from Anuradha College of Pharmacy Chikhli. I qualify my degree from Sant Gadgebaba Amravati University with Distinction, in 2019. I got highest score in organic chemistry award from Anuradha College of Pharmacy in 2018. Qualified GPAT with 145 marks in 2020. Now studying M. Pharmacy (Pharmaceutics) in R.C. Patel Institude of Pharmaceutical Education and Research, Shirpur, Maharashtra. I published about 3 research paper and 1 Review Article.

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