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RECENT ADVANCES IN NIOSOMAL DRUG DELIVERY - A REVIEW

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ABSTRACT: Treatment of infectious diseases and immunisation has undergone a revolutionary shift in recent years. Not only a large number of disease-specific biological have been developed, but also emphasis has been made to effectively deliver these biological. Nonionic surfactant vesicles (niosomes) represent an emerging class of novel vesicular systems have drawn a lot of attention in the area of modern drug delivery systems. Thus these areas need further exploration and research so as to bring out commercially available niosomal preparation. This article focuses on the recent advances in niosomal drug delivery, potential advantages over other delivery systems, formulation methods, methods of characterization and the current research in the field of niosomes.

KEYWORDS: Niosomes, Modern Drug Delivery Systems, Nonionic surfactant vesicles.

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1.INTRODUCTION

Niosomes are a novel drug delivery system (NDDS) has an object to deliver the drug at a rate directed by the needs of the body that is in a controlled manner during the period of treatment of a disease to enhance bioavailability, and reach the active ingredient to the target site [1]. In the niosomal drug delivery system medication is encapsulated in a vesicle. The vesicle is formed on admixture of non-ionic surfactant of the alkyl or dialkyl poly glycerol ether class of a bilayer (hence the name niosomes) and cholesterol with subsequent hydration in aqueous media. The niosomes are very small, and microscopic in size. Their size lies in the nanometric scale [2,3].One of the reasons for preparing niosomes is assumed higher chemical stability of the surfactants than that of

phospholipids, which are used in the preparation of liposomes. Due to the presence of ester bond, phospholipids are easily hydrolyzed [4]. The bilayer structure of niosomes being amphiphillic in nature could be used to deliver hydrophilic drugs in its aqueous core and lipophilic drugs in the bilayer which is made up of surfactants. Various additives in niosomes included nonionic surfactant as film forming agent, cholesterol as stabilizing and rigidizing agent for the bilayer and various charge inducers which was developing a charge on the surface of niosomes and stabilized the prepared formulation by the resulting repulsive forces [5]. Niosomal drug delivery has been studied using various methods of administration including intramuscular, intravenous, peroral and transdermal. In addition, as drug delivery vesicles, niosomes have been shown to enhance absorption of some drugs across cell membranes, to localize in targeted organs and tissues and to elude the reticuloendothelial system [6].

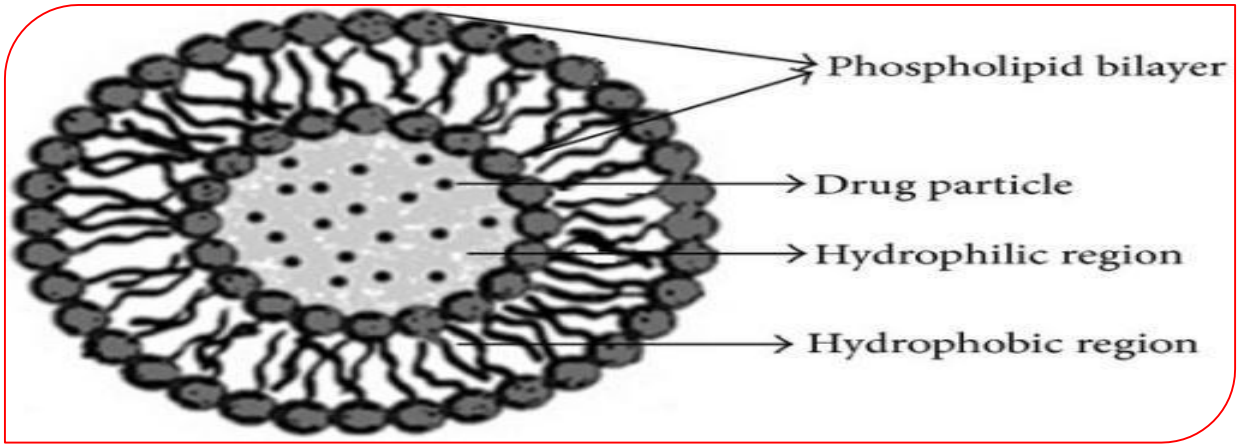


Figure 1: structure of bilayer niosome[1]

2.Salient Features Of Niosomes [7,8]

1. Niosomes are osmotically active and improve the stability of entrapped drug.
2. Niosomes surfactants are biodegradable, biocompatible and non-immunogenic.
3. Niosomes possess infrastructure consisting of hydrophilic and hydrophobic mostly together and so accommodate the drug molecules with a wide range of solubility.
4. The bilayers of the niosomes protect the enclosed active pharmaceutical ingredient from the heterogeneous factors present both inside and outside the body. So niosomes can be used for the delivery of labile and sensitive drugs.
5. Niosomes exhibit flexibility in their structural characteristics and can be designed according to the desired situation.
6. Better availability at the particular site, just by protecting the drug from biological environment.
7. The formulation is in the form of aqueous vehicle based suspension having greater patient compliance when compared to oily dosage forms.Niosomal dispersion being aqueous can be emulsified in a non-aqueous phase to regulate the drug release rate and to administer the vesicles in non-aqueous phase.

3. Advantages Of Niosomes [8, 9, 10, 11]

1. The vesicle suspension being water-based vehicle offers high patient compliance when compared to oily dosage forms.
2. Drug molecules of wide range of solubilities can be accommodated in the niosomes provided by the infrastructure consisting of hydrophilic, lipophilic and amphiphilic moieties.
3. Vesicle characteristics can be controlled by altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration.
4. They can release the drug in sustained/controlled manner.
5. Storage and handling of surfactants oblige no special conditions like low temperature and inert atmosphere.
6. They can act as a depot formulation, thus allowing the drug release in a controlled manner.
7. They enhance the oral bioavailability of poorly soluble drugs.
8. They possess stable structure even in emulsion form.
9. They are economical for large scale production.
10. They can protect the drug from enzyme metabolism.
11. They can enhance the permeation of drugs through skin.
12. Therapeutic concert of the drug molecules can be improved by tardy clearance from circulation.
13. They can protect the active moiety from biological circulation.
14. Niosomes can be made to reach the site of action by oral, topical as well as parenteral routes.

4. Disadvantages Of Niosomes [8, 10, 11]

1. Physical instability
2. Aggregation
3. Fusion
4. Leaking of entrapped drug
5. Hydrolysis of encapsulated drugs which limiting the shelf-life of the dispersion.

5. Types Of Niosomes [1, 8, 9]

The niosomes are classified as function of the number of bilayer (e.g. SUV, MUV) or as a function of size (e.g. LUV, SUV) or as a function of the method of preparation (e.g. REV, DRV). There are mainly three types of niosomes.

The various types of niosomes are described below: i) Multi lamellar vesicles (MLV), ii) Large unilamellar vesicles (LUV), iii) Small unilamellar vesicles (SUV).

5.1 Multi lamellar Vesicles (MLV) [8, 9]

It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of such vesicle is 0.5 to 10 μm diameter. MLV are most widely used niosomes. Which are simple to make and mechanically stable upon storage for long periods. These vesicles are mostly suited as drug carrier for lipophilic compounds.

5.2 Large Unilamellar Vesicles (LUV)

Such types of Niosomes are high aqueous to lipid compartment ratio, so that large volume of Bio-active materials can be entrapped with a very economical use of membrane lipids. The size of large unilamellar vesicles are greater than 0.10μm [8,9,12].

5.3 Small Unilamellar Vesicles (SUV)

Such types of niosomes are mostly prepared from multilamellar vesicles by sonication method, French pressextrusion method or Homogenization method. The size ofsmall unilamellar vesicles are 0.025-0.05 μm diameterwhich are thermodynamically unstable and are susceptibleto aggregation and fusion. Their entrapped volume is smalland percentage entrapment of an aqueous solute iscorrespondingly low [9,13].

6. Some Other Types OfNiosomes

6.1 Bola surfactant containing niosomes

Bola surfactant containing niosomes are thesurfactants that are made of omegahexadecylbis-(1-aza-18 crown-6) (bolasurfactant): span- 80/cholesterol in 2:3:1molar ratio [14].

6.2Aspasomes: Combination of acorbylpalmitate, cholesteroland highly charged lipid diacetyl phosphateleads to the formation of vesicles calledaspasomes. Aspasomes are first hydrated withwater/aqueous solution and then sonicated toobtain the niosomes. Aspasomes can be usedto increase the transdermal permeation ofdrugs. Aspasomes have also been used todecrease disorder caused by reactive oxygenspecies as it has inherent antioxidant property [15].

7. Mechanisms Of Niosomes Penetration Through Skin Delivery [15, 16]

Niosomes are the challenging tool for dermatological disorders. Niosomes have also been used in cosmetic and for delivery of peptide drugs. Topically applied niosomes can increase the residence time of the drug in the SC and epidermis while reducing the systemic absorption of drugs. They are thought to improve the horny layer properties both by reducing transepidermal water loss and by improving smoothness, reconstituting lost skin lipid. Thus niosomes act as penetration enhancers.

1. Adsorption and fusion of niosomes onto the surface of the skin leading to highthermodynamic activity gradient at the interface, which is the driving force forpermeation of lipophilic drugs.
2. The effect of vesicles as penetration enhancers reduces barrier properties ofstratum corneum. As surfactants are the components of niosomes, theyincrease transdermal permeation and percutaneous absorption by decreasing surface tension, improving wetting of skin and enhance distribution of drugs.
3. The lipid bilayers of niosomes act as a rate limiting barrier for drugs.

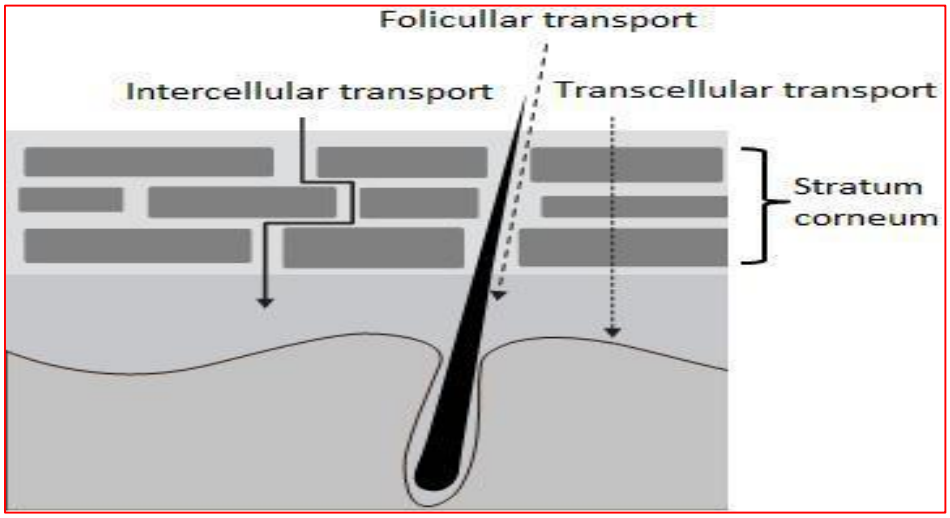


Figure 2: Skin transport pathways.[15, 16]

8. Structural Components Of Niosomes

The main components of niosomes are nonionic surfactants, hydration medium and lipids such as cholesterol. The list of materials used in the preparation of niosomes has been shown in Table 1.

8.1 Nonionic surfactants: Nonionic surfactants are a class of surfactants, which have no charged groups in theirhydrophilic heads. They are more stable and biocompatible and less toxic compared to their anionic, amphoteric, or cationic counterparts. Therefore they are preferred for formation of stable niosomes for *in vitro* and *in vivo* applications. Nonionic surfactants are amphiphilic molecules that comprise two different regions: one of them is hydrophilic (water-soluble) and the other one is hydrophobic (organic soluble). Alkyl ethers, alkyl esters, alkyl amides, fatty acids are the main nonionic surfactant classes used for niosome production. The hydrophilic-lipophilic balance (HLB) and critical packing parameter (CPP) values play a critical role in the selection of surfactant molecules for niosome preparation [17].

8.2 Cholesterol: Steroids bring about changes in fluidity and permeabilityof the bilayer and are thus important components. Cholesterol awaxy steroid metabolite is usually added to the non-ionicsurfactants to provide rigidity and orientational order. It does notform the bilayer itself and can be incorporated in large molarratios. Cholesterol is an amphiphilic molecule; it orients its OHgroup towards aqueous phase and aliphatic chain towardssurfactant's hydrocarbon chain. Rigidization is provided byalternative positioning of rigid steroidal skeleton with surfactantmolecules in the bilayer by restricting the movement of carbons ofhydrocarbon. Cholesterol is also known to prevent leakage byabolishing gel to liquid phase transition [18].

8.3 Charged molecule: Charged molecules increase the stabilityof the vesicles by the addition of charged groups tothe bilayer of vesicles. They increase surface charge densityand thereby prevent vesicles aggregation. They actby preventing the fusion of vesicles due to repulsive forces of thesame charge and provide higher values of zeta potential. Dicetyl phosphateand phosphatidic acid are most used negatively chargedmolecules for niosome preparation and, similarly, stearylamineand stearyl

pyridiniumchloride are well-known positivelychargedmolecules used in niosomal preparations [19].Normally,the chargedmolecule is added inniosomal formulationin an amount of 2.5–5mol%.However increasing the amountof charged molecules can inhibit niosome formation [17].

Table 1: The materials used in niosome preparation [17]

Sl. No.	Nonionic surfactants	Examples
1.	**Alkyl ethers**	
	a. Alkyl glycerol ethers	Hexadecyldiglycerol ether (C16G2)
	b. Polyoxyethylene glycol alkyl ethers (Brij)	Brij 30, Brij 52, Brij 72, Brij 76, Brij 78
2.	**Alkyl esters**	
	a. Sorbitan fatty acid esters (Spans)	Span 20, Span 40, Span 60, Span 80, Span 65,Span 85.
	b. Polyoxyethylenesorbitan fatty acid esters (Tweens)	Tween 20, Tween 40, Tween 60, Tween 80,Tween 65, Tween 85
3.	**Alkyl amides**	
	a. Glycosides	C-Glycoside derivative surfactant
	b. Alkyl polyglucosides	Octyl-decylpolyglucoside (OrCG110), decylpolyglucoside (OrNS10)
4.	**Fatty alcohols or fatty acids**	
	a. Fatty alcohols	Stearyl alcohol, cetyl alcohol, myristyl alcohols
	b. Fatty acids	Stearic acid, palmitic acid, myristic acid
5.	**Block copolymer**	
	a. Pluronic	Pluronic L64, Pluronic 105
6.	**Lipidic components**	
	Cholesterol and l-α-Soya phosphatidyl choline	
7.	**Charged molecule**	
	a. Negative charge	Diacetyl phosphate, phosphatidic acid, lipoamino acid, dihexadecyl phosphate
	b. Positive charge	Stearylamine, stearylpyridinium chloride, cetylpyridinium chloride

9. Methods Of Preparation Of Niosomes[6]

Various methods are reported for the preparation of niosomes such as:

9.1. Ether injection method: The ether injection method is essentially based on slow injection of niosomal ingredients in ether through a 14-gaugeneedle at the rate of approximately 0.25 ml/min into apreheated aqueous phase maintained at 60°C. The probable reason behind the formation of larger unilamellar vesicles is that the slow vaporization of solvent results in an ether gradient extending towards the interface of aqueous non-aqueous interface. The former may be responsible for the formation of the bilayer structure. Depending upon the conditions used thediameter of the vesicle range from 50 to 1000 nm.The disadvantage of this method is that a small amount of ether is frequently present in the vesicles suspension and is difficult to remove [10, 20, 21, 22].

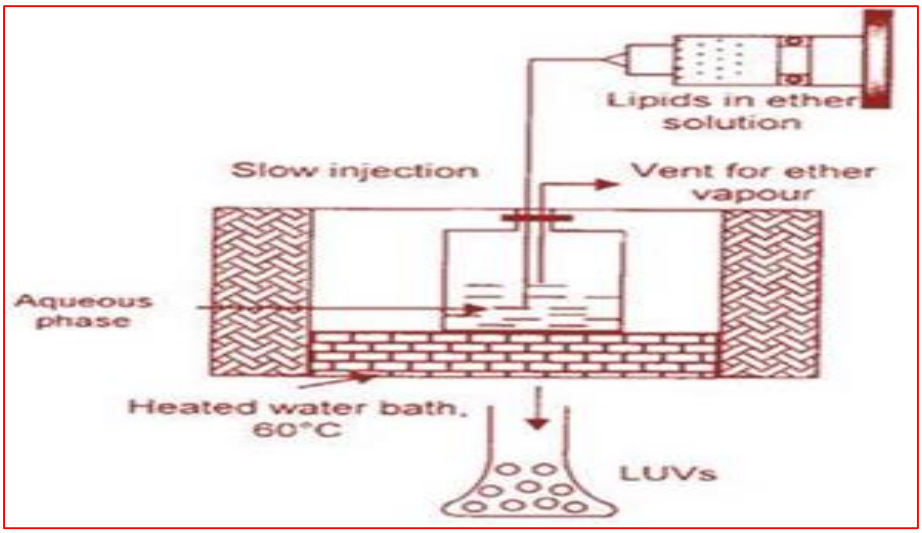


Figure 3: Ether injection method

9.2. Hand shaking method (Thin film hydration technique): The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes.[10, 20, 21, 22]It is noted that addition of the drug to the system depends on the nature of the drug, in which a hydrophilic drug can be added to the aqueous phase while a hydrophobic drug only can be dissolved inorganic solvent with other components [23].

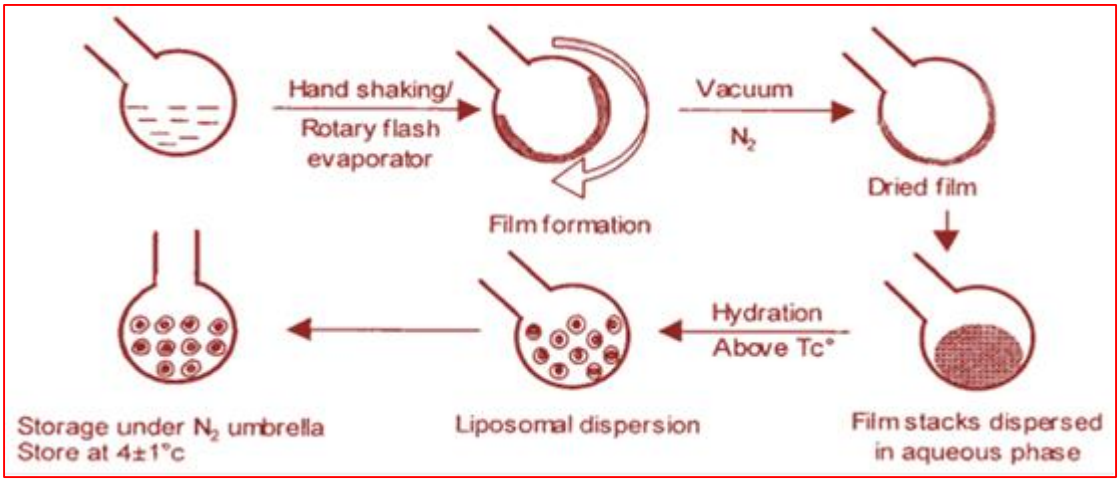


Figure 4: Thin film hydration tequnique

9.3 Sonication: In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes [10, 22]**.**

9.4 Reverse phase evaporation technique (REV): Cholesterol and surfactant (1:1) were dissolved in a mixture of ether and chloroform. Then an aqueous phase containing drug was added to this and the resulting two phases were sonicated at 4-5°C. The clear gel formed was further sonicated and after that the addition of a small amount of phosphate buffered saline (PBS) takes place. The organic phase was removed at 40°C under low pressure. The resulting viscous niosome suspension was then diluted with PBS and heated on a water bath at 60°C for 10 min to better yield of niosomes [5, 10].

9.5 Microfluidization: It is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a smaller size, greater uniformity and better reproducibility of niosomes formed [5, 22].

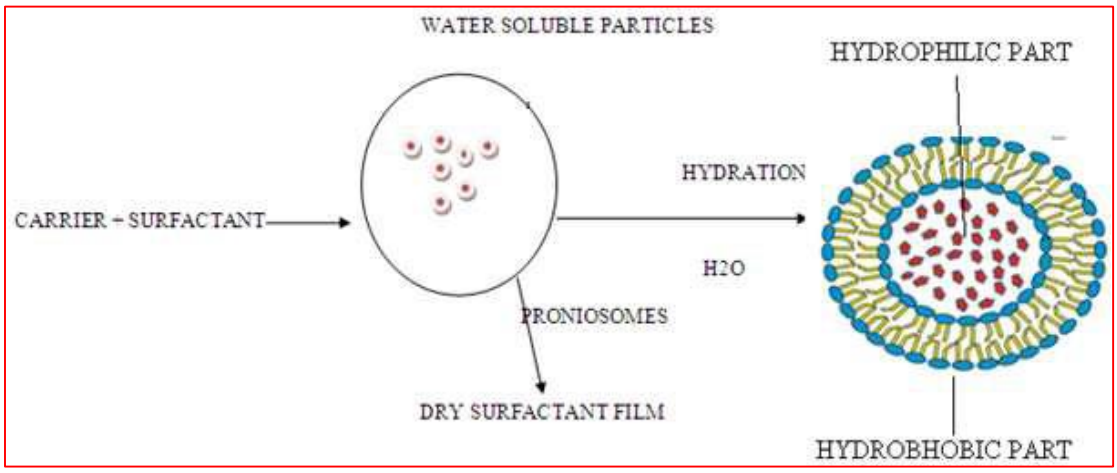
9.6 Multiple membrane extrusion method: Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug polycarbonate membranes, solution and the resultant suspension extruded through which are placed in series for up to 8 passages. Multiple membrane extrusion method is better for the controlling of niosome size [5, 22].

9.7 Trans membrane pH gradient (inside acidic) drug uptake process (remote loading): Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This

mixture is later heated at 60°C for 10 minutes to give niosomes [5, 10, 22].

9.8 Bubble method: In this method, surfactants, additives, and the buffer are added into a glass flask with three necks. Niosome components are dispersed at 70°C and the dispersion is mixed with homogenizer. After that, immediately the flask is placed in a water bath followed by the bubbling of nitrogen gas at 70°C. Nitrogen gas is passed through a sample of homogenized surfactants resulting in formation of large unilamellar vesicles [17,22].

9.9 Formation of niosomes from proniosomes: Proniosome technique includes the coating of a water-soluble carrier such as sorbitol and mannitol with surfactant. The coating process results in the formation of adry formulation. This preparation is termed "Proniosomes" which requires to be hydrated before being used. The niosomes are formed by the addition of the aqueous phase. This method helps in reducing physical stability problems such as the aggregation, leaking, and fusion problem and provides convenience in dosing, storage showing improved results compared to conventional niosomes [22].



10. Post-Preparation Processes[22, 23]

The main post-preparation processes in the manufacture of niosomes are downsizing and separation of un-entrapped material. After preparation, size reduction of niosomes is achieved using one of the methods given below:

a. Probe sonication results in the production of niosomes in the 100–140 nm size range.
b. Extrusion through filters of defined pore sizes.
c. Combination of sonication and filtration has also been used to obtain niosomes in the 200nm size range (e.g. doxorubicin niosomes).
d. Micro fluidization yields niosomes in nano range.
e. High-pressure homogenization also yields vesicles below 100nm in diameter.

As in most cases 100% of the bioactive agent cannot be encapsulated in the niosomal vesicles, the un-entrapped bioactive agent should be separated from the entrapped ones. This provides an advantage since this drug delivery system gives an initial burst to initiate therapy followed by a sustained maintenance dose.

11. Separation Of Un-Entrapped Drug

The removal of un-entrapped solute from the vesicles can be accomplished by various techniques, which include [10, 24]:

- Dialysis;
- Gel filtration (e.g. Sephadex G50);
- Centrifugation (e.g. 7000 rpm for 30 min for the niosomes prepared by hand shaking and ether injection methods);
- Ultracentrifugation (150000 rpm for 1.5 h).

11.1 Dialysis: The aqueous niosomal dispersion is dialyzed in dialysis tubing against suitable dissolution medium at room temperature. The samples are withdrawn from the medium at suitable time intervals, centrifuged and analyzed for drug content using suitable method (U.V. spectroscopy, HPLC etc.) [8, 10].

11.2 Gel filtration: The un-entrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and eluted with suitable mobile phase and analyzed with suitable analytical techniques [8, 10].

11.3 Centrifugation: The niosomal dispersion is centrifuged in water or saline. Niosomes get sediment down as pellet which is washed and resuspended to obtain a niosomal suspended free from un-entrapped drug. The supernatant containing the un-entrapped drug is separated [8, 25].

12. Factors Affecting Formulation OfNiosome

12.1 Drug: The physico-chemical properties ofencapsulated drug influence charge andrigidity of the niosome bilayer [26].The entrapment of drug inside the niosomes improves the vesicle size, probably by interaction of solute with surfactant head groups, enhancing the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size, the hydrophilic lipophilic balance of the drug affects degree of entrapment [27].

12.2 Type of surfactant:

12.2.1 Hydrophilic-Lipophilic Balance (HLB): HLB is a dimensionlessparameter, which is the indication of the solubility ofthe surfactantmolecule.TheHLB value describes the balancebetween the hydrophilic portions to the lipophilic portion ofthe nonionic surfactant. The HLB range is from 0 to 20 fornonionic surfactants.ThelowerHLB refers to more lipophilicsurfactant and the higher HLB to more hydrophilic surfactant.Surfactants with a HLB between 4 and 8 can be used for preparation of vesicle. Hydrophilic surfactants witha HLB value ranging from 14 to 17 are not suitable to form abilayer membrane due to their high aqueous solubility [17]. Howeverwith the addition of an optimumlevel of cholesterol,niosomes are indeed formed from polysorbate 80 (HLB value = 15) and tween 20 (HLB value = 16.7).Tween 20 forms stable niosome in the presence of equimolarcholesterol concentration. The interaction occurs betweenthe hydrophobic part of the amphiphile next to head groupand the 3-OH group of cholesterol at an equimolar ratioand this

interaction could explain the effect of cholesterol onthe formation and hydration behavior of Tween 20 niosomal membranes.Drug entrapment efficiency of the niosomes is alsoaffected by HLB value of surfactant. Shahiwala et al.have incorporated nimesulide into niosomes using lipid filmhydration technique by changing the HLB. They found thatas the HLB value of surfactant decreases from 8.6 to 1.7, entrapment efficiency decreases.

12.2.2 Critical Packing Parameter (CPP) [17]: During the niosomalpreparation, the geometry of the vesicle depends upon thecritical packing parameter. On the basis of the CPP of a surfactant,the shape of nanostructures formed by self-assemblyof amphiphilic molecules can be predicted. Critical packingparameter depends on the symmetry of the surfactant andcan be defined using following equation:

$$\boldsymbol{cpp = \frac{v}{lc \times ao}}$$

Where,

V= hydrophobic group volume,

lc= is the critical hydrophobic group length,

$a0$ = is the area of hydrophilic head group.

CPP≤0.5 micelles formation, CPP=(0.5-1.0) spherical vesicles formation, CPP≥1.0 inverted micelles form.

With increase in the HLB of surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6), the mean size of niosome enhances proportionally as surface free energy reduces with an increase in hydrophobicity of surfactant. The bilayers of the vesicles are either called liquid state or in gel state, depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol [24].In the gel state, alkyl chains are present in a well ordered structure, and in the liquid state, the structure of the bilayer is more disordered. The surfactants and lipids are characterized by the gel-liquid phase transition temperature (TC). TC of surfactants also affects entrapment efficiency, i.e. span 60 having higher TC provides better entrapment [13].

12.3 Membrane composition: The stable niosomes are prepared by the addition of different additives along with surfactants and drugs. Niosomes formed have a number of morphologies and their permeability and stability properties can be altered by manipulating membrane characteristics by different additives. The mean size of niosomes is influenced by membrane composition such as Polyhedral niosomes formed by C16G2: solulan C24 in ratio (91:9) having bigger size (8.0 ± 0.03mm) than spherical/tubular niosomes formed by C16G2: cholesterol: solulan C24 in ratio (49:49:2) (6.6±0.2mm). Addition of cholesterol molecule to niosomal system provides rigidity to the membrane and reduces the leakage of drug from noisome [26].

12.4 Methods of preparation: Jadon*et al*. compared griseofulvin niosomes prepared by ether injection method and thin film method and they found that the former method produced niosomes

with a smaller vesicle size but lower entrapment efficiency compared to those prepared by the latter. The higher entrapment efficiency of niosomes prepared by thin film method might be the result of partly uniform vesicle size and due to well-packed bimolecular film formation via this method.[28]Hand shaking method forms vesicles with greater diameter (0.35-13nm) as compared to the ether injection method (50-1000nm). Small sized niosomes can be produced by reverse phase evaporation (REV) method. Micro-fluidization method gives greater uniformity and small size vesicles. Parthasarthi et al prepared niosomes by Trans membrane p^H gradient (inside acidic) drug uptake process. Niosomes obtained by this method showed greater entrapment efficiency and better retention of drug [25].

12.5 Resistance to osmotic stress: The addition of a hypertonic salt solution to a suspension of niosomes brings reduction in diameter of niosomes, in hypotonic salt solution, there is initial slow release with slight swelling of vesicles probably due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress [25].

12.6 Temperature of hydration: Hydration temperature influences the shape and size of the niosome. For ideal condition it should be above the gel to liquid phase transition temperature of system. Temperature change of niosomal system affects assembly of surfactants into vesicles and also induces vesicle shape transformation [29].Scientists reported that a polyhedral vesicle formed by C16G2: solulan C24 (91:9) at 25°C which on heating transformed into spherical vesicle at 48°C, but on cooling from 55 ^{0}C, the vesicle produced a cluster of smaller spherical niosomes at 49°C before changing to the polyhedral structures at 35°C. In contrast vesicle formed by C16G2: cholesterol: solulanC24 (49:49:2) shows no shape transformation on heating or cooling. Along with the above mentioned factors, volume of hydration medium and time of hydration of niosomes are also critical factors. Improper selection of these factors may result in formation of fragile niosomes or creation of drug leakage problems [25].

13. Characterization Of Niosomes

13.1 FTIR: The FTIR study is carried put to find out whether any interactions are there between the drug and the excipients used in the formulation [1].

13.2 Vesicle diameter: Niosomes are spherical and so their diameter can be determined by using Light Microscopy, Freeze fracture electron microscopy and photon correlation microscopy. Freeze thawing is also applicable for such measurement [6, 9].

13.3 Vesicle Morphology: The niosomes were observed under a scanning electron microscopy (SEM) (JSM 6100 JEOL, Tokyo, Japan). They were mounted directly onto the SEM sample stub using double sided sticking tape and coated with gold film of thickness of 200 nm under reduced pressure of 0.001 mmHg. Photographs were taken at suitable magnification [16].

13.4 Vesicle charge: Vesicle charge can play important role in the behavior of niosomes *in vitro* and

in vivo. Charged niosomes are more stable against aggregation and fusion than uncharged vesicle. In order to obtain an estimate of the surface potential, the zeta potential of individual niosomes can be measured by micro electrophoresis. Another approach is the use of p^H-sensitive fluorophores. Dynamic light scattering have been used to measure the zeta potential used now a days [9].

13.5 Bilayer formation: Bilayer vesicle formation can be characterized by x-cross formation due to the assembly of non-ionic surfactants under light polarization microscopy [24].

13.6 Number of lamellae: Number of lamellae in vesicles is characterized by NMR spectroscopy, electron microscopy and small angle X-ray scattering [24].

13.7 Membrane rigidity and homogeneity: Membrane rigidity influences the bio distribution and bio degradation of niosomes. The bilayer rigidity of vesicles can be determined by the mobility of fluorescence probe as function of temperature. Membrane homogeneity can be identified by P-NMR, differential scanning calorimetry (DSC), fourier transform-infra red spectroscopy (FT-IR) and fluorescence resonance energy transfer (FRET) [24].

13.8 Drug loading and encapsulation efficiency [23, 24]: Drug loading and encapsulation efficiency of niosomal dispersion is determined after the separation of un-entrapped drug After preparing niosomal dispersion, un-entrapped drug is separated by dialysis, centrifugation, or gel filtration as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analyzing the resultant solution by appropriate drug assay method.

Entrapment efficiency = (Amount entrapped / total amount) x 100.

13.9 *In-vitro* drug release: Release of the drug can be monitored by dialyzing niosomal suspension against the buffer at definite temperature and determining the drug content of dialysate [30].

13.10 Stability studies: Stability studies are done by storing niosome at two different conditions, usually 4 ± 1 °C and 25 ± 2 °C. Formulation size, shape and number of vesicles per cubic mm can be assessed before and after storing for 30 d. After 15 and 30 d, residual drug can also be measured. Light microscope is used for determination of size of vesicles and the numbers of vesicles per cubic mm is measured by haemocytometer [31].

$$\text{Number of niosomes per cubic mm} = \frac{\text{Total number of niosomes x dilution factor}}{\text{Total no. of small squares counted}} 400$$

14. Application OfNiosomes[26, 30, 31]

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Some of their therapeutic applications are discussed below.

14.1 Niosomes as drug carriers: Niosomes have also been used as carriers for iobitridol, a diagnostic agent used for X ray imaging. Topical niosomes may serve as solubilization matrix, as a local depot for sustained release of dermally active compounds, as penetration enhancers, or as rate-limiting membrane barrier for the modulation of systemic absorption of drugs.

14.2 Drug targeting: One of the most useful aspects of niosomes is their ability to target drugs. Niosomes can be used to target drugs to the reticuloendothelial system. The reticulo-endothelial system (RES) preferentially takes up niosome vesicles. The uptake of niosomes is controlled by circulating serum factors called opsonins. These opsonins mark the niosome for clearance. Such localization of drugs is utilized to treat tumors in animals known to metastasize to the liver and spleen. This localization of drugs can also be used for treating parasitic infections of the liver. Niosomes can also be utilized for targeting drugs to organs other than the RES. A carrier system (such as antibodies) can be attached to niosomes (as immunoglobulin's bind readily to the lipid surface of the niosome) to target them to specific organs.

14.3 Anti-neoplastic treatment: Most antineoplastic drugs cause severe side effects. Niosomes can alter the metabolism; prolong circulation and half-life of the drug, thus decreasing the side effects of the drugs. Niosomes, decreases rate of proliferation of tumor and higher plasma levels accompanied by slower elimination.

14.4 Delivery of peptide drugs: Oral peptide drug delivery has long been faced with a challenge of bypassing the enzymes which would breakdown the peptide. Use of niosomes to successfully protect the peptides from gastrointestinal peptide breakdown is being investigated. In an *in-vitro* study conducted by oral delivery of a vasopressin derivative entrapped in niosomes showed that entrapment of the drug significantly increased the stability of the peptide.

14.5 Use in studying immune response: Due to their immunological selectivity, low toxicity and greater stability; niosomes are being used to study the nature of the immune response provoked by antigens. Non-ionic surfactant vesicles have clearly demonstrated their ability to function as adjuvants following parenteral administration with a number of different antigens and peptides.[26]

14.6 Niosomes as carriers for haemoglobin: Niosomes can be used as carriers for haemoglobin within the blood. The niosomal vesicle is permeable to oxygen and hence can act as a carrier for haemoglobin in anemic patients.

14.7 Leishmaniasis: Leishmaniasis is a disease in which a parasite of the genus Leishmania invades the cells of the liver and spleen.Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting organism resides in the organ of reticuloendothelial system (RES). The commonly prescribed drugs are antimonials, which are related to arsenic, and at high concentration they damage the heart, liver and kidney. It was reported that increased sodium stibogluconate efficacy of niosomal formulation and that the effect of two doses given on successive days was additive. Pawar SD et al reported that the use of niosomes to administer higher levels of the drug without triggering of the side effects, and thus allowed greater efficacy in treatment.

14.8 Transdermal drug delivery: The major drawback of transdermal route of delivery is slow penetration of drug through skin, and increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes.

14.9 Cosmetic delivery: The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L'Oreal. Niosomes were developed and patented by L'Oreal in the 1970s and 80s. The first product 'Niosome' was introduced in 1987 by Lancôme.[26, 29] The advantages of using niosomes in cosmetic and skin care applications include their ability to increase the stability of entrapped drugs, improved bioavailability of poorly absorbed ingredients and enhanced skin penetration.

14.10 Hormone delivery: The *in-vitro* permeation of estradiol from vesicular formulations through human stratum corneum was studied. The vesicles were composed of non-ionic *n*-alkyl polyoxyethylene ether surfactants (CnEOm). Two mechanisms are proposed to play an important role in vesicle–skin interactions, *i.e*., the penetration enhancing effect of surfactant molecules and the effect of the vesicular structures caused by their adsorption at the stratum corneum suspension interface.

14.11 Neoplasia: Doxorubicin, the anthracyclic antibiotic with broad spectrum anti-tumor activity, shows a dose dependent irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S- 180 tumor increased their life span and decreased the rate of proliferation of sarcoma. Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination.

14.12 Vaccine delivery: An interesting group of vaccine carrier systems are formulations based on non-ionic surfactant vesicles (niosomes) which themselves are only weekly immunogenic. Niosomes are gaining wide attention as per oral vaccine delivery system and for topical immunization. Influence of the varying proportion of surfactant, cholesterol, and dicetyl phosphate on the morphology, particle size, entrapment efficiency, and *in-vitro* antigen release from niosomes was investigated. The immune stimulating activity was investigated and it was observed that topical niosomes elicited a comparable serum antibody titer and endogenous cytokines levels as comparedto intramuscular recombinant HBsAg and topical liposome's.

14.13 Diagnostic imaging with niosomes: Niosomes are considered as a carrier of iobitridol, a diagnostic agent for X-ray imaging. The niosomes prepared using the film hydration method followed by sonication. Method allows the increasing encapsulation and the stability of vesicles were carried out.

15. Other Applications

15.1Sustained Release: Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation [25].

15.2Localized drug action: Drug delivery through niosomes is one of the approaches to achieve

localized drug action, since their size andlow penetrability through epithelium and connective tissue keeps the drug localized at the site of administration [25].

2. CONCLUSION

The technology utilized in niosomes is still greatly in its infancy, and already it is showing promise in the fields of cancer and infectious disease treatments. The system is already in use for various cosmetic products. Niosomes represent a promising drug delivery technology various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral, etc. and much research has to be inspired in this to juice out all the potential in this novel drug delivery system. The ionic drug carriers are relatively toxic and unsuitable whereas niosomal carriers are safer. And also handling and storage of niosomes require no special conditions. Vesicular drug carriers like niosomes can be transported by macrophages which are known to infiltrate tumor cells. It may be possible to take advantage of these activated macrophage system in delivering the anti-tumor agents within vesicles more quantitatively to tumour sites. So far only animal experimentation of this targeted drug delivery system is reported but further clinical investigations in human volunteers, pharmacological and toxicological investigations in animals and human volunteers may help to exploit niosomes as prosperous drug carriers for targeting drugs more efficiently, for treating cancer, infection and AIDS etc.There is lot of scope to encapsulate toxic anti-cancer drugs, anti-infective drugs, anti-inflammatory drugs, anti-viral drugs, etc. in niosomes.

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CONFLICT OF INTEREST

Authors have no any conflict of interest.

REFERENCES

1. Singh D, Upadhyay P. Niosomes: a novel vesicular approach. World J Pharmacy Pharm Sci. 2016; 5(12):1586-92.
2. Gadhiya P, Shukla S, Modi D, Bharadia P. Niosomes in targeted drug delivery – a review. Int J Pharm Res Scho. 2012; 1(2):59-72.
3. Gurjar P, Naik N, Chouksey S**.** Niosome: a promising pharmaceutical drug delivery. Int J Pharm Analysis. 2014; 2(5):425-31.
4. Verma KN, Rai AK, Gulzar A, Singh AP. Niosomes:An approach to current drug delivery-a review. Int J Adv Pharma. 2017; 06 (02):41-8.
5. Singh S. Niosomes: a role in targeted drug delivery system. Int J Pharm Sci Res. 2013; 4(2):550-57.
6. Gandhi A, Sen SO, Paul A. Current trends in niosome as vesicular drug delivery system. Asian J Pharm Life Sci. 2012; 2(2):339-53.

7. Gowri R, Balaji P, Vijayalakshmi P, Preethy MG, Karthik RP. Niosomes – a vesicular drug delivery system. Int J Curr Res. 2013; 5(8):2239-44.
8. Sonule M, Gandhi M, Paralkar S, Dabhade D, Pagar S. Niosomes: novel drug delivery system. Int J Pure App Bio Sci. 2014; 2(2):267-74.
9. Parmar RP, Parmar RB. Conceptual aspects of vesicular drug delivery system with special reference to niosome. Asian J Pharm Tech. 2013; 3(2):52-59.
10. Chandu VP, Arunachalam A, Jeganath S, Yamini K, Tharangini K, Chaitanya G. Niosomes: a novel drug delivery system. Int J novel trends Pharm Sci. 2012; 2(1):25-31.
11. Maurya R, Pathak K, Saxena P, Tiwari J. A review on novel drug delivery system – niosomes. Asian J Pharm Res Dev. 2013; 1(4):51-59.
12. Babu VL, Mathew ST, Jayaveera KN, PrasanthVV. Niosomes – vesicular drug delivery system. Int J Pharm. 2013;3(1):180-85.
13. Kazi MK, Asim SM, Nikhil B, Arijit G, Sugata C. Niosome: A future of targeted drug delivery systems. J Adv Pharm Tech Res. 2010; 1(4):374-80.
14. Krishnagopal D, Alpana R. niosome as a novel drug delivery system a review. Int J App Pharm. 2014; 5(1):1-7.
15. Rahimpour Y Hamishehkar H. Niosomes as carrier in dermal drug delivery. Recent Adv Novel Drug Carrier System. 2012; 141-64.
16. Srivastava NS, Thakur S, Kaur J. Niosomes: a novel approach for topical delivery of drugs. Int J Pharm Tech. 2016; 8(2):11712-31.
17. Seleci DA, Seleci M, Walter JG, Stahl F, Scheper T. Niosomes as nanoparticular drug carriers: fundamentals and recent applications. J Nanomaterials. 2016:1-13.
18. Sankhyan A, Pawar P. Recent trends in niosome as vesicular drug delivery system. J Applied Pharm Sci. 2012; 2(6):20-32.
19. Vasistha P, Alpana R. Non-ionic provesicular drug carrier: an overview. Asian J Pharm Clinical Res. 2013; 6(1):38-42.
20. Mehta AK, Dubal AP, Mane PD, Deshmukh HA. Recent trends in niosomes as nanocarriers. Unique J Pharm Bio Sci. 2013; 1(2):12-17.
21. Tangri P, Khurana S.Niosomes: Formulation and evaluation. Int J Biopharma. 2011; 2(1):47-53.
22. Keservani RK, Sharma AK, Ayaz MD, Kesharwani RK. Novel drug delivery system for the vesicular delivery of drug by the niosomes. Int J Res Cont Rel. 2011; 1(1):1-8.
23. Bagheri A, Chu BS, Harisun Y. Niosomal drug delivery systems: formulation, preparation and applications. W App Sci J. 2014;32 (8):1671-85.
24. Shaji J, Shah A. Niosomes: a novel drug delivery system. W J Pharm Res 2015; 4(6):853-76.
25. Vadlamudi C H, Sevukarajan M. Niosomal drug delivery system-a review. Indo Am J Pharm Res. 2012; 2(9).

26. Sharma P, Jain A P, Pandey P, Gupta R, Roshan S. Niosome a novel approach for drug delivery system: an overview. Asian J Pharm Sci Res. 2013; 3(5):18-30.
27. Cummings J, Staurt JF, Calman KC. Determination ofadriamycin, adriamycinol and their 7-deoxyaglycones inhuman serum by high performance liquid chromatography. J Chromatogr. 1984;311:125-33.
28. Tiwari R, Ansari VA, Singh S, Khalid MD, Akhtar J. Liposomes: the novel approach in cosmaceuticals. World J Pharm Pharm Sci. 2015;4(6):1616-40.
29. Madhav NVS, Saini A. Niosomes: a novel drug delivery system. Int J Res Pharm Chemistry. 2011; 1(3):498-511.
30. Kalra N, Jeyabalan G. Niosomes: A versatile drug delivery system. Res J life Sci Bioinformatics Pharm Chem Sci. 2016;2(4):44-54.
31. Gopalakrishnan S, Chenthilnathan A. Niosomes – A novel drug delivery device. Res J Pharm Bio Chemistry Sci. 2012;3(3):1090-98.