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RECENT THERAPEUTIC ADVANCES IN NIOSOMAL DELIVERY SYSTEMS: A COMPREHENSIVE OVERVIEW

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ABSTRACT

Nanotechnology is multidisciplinary area of research with tremendous applications in drug delivery. The vesicular nano-carrier namely, niosome is advanced novel vesicular based drug delivery system. Niosome is non-ionic surfactant based self assembled nano-vesicular carrier within size ranges between 10-1000 nm which formed by non-ionic surfactant and cholesterol followed by hydration with aqueous medium and which have loading capability for both hydrophobic and hydrophilic drug molecules. Niosome is most promising carrier for drug delivery with potential application and advantages in treatment of various diseases such as cancer, diabetes, HIV, skin disorders, etc. Here we have reported method of preparation of niosomes, significant features, advantages, disadvantages, characterization and applications of niosome in various areas. Niosome is proven as promising carrier in health sciences.

1. INTRODUCTION

Vesicle based dosage forms are most extensively investigated novel drug delivery systems. The word '*vesicle'* is derived from Greek word which means '*a bubble of liquid within a cell'*. In cell biology, in detail, vesicle can be termed as small, intracellular organelle, enclosed by lipid based membrane which can store or transport substance within a living cells[1]. The vesicle can form naturally or can be synthesized artificially. The synthesized vesicles are termed as vesicular nano-carriers such as liposome, niosome etc. These novel drug delivery system aims to fulfill two basic prerequisites that it delivers drug at required rate according to need and period of disease treatment in human body. And another it creates channel of active entity at particular site of action. It results in number of benefits such as various route of administration, sustained drug delivery system, targeted drug delivery with reduced side effect and toxicity problems[2]. The vesicular formation is occurs based on properties of lipid membrane. Lipids forms well organized number of circular lipid bilayered vesicles, when a surfactant molecule comes in contact with aqueous media. Vesicles get arranged on the basis of diverse range of amphiphillic building blocks. The bilayer structural arrangements of lipids are similar to that of biological membranes and hence, lipid vesicle can be considered as biomembrane model. These magic bullets of vesicle are having tremendous application in immunology, diagnostic areas, therapeutic applications, genetic engineering etc. Till date there are so many vesicular drug delivery systems are developed including an examples of liposome, niosome, ethosome etc.[3] (Figure 1). Here we are focusing on niosome based vesicular delivery system.

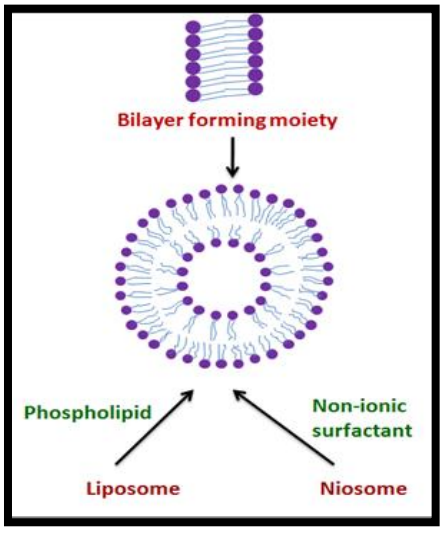


FIGURE 1: FORMATION OF VESICULAR DRUG DELIVERY SYSTEMS

A niosome is non-ionic surfactant based self assembled nano-vesicular carrier within size ranges between 10-1000 nm which formed by non-ionic surfactant and cholesterol when both comes in contact with aqueous medium. They have loading capability for both hydrophobic and hydrophilic drug molecules[4]. Niosomes are reported to be more beneficial than previously reported vesicles. Niosome exhibit more penetration as compared to emulsions. Although they are structurally similar to liposome but they exhibit more stability and more economy due to material used in their preparation.

Basically niosomes formulated by using cholesterol and non-ionic surfactant. The surfactant molecules arrange themselves in such a manner that the outer layer formed by hydrophilic head whereas the hydrophobic tails arranges oppositely to form spherical bilayer structure. Here hydrophilic part remains in contact with aqueous core while, hydrophobic parts oriented away from aqueous core forming bilayer (Figure 2). This amphiphillic vesicular drug delivery system has potential application in various area of therapeutics.

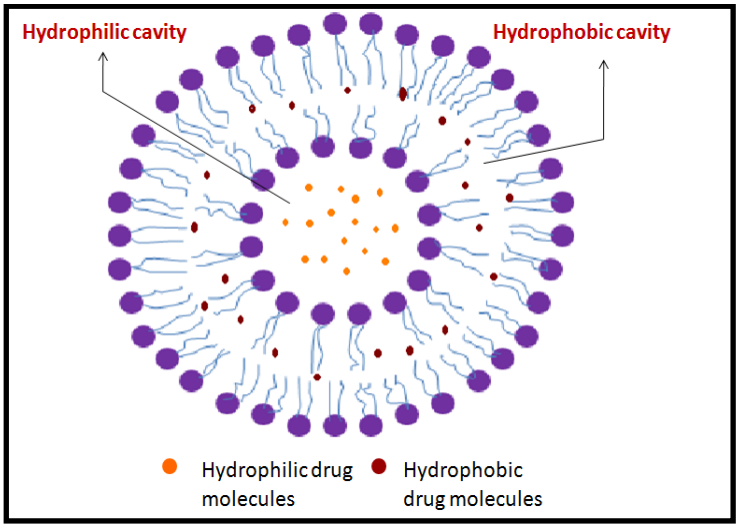


FIGURE 2: STRUCTURE OF NIOSOME

1.1. Significant characteristics of Niosomes

- As compared to liposome, vesicles of niosomes are more osmotically active.
- Niosomes are chemically more stable and can be stored for longer period of time.
- Niosome surfactants are suitable as they are biodegradable,safer, non-immunogenic.
- Niosome are more biocompatible and have lower toxicity problems because of their non- ionic constituents.
- The structural amphoteric features of niosomes makes them excellent carrier for hydrophobic as well as hydrophilic drug moiety. They can easily accommodate hydrophobic drug into lipid bilayer and hydrophilic drug in aqueous core.

- The raw materials for niosome synthesis are easily accessible.
- They possess ease of surface modification for better performance of drugs because of functional groups present on their hydrophilic heads.
- Niosome can be designed according their required action as they display an versatile structural features based upon their respective surfactant composition, bilayer fluidity and particle size.
- They result in improvement of therapeutic index of drug at particular targeted site of action as they protect drug moieties from biological environment and reduce their clearance from body ultimately exhibit controlled drug delivery system[5,6].

1.2. Advantages of niosomes

- Niosomal vesicular dispersions are aqueous base. Being water based formulation it offers improvement in patient compliance as compared to oil based formulations.
- They result into enhancement of bioavailability of entrapped drugs.
- Handling, storage conditions for surfactants are simple so they are easily accessible.
- Niosomes exhibit increase in skin penetration of drugs.
- Niosomes can be administered by variety of route of administration such as oral, parenteral, topical etc.
- The niosomal vesicles exhibits controlled drug release fashion.
- Niosomes have capablility to produce sustain release drug effect, which can decrease frequency and dose of administration[7].

1.3. Disadvantage of niosomes:

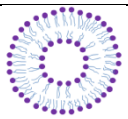
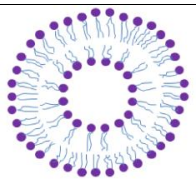
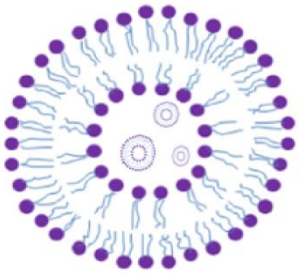
- Physical instability problems such as aggregation and fusion of vesicles may occur.
- Leakage of entrapped drug and hydrolysis of niosomal vesicles which may affect on shelf life of product.
- Low practical production yield, high production cost and time consuming process.

The various size reduction procedures require sophisticated instruments such as extrusion, probe sonication which are costly and time consuming[8].

2. TYPES OF NIOSOMES

Classification of niosomes is based upon number of bilayers formed in the niosomal structure as Multilamellar Vesicles (MLV) and Unilamellar vesicles(UV), where depending upon size of UV, it is further classified as Small Unilamellar Vesicles (SUV) and Large Unilamellar Vesicles (LUV)[4]. There are mainly 3 basic types of niosomes (Table 1).

TABLE 1 : KEY DIFFERENCE BETWEEN DIFFERENT TYPES OF NIOSOMES

Parameter	Small Unilamellar Vesicle (SUV)	Large Unilamellar Vesicle (LUV)	Multi Lamellar Vesicle (MLV)
Description	More prone to aggregation and fusion. Thermodynamically unstable. Low loading capacity and % entrapment efficiency.	It has a high aqueous/lipid compartment ratio	It consists of a number of bilayer surrounding the aqueous lipid compartment separately.
Size (µm)	0.025 – 0.05	> 10	0.5 – 10
Structure			

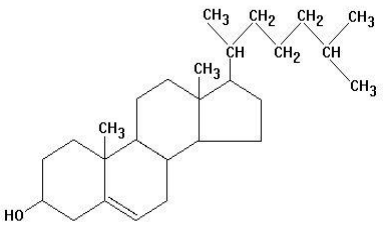
3. KEY COMPONENTS OF NIOSOMES

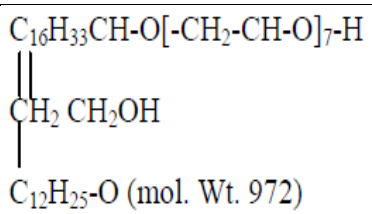
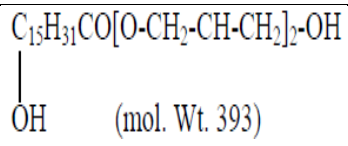
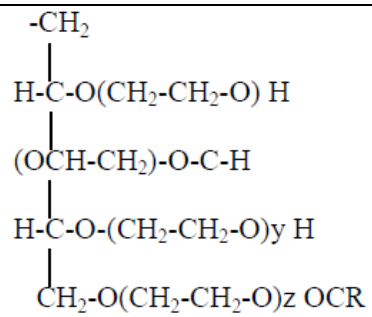
Major constituents of niosomes[7] are as follows -

3.1. Cholesterol

3.2. Nonionic surfactants

TABLE 2 : LIST OF COMPONENTS USED IN THE PREPARATION OF NIOSOMES

Component	Descriptions	Examples
Cholesterol	Offers grimness and perfect spherical posture to niosomal vesicles.	
Nonionic surfactants	The non ionic surfactants possess a hydrophilic head and a hydrophobic tail plays a major role in the formation of niosomes.	E.g.Spans, Tweens, Brijs, etc.

• Ether linked surfactant	In which the hydrophilic, hydrophobic moities are ether linked like polyoxyetylene alkyl ethers with general formula CnEOm.	
• Ester linked	Hydroplilic and hydrophobic moities are ester linked.	
	Sorbital esters are combination of fractional esters of sorbital mainly mono and di-anhydrides along with oleic acid.	

4. FACTOR GOVERNING NIOSOME FORMATION

4.1. Structure of non-ionic surfactant

The niosome formation basically involves the presence of an amphiphiles and aqueous solvent but sometime cholesterol is required in the formulation of niosomes because it gives proper grimness, perfect alligned shape and geometrical structural orientation. Cholesterol plays an important role in stabilization of niosomal suspension by avoiding the formation of aggregates which is attributed to strong electrostatic repulsive forces.

Surfactant level used generally 10-30 mM (1-2.5% w/w) to make niosomal dispersion. During hydration process the water:surfactant ratio taken have major impact on the structure and properties of the niosome system. Surfactant/lipid level is directly proportional to both the entrapment efficiency of drug and the viscosity of niosmal dispersion[9].

4.2. Properties of drug

Physicochemical properties of active ingredient which is to be encapsulated have more prominent effect on surface charge and grimness of the niosome microstructures.

The surface charge develops mainly due to molecular interaction between drug molecule and polar head of the surfactant. The most commonly employed stabilizers in order to avoid the aggregation of vesicles are dicetyl phosphate (DCP)[10].

4.3. Surfactant molecule

Critical packing parameter (CPP) is considered as key property of surfactant which reflects geometry of niosomal vesicle. CPP can be determined using formula mentioned below,

CPP (Critical Packing Parameters) = V/ lc× a0

Where, v = volume of hydrophobic group,

lc = length of critical hydrophobic group

a0 = area of hydrophilic head group.

CPP value gives an idea about structure which is listed as follows and indicates type of miceller structure formed.

If CPP < ½ formation of spherical micelles,

If ½ < CPP < 1 formation of bilayer micelles,

If CPP > 1 formation inversed micelles[11,12].

4.4. Temperature of hydration

The shape and size of niosomes are majorly influenced by temperature conditions of during niososmes formation. The thermal changes occurring affects assembly structure of surfactant and ultimately affects shape and size of niosomal vesicles. The ideal conditions for niosome formations should be carried out above phase transition temperature[13,14].

5. METHOD'S OF PREPARATION OF NIOSOMES

5.1. Ethanol injection method

Ethanol injection method offers advantage that it avoids both sonication and high pressure, first described by Batzri and Korn in 1973 to develop SUVs. Briefly in this technique, surfactant dissolved in ethanol and forcefully injected in aqueous media using syringe.

The whole system stirred using magnetic stirrer in order to evaporate ethanol which results in formation of niosomal vesicles in the size range of 0.025-0.05 μcm in diameter[15].

5.2. Ether injection method

It is slow injection technique. In this ether injection method (EIM), mixtures of non ionic surfactant and cholesterol dissolved in organic solvent like ether and it is slowly injected into aqueous phase having drug at constant temperature above the boiling point of organic solvent. The system stirred continuously to allow evaporation of ether which gives circular single layered niosomal vesicles with high entrapment efficiency and nano-size range ranging from 50-1000 nm. There are various examples are reported where rifampicin, adriamycin, diclofenac sodium, gadobenate, salbutamol loaded niosomes prepared using ether injection technique[15,16].

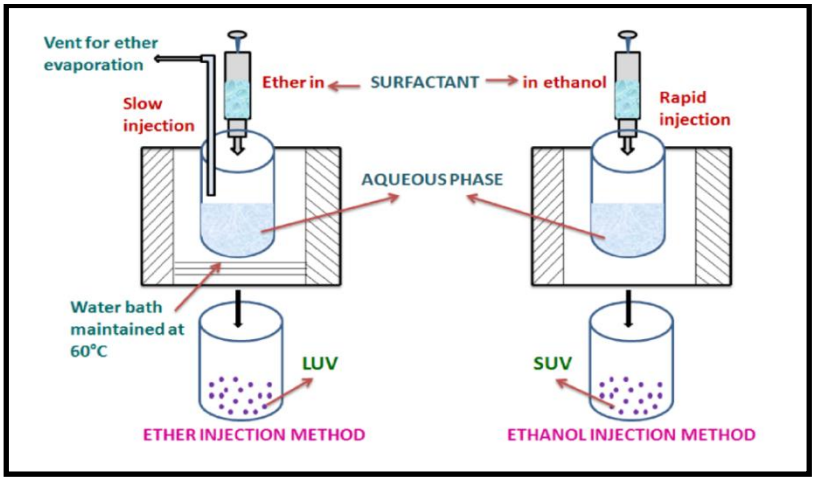


FIGURE 3 : ILLUSTRATION OF ETHER AND ETHANOL INJECTION METHOD

5.3. Hand shaking method (Thin film hydration technique)

Thin film hydration is most commonly used technique to prepare niosome (Figure 4). It is easy and fast method of preparation of concentrated and uniform mixture of niosomal suspension. Briefly, in round bottom flask (RBF), surfactant and cholesterol both added and solubilized with sufficient quantity of organic solvent. Further the organic solvent is allowed to evaporate at room temperature (20°C) using rotary evaporator which leaves watery film on the inner wall of the RBF. The film was dried in desiccator and then rehydrated with aqueous medium/buffer containing drug at 50-60°C with little stirring results in multi layered vesicle formation[15,17].

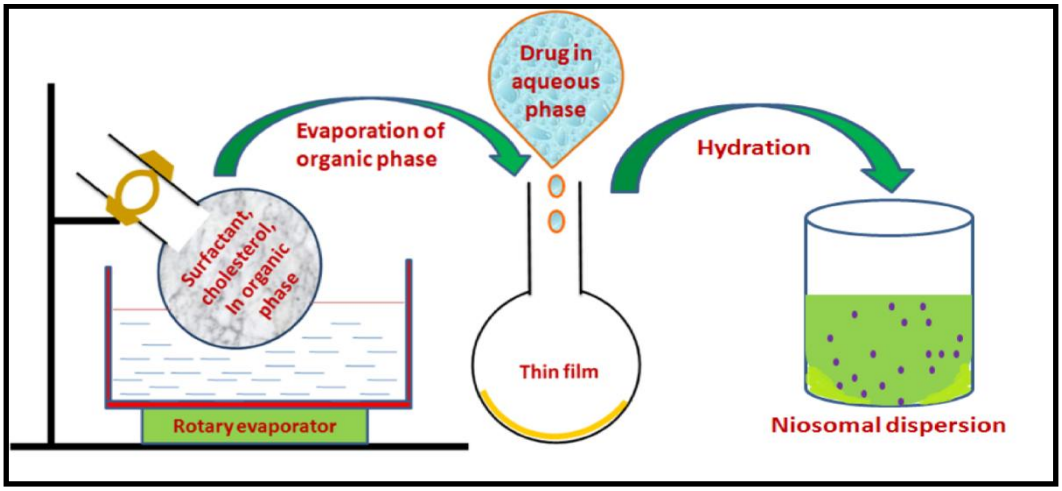


FIGURE 4 : PREPARATION OF NIOSOME BY HAND SHAKING METHOD (THIN FILM HYDRATION).

5.4. The bubble method

It is advanced approach of single step synthesis of vesicular systems such as liposomes and niosomes. The major advantage of this technique is that it does not require any organic

solvents or detergents or higher shear forces during synthesis of liposomes and niosomes. The mechanism of 'bubble method' is based upon introducing inert gas such as nitrogen gas through mixtures of non-ionic surfactant and cholesterol resulting into formation of stable dispersions of niosomes in size ranging between 0.2 um-0.5um (Figure 5).

In brief, in this technique, a bubbling unit i.e glass reactor of round bottom flask with three necks is preferably employed. Non-ionic surfactant and cholesterol are disperse in an aqueous media and the mixture is pour into this reactor which kept in water to maintain temperature conditions at 70° C. In first neck occupied with thermometer, middle one consists of water-cooled reflux and third one is with nitrogen supply. The mixtures of non-ionic surfactant and cholesterol is then mixed properly for 15 second by using homogenizer and instantly nitrogen gas is bubbled through it at 70° C. at the starting of the bubbling process there is excessive foaming of the dispersion which can be avoided by increasing nitrogen gas flow (5-7L/min.)[18].

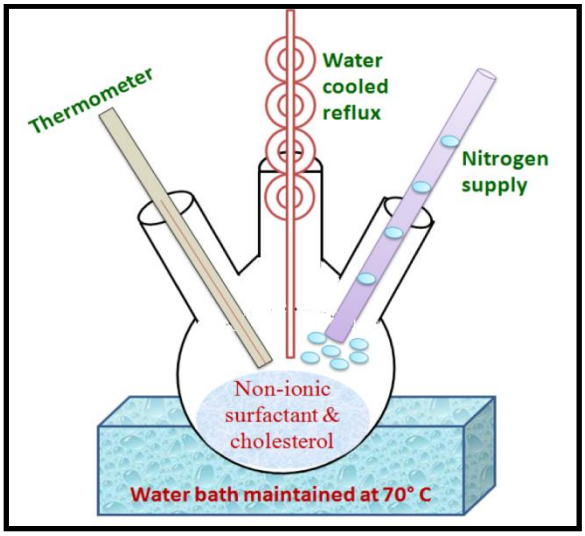


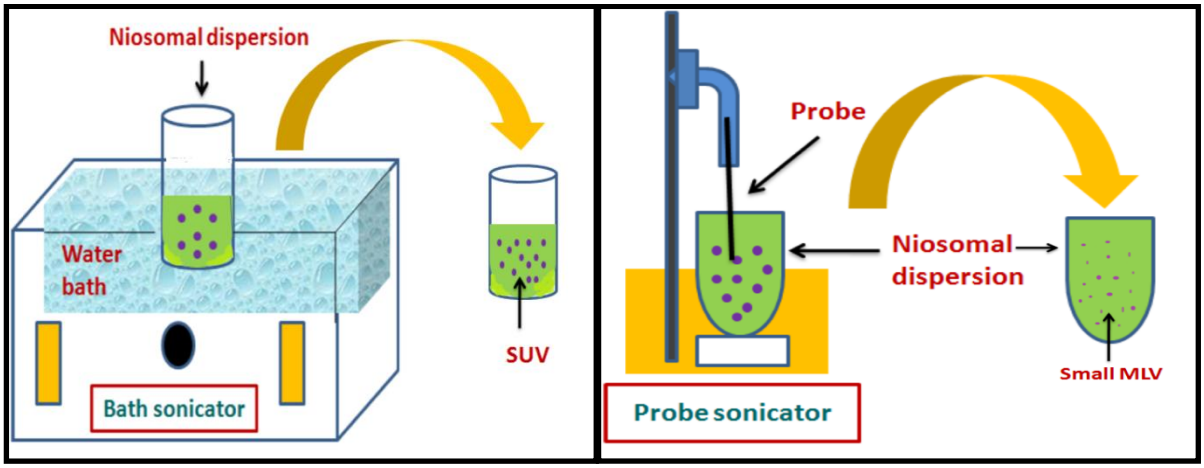
FIGURE 5 : ASSEMBLY OF BUBBLING UNIT

5.5. Reverse phase evaporation

Reverse phase evaporation technique involves vaporization of organic solvent. In the mixture of ether and chloroform, Cholesterol and surfactant (1:1) are dissolved followed by addition of aqueous solution of drug results in formation of two layers. Sonication of the whole system at 4-5°C leads to formation of transparent gel in which a small amount of phosphate buffer saline (PBS) is added and then it is sonicated. Removal of organic phase under low pressure at 40°C gives niosomal dispersion which is further diluted with PBS. After dilution heating of final niosomal dispersion on a water bath at 60°C for 10 min yields vesicles[15,19].

5.6. Sonication

It is most commonly used technique for the development of nano-size niosomes. Two techniques of sonication are employed a. Bath sonication and b. Probe sonication (Figure 6). In probe sonication technique, drug solution in PBS is added into cholesterol/non-ionic surfactant mixtures. The whole system is allowed to sonicate for 3 minutes at 60°C through probe sonicator which results in nano sized vesicles[20]. Probe sonication is one of the techniques to reduce the particle size of niosomes[21]. Kumar et al., (2013)[22] reported encapsulation of pregabalin in niosomes by using film hydration technique followed by bath sonication for achieving prolonged release & longer duration of action.



(a) **(b)**

FIGURE 6 : PREPARATION OF NIOSOME BY A) BATH SONICATOR B) PROBE SONICATOR

5.7. Extrusion method

This method has good control over vesicle size.

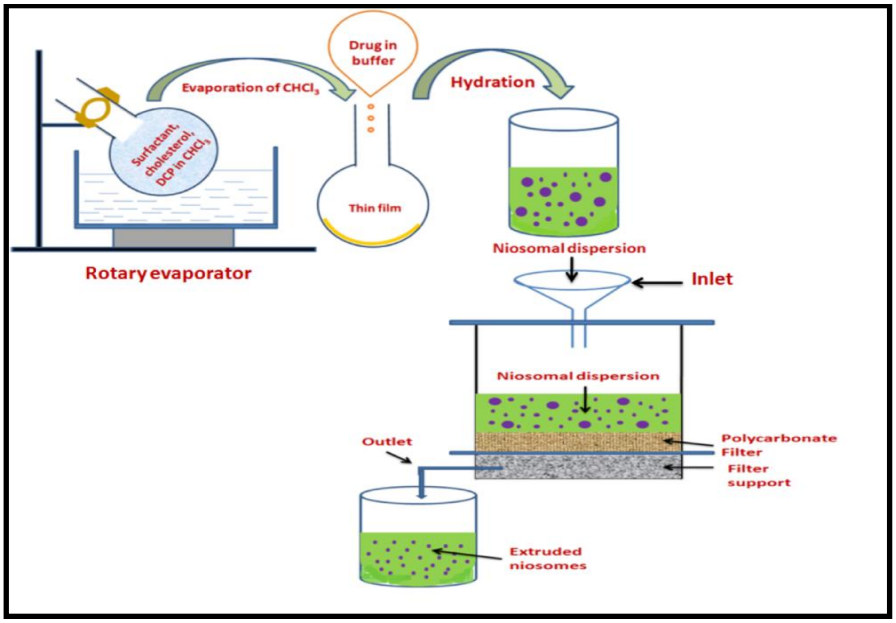


FIGURE 7 : REPRESENTATION OF MULTIPLE MEMBRANE EXTRUSION METHOD

In this method, mixture of cholesterol, non-ionic surfactant and dicetyl phosphate is solubilized in an organic phase and further evaporated to produce transparent film. The film is dried in desiccator followed by hydration using aqueous phase containing drug. The whole system is then extruded via series of polycarbonate membranes (Figure 7). The resulting suspension contains vesicles of uniform size[23].

5.8.Remote Loading Technique

In this method cholesterol and non-ionic surfactants are dissolved in organic solvent like chloroform. The resultant mixture is then vaporized using rotary evaporator to produce watery film on inner surface of the RBF. Hydration of film is done using aqueous 300 mM citric acid solution (pH 4.0) with the help of cyclo-mixer which gives suspension with multilamellar vesicles. Resultant suspension is frozen and thawed 3 times. Further it is sonicated to produce niosomal suspension which is stirred at high speed on addition of aqueous drug solution. pH of the system is increased to 7.0-7.2 with 1M disodium phosphate followed by heating at 60°C for 10 minutes leads to formation of drug loaded niosomal dispersion [24] (Figure 8).

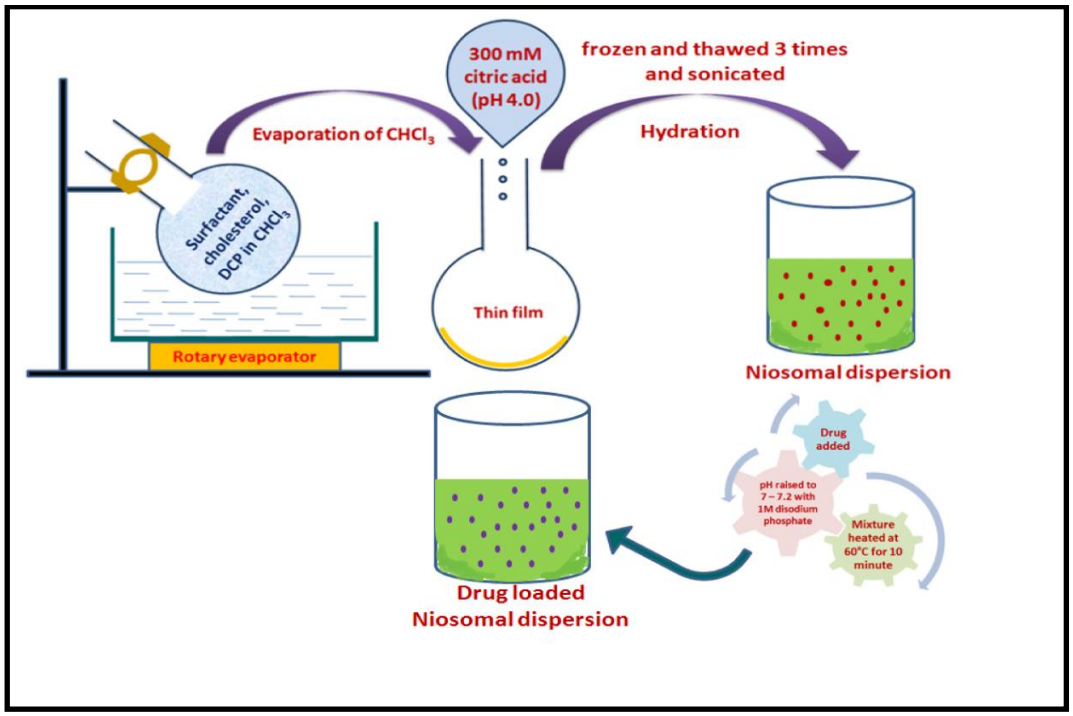


FIGURE 8 : REMOTE LOADING TECHNIQUE

5.9. Micro fluidization method

One of the novel methods used to prepare Unilamellar vesicles with uniform size distribution is micro fluidization. It is based upon the principal of engulfing of two fluids allowing them to merge with each other at drastic celerity in a reaction container. A microfludizer pumps the

fluid at extreme pressure (10,000 psi). Further, it is pushed with pressure through narrow canal, in order to mix two streams of fluid which results in successive transfer of energy. Lipids can be incorporated into streams of fluid which can be recycled via pump to get spherical vesicles. This method helps in producing small uniform sized niosomes which are reproducible[25].

5.10. Formation of niosomes from proniosomes

In this technique water soluble carriers (for e.g. sorbitol, maltodextrin, etc.) are first covered by surfactant. Cholesterol and surfactant is dissolved in organic solvent to prepare coating solution which is then sprinkled on fine particles of carrier followed by evaporation of the organic solvent using rotary evaporator leaves a lean covering of surfactant over the surface of carrier. The obtained surfactant coated dusty formulation is termed as 'Proniosome' which is agitated with aqueous solution of drug at a temperature higher than average transition phase temperature of the surfactant will result in formation of niosome[26] (Figure 9).

$T > Tm$

Where,
T = Temperature
Tm = mean phase transition temperature

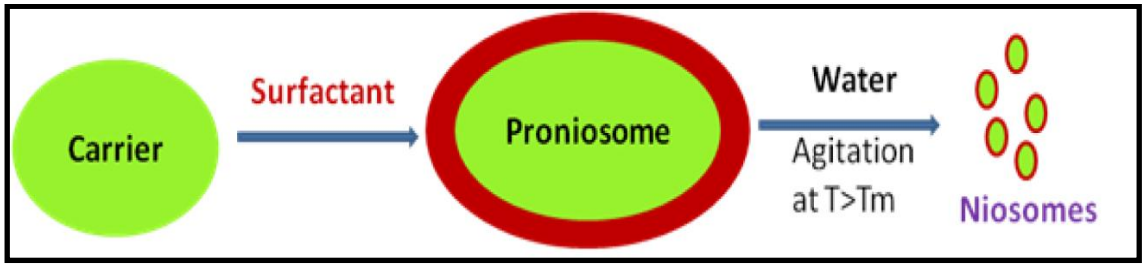


FIGURE 9 : FORMATION OF NIOSOMES FROM PRONIOSOMES

5.11. Emulsion method

In this method o/w emulsion is prepared. Organic phase is prepared by mixing surfactant and cholesterol in organic solvent whereas aqueous phase contains drug. By using these two phases oil in water emulsion is developed and evaporation of organic phase leads to formation of niosomes in the aqueous phase[13,27].

5.12. Lipid injection method

There are two ways to prepare niosomes using this technique. We can either prepare melted mixture of lipids and surfactant or melted lipid. In the former process mixture is injected in agitated warm aqueous solution of drug whereas in later process drug is solubilized in molten lipid and this mixture is then injected into agitated, heated aqueous solution of surfactant. This technique lacks the use of organic solvents[28].

5.13. Membrane contactor based technique

The membrane contactor experimental set-up composed of a positive displacement pump, a pressurized vessel, equipped with a manometer (M1), connected on one side to a nitrogen bottle and on the other side to the Shirasu porous glass (SPG) tubular membranes with two manometers (placed at the inlet and outlet of the module).

SPG membrane made up of phase-separated glass leaching in the Na_2–O–CaO–MgO–Al_2O_3–B_2O_3–SiO_2 system, which is synthesized from volcanic ash, called Shirasu, used as the key raw material. SPG membrane is of length 0.125m, inner diameter 1×10^{-2}m and thickness 1×10^{-3}m leading to an active membrane surface of $3.9 \times 10^{-3}m^2$.

In this technique the ethanol phase is kept in the pressurized vessel. The connecting valve attached to the nitrogen bottle which is kept in opened position and the nitrogen pressure set at a fixed level. The aqueous phase is pumped through the membrane module tangentially. Operation should be performed in an open loop configuration to avoid the recirculation of formed nano-vesicles in the experimental set-up, which might lead to their degradation. Hence, the flow rates of both aqueous and organic phases set to allow the circulation at the same time. Pressure of dispersed phase and flow rate of aqueous phase is set to 1.7 bar and 1.2 l/min respectively. Thus, as the water arrived to the membrane device inlet, the valves connecting the pressurized vessel to the filtrate side of the device get opened so that the organic phase permeated through the pores into the aqueous phase. Spontaneous nano-vesicle formation occurred as soon as the organic solution comes in contact with the aqueous phase. The experiment stopped when air bubbles started to appear in the tube connecting the pressurized vessel to the membrane module, indicating that the pressurized vessel get empty. Then, the suspension was stabilized for 15 min under magnetic stirring. Experiment should be conducted at 60 ± 2°C. Finally, the ethanol is removed by rotary evaporation under reduced pressure[29].

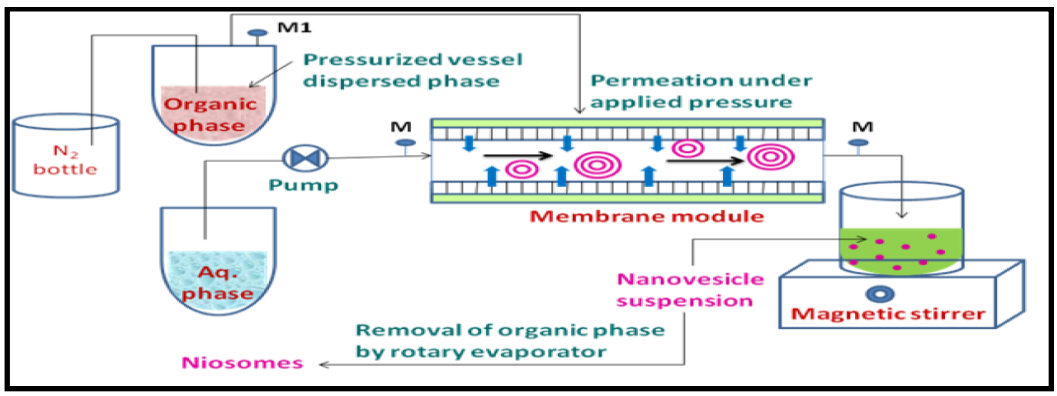


FIGURE 10 : REPRESENTATION OF MEMBRANE CONTACTOR TECHNIQUE

5.14. Heating method

Many vesicular systems involve use of organic solvents and detergents for solublilization of lipids. Traces of these organic solvents in final formulation may lead to cause toxicity problems and instability conditions[30]. The advantages of this 'Heating method' are that it is one pot synthesis technique, low toxicity problems as there is no use of detergent or organic solvent or any hazardous components and scalable methodology, for preparation of stable and safe niosomes[31]. In brief in this, mixture of cholesterol and non-ionic surfactant hydrated separately in phosphate buffer (PH 7.4). Under N_2 conditions and procedure should be carried out at ambient temperature. After lowering don temperature at 60°C, surfactant hydrated medium is added in cholesterol for 15 minutes with continuous stirring. Niosomal dispersion kept standing at room temperature for 30 minutes. It is then store in 4-5°C for further use[4].

5.15. Freeze and thaw method

Freeze and thaw technique used to prepare multilamellar vesicles. Freezing of niosomal suspension prepared by thin film hydration is done in liquid nitrogen for 1 min. and further the system is thawed in water bath at 60° C for another 1 min. result in formation of multilamellar vesicle.

5.16. Dehydration and Rehydration

In this technique, vesicles are prepared by thin film hydration or sonication. These primarily prepared vesicles mixed in an aqueous solutions containing encapsulating material and dried using liquid nitrogen followed by freeze-drying to prepare niosomal powder. During drying process vesicles get dehydrated and small vesicles fused to form multilamellar film in which encapsulating material effectively sandwiched between successive layers of film.

On rehydration of film with phosphate buffer pH – 7.4 at 60° C results in formation of large vesicles with encapsulation of significant proportion of encapsulating material. The optimum lipid to encapsulating material ratio is 1:2 to 1:3. In this method formation of niosomes depends on controlled drying and rehydration processes[13,32].

6. REMOVAL OF FREE DRUG[7]

Elimination of free drug remained in the system due to unentrapment into the vesicles can be done by following techniques-

6.1. Dialysis

In this method hydrous niosomal dispersion is dialyzed using dialysis tubing across suitable dissolution media at ambient temperature. The aliquots of dissolution media are withdrawn at suitable time intervals, centrifuged and analyzed for drug content using analytical techniques (U.V. spectroscopy, HPLC etc).

6.2. Gel Filtration

In this niosomal dispersion is eluted with suitable mobile phase using Sephadex-G-50 column and analyzed with efficient analytical techniques.

6.3. Centrifugation

The niosomal dispersion is centrifuged. Supernatant is removed and pellet obtained is washed with suitable media and resuspended to obtain niosomal dispersion free from unentrapped drug.

7. FACTORS AFFECTING VESICLES SIZE, ENTRAPMENT EFFICIENCY, AND RELEASE CHARACTERISTICS

7.1. Drug

Increase in vesicle size is may be due to encapsulation of drug in vesicles, by stearic interaction and mutual electrostatic repulsion of the surfactant bilayer. The HLB of surfactant affects entrapment efficiency of niosomes[19].

7.2. Type of surfactant and its concentration

- HLB of surfactants directly proportional to the average size of niosomes which is contributed to increase in hydrophobicity of surfactants molecule the surface free energy reduces[11].
- The type of lipid or surfactant used and reaction temperature governs the structural features of niosomes. If the skeletal of surfactant bilayer is unorganized then it will be in liquid state and if hydrophobic tails of surfactant present in a well ordered structure it will be in the gel state.
- Phase transition temperature of surfactants also affects drug entrapment efficiency of nisomes[33].

7.3. Cholesterol content and charge

- As the cholesterol concentration increases, it will results in increase in chain order of liquid state bilayer whereas reduces chain order of gel state bilayer. The gel state is converted to a liquid ordered state at a large concentration of cholesterol. Increase in cholesterol content increases rigidity of bilayer which may cause decrease in the rate of drug release.
- In multilamellar vesicle, the interlamellar distance between successive bilayer leads to increase due to presence of charge which results in higher entrapment[14].

7.4. Methods of Preparation

There are different techniques used to produce niosomes of different sizes, this has been earlier reported by Khandare *et al*. Thin film hydration technique develops vesicles with smaller diameter (0.35-13nm) whereas ether injection method (50-1000nm). Microfluidization technique produces small uniform vesicles with reproducibility. Reverse Phase Evaporation (REV) method also gives small sized niosomes[34].

7.5. Protection against osmotic stress

Incorporation of hypertonic solution in niosomal dispersion results in reduction in diameter of vesicle. It shows initial slow release due to inhibition of eluting fluid from vesicles because of light inflammation of vesicles. Later faster drug release obtained which may be due to structural detachment of vesicles under osmotic stress[35].

8. CHARACTERIZATION TECHNIQUES FOR NIOSOMES

TABLE 3 : TECHNIQUES USED TO EVALUATE NIOSOME

Sr. No.	Parameter	Methods of characterization
1.	Particle size	Laser light scattering method, Transmission electron microscopy,
2.	Bilayer formation	Light polarization microscopy used for analyzing X-cross preparation.
3.	Acerbity of membrane	Estimated using flexibility of fluorescence probe with respect to temperature conditions.
4.	Number of lamellae	X-ray scattering, NMR spectroscopy and electron microscopy.
5.	Drug content	Niosomes equivalent to 40mg of drug is taken into a standard volumetric flask. Then they are lyses with suitable organic solvent by shaking. Then dilutions can be made for appropriate analyzing the resultant by suitable method.
6.	Entrapment efficiency	Free drug is removed by centrifugation and entrapped drug in niosomes is estimated by dispersing vesicles in suitable solvent using suitable analytical technique. Entrapment efficiency (EE) = (Amount entrapped/ total amount) x100.
7.	*In vitro* dissolution study	Franz diffusion cell method, Dialysis bag method, Reverse dialysis technique.

9. THERAPEUTIC APPLICATIONS OF NIOSOMES

9.1. Gene Delivery

Niosomes are reported as promising nano-carriers for gene delivery. Recent reports concluded that cationic charged niosmes was effectively used for gene delivery to retina. In this after ocular administration, the genetic expression of EGFP was estimated in different cellular portions of the retina depending on different administration route. It is therefore concluded as effective nano-vesicular system in order to treat inherited ocular disorders. Similarly polysorbate non-ionic surfactant based niosomes vesicles are also reported to have promising nano-carriers for gene delivery[36,37].

9.2. Antineoplastic Treatment

Most of antineoplastic drugs suffered with severe side effects associated with them. Niosome vesicular system can be beneficial in order to decrease in side effects by altering mechanism of action, prolongation of circulation and half time of drug. The niosome loaded doxorubicin and methotrexate reported more beneficial in decreasing rate of proliferation of tumor with increased plasma drug concentration and slow rate of elimination as compared to their unloaded drugs[38]. Niosome loaded vincristine sulphate reported as most beneficial and promising nano-carriers when it was evaluated in tumor bearing mice. The lesser toxicity and enhancement of antitumor activity was observed which indicated noisome is an ideal nano-vesicles for anticancer therapy[39].

9.3. Drug Targeting

Niosomes possess beneficial ability of targeting site of action. Targeting of drugs to reticulo-endothelial system (RES) is successfully done using niosomes. The RES holds up niosome vesicles and this uptake of niosomes is influenced by opsonins (circulating serum factors). Opsonins render the niosome for clearance. This process of localization of active pharmaceutical ingredient can be useful in the treatment of cancer cells, different parasitic infections and can also be applicable to target particular organ other than RES[40].

9.4. Leishmaniasis treatment

Leishmaniasis is a disease caused by ‘Leishmania’ genus which is protozoan parasites which invades itself into visceral organs such as liver, spleen and bone marrow hence, termed as visceral leishmaniasis. It is second largest killer diseases which responsible to cause 200,000 to 400,000 infections each year worldwide. Due to parasite migration into visceral organ, it remains untreated and result in larger mortality[41].

The most commonly prescribed drug for treatment of Leishmaniasis is antimonial which is a derivative of antimony, when used in higher doses, it results into liver, kidney and cardio toxicity problems. The niosome nanocarrier's use in treatment of Leishmaniasis is shown reduction in side effects and greater efficacy even when used at higher concentration[34]

9.5. Peptide delivery

The peptide loaded niosomes is reported as new approach in order to overcome limitations of peptides by peroral route of administration such as enzymatic degradations[42].

The charge dependent niosome loaded peptides such as bacitracin (BCT), insulin, bovine serum albumin (BSA) suggested that niosome vesicle can able to entrap varieties of peptide molecule with different charges with higher entrapment efficiency[43]**.**

9.6. Studying Immune Response

In order to study the immune response produced by antigens, niosomes can be used. Earlier it was reported that delivery of antigens via niosomes gives enhanced immunological activity, stability, specificity and reduced harmful adverse effects[44].

9.7. Nanocarieer for Hemoglobin delivery

Niosomes loaded hemoglobin is one of the novel application of niosomal vesicular systems. The spectroscopic investigation suggested that niosomal dispersions show a visible spectrum which was super immense with the forms that are free of hemoglobin. The physicochemical properties and oxyphoric studies indicated that these negatively charged vesicular systems was shown oxygen permeability and physical stability. Thus it could be excellent carrier in treatment of anemia suffered patient[45,46].

9.8. Cosmetic delivery

Non-ionic based niosomal spherules are more advantageous in cosmetics treatment. These are beneficial in skin care treatment, ageing treatments as well as topical administration of varieties of drugs results into enhancement of skin drug delivery[47].

The discovery and proper delivery of active ingredients which are playing an important role in solving skin and hair problems is a primary step in cosmetic formulation development. The deterioration of these active ingredients is a big problem which has been solved by synthesizing niosomal vesicle. In the 1970s, L'Oreal's researchers proved that niosomes to be an ideal vehicle for transporting active ingredients such as retinol or vitamin E (anti-free radicals). The first niosome cream was introduced by Lancôme, 1986 (marketed by loreal company)**.**

9.9. Niosomes for transdermal application

Drug loaded niosomes for transdermal application result in increase skin penetration rate. Terbinafine Hydrochloride loaded niosomes for Transdermal administration indicated that formulating niosome loaded transdermal gel result into better effect due to its increased skin penetration[48,49] and Kumar et al., 2013[50] investigated investigated potential of niosome as a transdermal drug delivery carrier for Miconazole and Econazole. Topically applied niosomes loaded drugs result into increase in residence time of drug in the stratum corneum and epidermis as well as reduces the systemic absorption of the drug[49,50].

9.10. Vaccine delivery

Niosomes are reported as novel nano-carriers for peroral vaccine delivery system[51]. Vyas group reported topical delivery of deoxyribonucleic acid using niosomal delivery system for purpose of hepatitis B immunization.DNA encoding hepatitis B surface antigen (HBsAg) was loaded into niosomes with entrapment of 45.4%.In BALB/c mice, when administered topically, it showed comparable serum anti HBsAg and cytokine as compared to liposomes. Vaccine delivery using noisome showed advantages of low cost and higher stability[52].

There are number of drugs, administered by different routes by preparing niosomes which are enlisted in Table 4.

TABLE 4 : LIST OF NIOSOME FORMULATION

Way of incorporation into the body	Names of drugs
Intravenous	Doxorubicin, Methotrexate, Sodium Stibogluconate, Iopromide, Vincristine, Diclofenac Sodium, Flurbiprofen, Centchroman, Indomethacin, Colchicine, Rifampicin, Tretinoin, Transferrin and Glucose ligands, Zidovudine, Insulin, Cisplatin, Amarogentin, Daunorubicin, Amphotericin B, 5-Fluorouracil, Camptothecin, Morin hydrate, Adriamycin, Hydroxycamptothecin, Cytarabine Hydrochloride.
Intramuscular	Anti-HbsAg, Bovine serum albumin, 5,6-Carboxyfluorescein, Luteinizing hormone releasing hormone.
Peroral	Insulin, DNA vaccines, Peptides, Ergot alkaloids, Proteins, Norfloxacin, Ciprofloxacin, paclitaxel, Valsartan, Hydroxychloroquine, Antioxidants (gallic acid, ascorbic acid).
Transdermal	Lurbiprofen, Enoxacin, Piroxicam, Estradiol, Ketorolac, Levonorgestrol, Dithranol, Nimesulide, Ketoconazole, Minoxidil, Vinpocetine, Tenoxicam, ellagic acid, Gallidermin.
Ocular route	Timolol Maleate, Cyclopentolate, Naltrexone, pCMSEGFP.
Nasal route	Sumatriptan, Influenza Viral Vaccine.
Inhalation	Trans-retinoic acids.

10. CONCLUSION

Niosome based novel drug delivery system represents as promising nano-carriers with immense potential for wider applications of drug delivery, cosmetic development, peptide and vaccine delivery etc. The present review includes various preparation techniques, characterization, formulation aspects and applications of niosomes. It overall results into formation of ideal nano-vesicular system as compared to liposome in aspects of stability and cost for effective treatment of various diseases.

REFERENCES

1. Giram P. S., More S. R., and Parwe S. P., "Formulation Development with Box-behnken design Study of Ondansetron HCl Ethosome for chemotherapy induced nausea vomiting", World J Pharm Sci., 2015; Vol. 3(2): 288-298.
2. Chiranjeevi G., Muthukumaran M., and Krishnamoorthy B., "A Review on Potency of Vesicular Systems in Targeting Drug Delivery", RJPBCS, 2013; Vol. 4(2): 156.
3. Bansal S., Kashyap P. C., Aggarwal G., and Harikumar S. L., "A comparative review on vesicular drug delivery system and stability issues", ijrpc, 2012; Vol. 2(3): 2231.
4. Saeid M., Afra H., "Nano-niosomes as nanoscale drug delivery systems: An illustrated review", Journal of Controlled Release, 2014; 185: 22–36.
5. Makeshwar K. B., Wasankar S. R., "Niosome : a novel DDS", Asian J.pharm. res., 2013; Vol. 3(1): 16-20.
6. Kumar A., Pal J. L., Jaiswal A., Singh V., "Review on niosome as novel drug delivery system", International Research Journal of Pharmacy, 2011; Vol. 2(5): 61-65.
7. Chandu V. P., Arunachalam A., Jeganath S., Yamini K., Tharangini K., Chaitanya G., "Niosomes: A Novel Drug Delivery System", International Journal of Novel Trends in Pharmaceutical Sciences, 2012; Vol. 2(1): 25-31.
8. Gandhi M., Paralkar S., Sonule M., Dabhade D., Pagar S., "Niosomes: Novel Drug Delivery System" Int. J. Pure App. Biosci., 2014; Vol. 2(2): 267-274.
9. Tarekegn A., Joseph N. M., Palani S., Zacharia A., Ayenew Z., "Niosomes in targeted drug delivery: some recent advances", IJPSR, 2010; (9): 1-8.
10. Stafford S., Ballie A. J., Florence A. T., "Drug effect on the size of chemically defined nonionic surfactant vesicles", J Pharm Pharmacol, 1988; (26): 40.
11. Agarwal S., Bakshi V., Villa P., Raghuram A. P., Pandey S., Udupa N., "Effect of cholesterol content and surfactant HLB on vesicle properties of niosomes", IJPS, 2004; Vol. 66(1): 121-123.
12. Biswal S., Murthy P. N., Sahu J., Sahoo P., Amir F., "Vesicles of Non-ionic Surfactants (Niosomes) and Drug Delivery Potential", International Journal of Pharmaceutical Sciences and Nanotechnology, 2008; Vol. 1(1): 1-8.
13. Uchegbu F. I., Vyas P. S., "Non-ionic surfactant based vesicles (niosomes) in drug delivery", Int J Pharm, 1998; 172: 33-70.
14. Lohumi A., Rawat S., Sarkar S., Sipai A. B., Yadav M. V., "A novel drug delivery system: niosomes review", Journal of Drug Delivery & Therapeutics, 2012; Vol. 2(5): 129-135.
15. Sundaresan P., Sravanthi C., Gowtham T., "Evaluation of aceclofenac niosomes prepared by various techniques", Int. J. Pharm. Sci. Rev. Res., 2012; Vol. 16(1): 75-78.
16. Rangasamy M., Ayyasamy B., Senthilkumar R., Gummadevelly S., Shaik S., "Formulation and *in-vitro* evaluation of niosome encapsulated acyclovir", Journal of Pharmacy Research, 2008; Vol. 1(2): 163-166.
17. Alcantar N., Williams E. C., Toomey R., "Niosome-hydrogel drug delivery system", US Patent 20100068264, 2010.
18. Herre T., Steenbergen M. J. V., Johan C. H. B., Daan J. A. C., "A Novel Technique for the One-Step Preparation of Liposomes and Nonionic Surfactant Vesicles without the Use of Organic Solvents.

Liposorne Formation in a Continuous Gas Stream: The 'Bubble' Method", Journal of pharmaceutical Sciences, 1994; Vol. 83(3): 276-280.

19. Raja N. R. A., Chandrashekhar G., Pillai G. K., Udupa N., "Antiinflammatory activity of Niosome encapsulated diclofenac sodium with Tween -85 in Arthitic rats", Ind J Pharmacol, 1994; (26): 46-48.
20. Baillie A. J., Coombs G. H., Dolan T. F., "Non-Ionic Surfactant Vesicles, Niosomes as Delivery System for the Anti-Leishmanial Drug Sodium Stribogluconate", J Pharm Pharmacol, 1986; 38: 502-505.
21. Zerrin, S. B., Yuksel, N., "Investigation of Formulation Variables and Excipient Interaction on the Production of Niosomes", AAPS PharmSciTech, 2012; Vol. 13(3): 826–835.
22. Kumar Y. P., Kumar K.V., Shekar R. R., Ravi M., Kishore V. S., "Formulation and Evaluation of Econazole Niosomes", Sch. Acad. J. Pharm., 2013; Vol. 2(4): 315-318.
23. Junyaprasert V. B., Teeranachaideekul V., Supaperm T., "Effect of Charged and Non-ionic Membrane Additives on Physicochemical Properties and Stability of Niosomes", AAPS Pharm. Sci. Tech., 2008; Vol. 9(3): 851-859.
24. Mayer L. D., Bally M. B., Hope M. J., Cullis P. R., "Uptake of antineoplastic agents into large unilamellar vesicles in response to a membrane potential", Biochem Biophys Acta, 1985; 816: 294-302.
25. Cook E. J., Lagace A. P., "Apparatus for forming emulsions", US Patent. 4254553, 1985.
26. Akhilesh D., Hazel G., Kamath J. V., "Proniosomes – A Propitious Provesicular Drug Carrier", International Journal of Pharmacy and Pharmaceutical Science Research, 2011; Vol. 1(3): 98-103.
27. Hao, Y., Zhao, F., Li, N., Yang, Y., Li, K., "Studies on a high encapsulation of colchicines by a noisome system", Int J Pharm, 2002; (244): 73-80.
28. Kazi M. K., Mandal A. S., Biswas N., Guha A., Chatterjee S., Behera M., "Niosome: A future of targeted drug delivery systems", J Adv Pharm Tech Res, 2011; (62): 122.
29. Pham T. T., Jaafar-Maalej C., Charcosset C., Fessi H., 2012. "Liposome and niosome preparation using a membrane contactor for scale-up. Colloids and Surfaces B", Biointerfaces, 2012; 94: 15– 21.
30. Mozafari M. R., Reed C. J., Rostron C., "Cytotoxicity evaluation of anionic nanoliposomes and nanolipoplexes prepared by the heating method without employing volatile solvents and detergents", Pharmazie, 2007; 62: 205–209.
31. Marianecci C., Marzio L. D., Rinaldi F., Celia C., Paolino D., Alhaique F., Esposito S., Carafa M., "Niosomes from 80s to present: The state of the art", Advances in Colloid and Interface Science, 2014; 205: 187–206.
32. Hope M. J., "Generation of multilamellar and unilamellar phospholipid vesicles", Chem. Phys. Lipids, 1986; 40: 89–107.
33. Khandare J. N., Madhavi G., Tamhankar B. M., "Niosomes Novel Drug Delivery System", Eastern Pharmacist, 1994; (37): 61-64.
34. Tyagi S., Patel C. J., Parashar T., Soniya, "Novel Drug Delivery System (NDDS): Niosomes", Journal of Biomedical and Pharmaceutical Research, 2012; 1(3): 14-21.
35. Malhotra M., Jain N. K., "Niosomes as Drug Carriers", Indian Drugs, 1994; (31): 81-86.
36. Puras G., Mashala M., Zárate J., Agirrea M., Ojedaa E., Grijalvob S., Eritjab R., Diaz-Tahocesb A., Martínez Navarreteb G., Avilés-Triguerose M., Fernándezb E., Pedraz J. L., "A novel cationic niosome formulation for gene delivery to the retina", Release Volume, 2014; 27–36.
37. Huang Y., Rao Y., Chen J., Yang V. C., Liang W., "Polysorbate cationic synthetic vesicle for gene delivery", WILEY PERIODICALS, INC. 2011; 513-519.
38. Cummings J., Staurt J. F., Calman K. C., "Determination of adriamycin, adriamycinol and their 7-deoxyaglycones in human serum by high-performance liquid chromatography", J. Chromatogr, 1984; 311: 125-133.
39. Parthasarathi G., Udupa N., Umadevi P., Pillai G. K., 1994. "Niosome encapsulated of vincristine sulfate: improved anticancer activity with reduced toxicity in mice", J Drug Target, 1994; Vol. 2(2): 173-82.
40. Kazi K. M., Mandal A. S., Biswas N., Guha A., Chatterjee S., Behera M., Kuotsu K., "Niosome: A future of targeted drug delivery systems", J Adv Pharm Technol Res., 2010; Vol. 1(4): 374–380.
41. Desjeux P., "The increase of risk factors for leishmaniasis worldwide", Transactions of the Royal Society of Tropical Medicine and Hygiene, 2001; Vol. 95(3): 239–43.

42. Manosroi A., Khanrin P., Werner R. G., Götz F., Manosroi W., Manosroi J., 2010. "Entrapment enhancement of peptide drugs in niosomes", J Microencapsul, 2010; Vol. 27(3): 272-80.
43. Lehr C. M., Kok W., Junginger H. E., Verhoef J. C., Bouwstra J. A., "Niosomes for oral delivery of peptide drugs", Release Volume, 1992; 145–153.
44. Maheswari et al, "Non-ionic surfactant vesicles mediated transuctaneous immunization against hepatitis B", International Immunopharamcology, 2011; Vol. 10(10): 1516-1522.
45. Moser P., Marchand-Arvier M., Labrude P., Handjani-Vila R. M., Vigneron C., "Hemoglobin niosomes. I. Preparation, functional and physico-chemical properties, and stability", Pharm Acta Helv, 1989; Vol. 64(7): 192-202.
46. Nancy, France, "Hemoglobin niosomes. II. In vitro interactions of plasma proteins and phagocytes", Pharmaceutica Acta Helvetiae, 1990; Vol. 65(3): 82-92.
47. Handjani R. M., Vanlerberghe A., Zabotto G., Griat A., Jacqueline, "Cosmetic and pharmaceutical compositions containing niosomes and a water-soluble polyamide, and a process for preparing these compositions", United States Patent 4830857, 1989.
48. Sathali A. H., Rajalakshmi G., "Evaluation of Transdermal Targeted Niosomal Drug Delivery of Terbinafine Hydrochloride", International Journal of PharmTech Research, 2010; Vol. 2(3): 2081-2089.
49. Firthouse P. U. M., Halith S. M., Wahab S. U., Sirajudeen M., Mohideen S. K., "Formulation and Evaluation of Miconazole Niosomes", International Journal of PharmTech Research, 2011; Vol. 3(2): 1019-1022.
50. Kumar P. A., Singh R., Karthick K., Arulkumaran K.S.G., "Formulation and evaluation of sustained released niosomes containing pregabalin", Int. J. of Pharm. & Life Sci., 2013; Vol. 4(7): 2770-2774.
51. Rentel C. O., Bouwstra J. A., Naisbett B., Junginger H. E., 1999. "Niosomes as a novel peroral vaccine delivery system", International journal of pharmaceutics, 1999; Vol. 186(2): 161-7.
52. Vyas S. P., Singh R. P., Jain S., Mishra V., Mahor S., Singh P., Gupta P. N., Rawat A., Dubey P., "Non-ionic surfactant based vesicles (niosomes) for non-invasive topical genetic immunization against hepatitis B", International Journal of Pharmaceutics, 2005; Vol. 296(1-2): 80-86.
53. Abdelkader H., Ismail S., Kamal A., Alany R. G., "Design and evaluation of controlled release niosomes and discomes for naltrexone hydrochloride ocular delivery", 2011; Vol.100(5): 1833–1846.
54. Ali, N., Harikumar, S. L., Kaur, A., 2012. Niosomes: an excellent tool for drug delivery. IJRPC 2 (2), 479-487.
55. Chauhan, S., Luorence, M. J., 1989. The preparation of polyoxyethylene containing non-ionic surfactant vesicles. J Pharm Pharmacol (41), 6.
56. Kazi, M. K., Mandal, A. S., Biswas, N., Guha, A., Chatterjee, S., Behera, M., 2011. Niosome: A future of targeted drug delivery systems. J Adv Pharm Tech Res (62), 122.
57. Kumar, A., Badde, S., Kamble, R., Pokharkar, V. B., 2010. Development and Characterization of Liposomal Drug Delivery System for Nimesulide. Int J Pharm Pharm Sci. 2(4), 87-89.