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Non-Ionic Surfactant Vesicles, One of The Efficient Tool For Transdermal Delivery

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Abstract: To treat the numerous diseases, researchers are now focusing on developing efficient, suitable, and site-specific drug delivery. Niosomes are one of the distinct carriers utilized to deliver drugs to particular regions. Niosomes comprises of non-ionic surfactants that are amphipathic; hence, both hydrophilic and lipophilic drug delivery are possible through niosomal vesicles. Niosomes take precedence over liposomes in terms of chemical stability, entrapment efficiency, improved bioavailability, and cost effectiveness. There are several routes to deliver niosomes. However, transdermal delivery of niosomes is the object of our interest here. The current review delivers a concise and generalized summary of niosomes, addressing their introduction, advantages and disadvantages, desirable structure and composition, formulation methods, influencing factors that affect niosome formation, transdermal delivery - The most important mechanism of action of niosomes as permeation enhancers and the application of niosomes through various routes.

Keywords: Niosome, Nonionic surfactant, Permeation enhancer, Site specific delivery, Transdermal delivery.

INTRODUCTION

The objective of a targeted drug delivery system is to avoid non-target sites and reach the maximum concentration of drug at the target site, which ultimately reduces the side effects[1]. The system by which an entrapped drug is released from the vesicles and reaches a specific region is known as the vesicular drug delivery system. These vehicles are used for drug targeting and controlled drug release. Furthermore, it helps to improve the penetration of the drug, which has the least skin penetration. Drug delivery uses niosomes as colloidal vesicular carriers[2]. In 1975, L'Oreal (the cosmetic industry) developed and patented the first niosome formulation[3]. Alec Douglas Bangham We first discovered a liposome as a vesicular carrier for drug targeting, but it has a number of problems, including toxicity,

high cost, instability, and varying phospholipid purity. Due to these restrictions, niosomal research has become popular[4]. Both niosomes and liposomes have essentially the same properties, but from the point of view of stability, niosomes, which are made of non-ionic surfactant, are more stable than liposomes, which are made of phospholipid that readily hydrolyzes due to an ester link, leading to chemical instability. So, niosomes are used as a substitute for liposomes[2].

STRUCTURE AND COMPONENT OF NIOSOME

Niosomes are microscopic, non-ionic surfactant-based multi-lamellar or unilamellar vesicles in which an aqueous solute solution is completely enclosed by a membrane, comprised of non-ionic surfactant macromolecules as bilayers (Structure of Niosomes – as describe in Figure 1)[5]. When the right ratio of cholesterol and surfactant is used and the temperature is above the gel-to-liquid transition point, a thermodynamically stable bilayer structure is formed[6]. The arrangement of non-ionic surfactant in the niosome is such that the hydrophilic end faces outward and the hydrophobic end faces each other, resulting in a bilayer[7]. Hydrophilic and lipophilic Drug delivery through the niosome is practicable; it is a distinctive delivery system that traps hydrophilic drugs in the center region and lipophilic drugs in the non-polar area of the bilayer. For better understanding, see Fig. 1, which clearly depicts the distinct sites for drug entrapment[8].

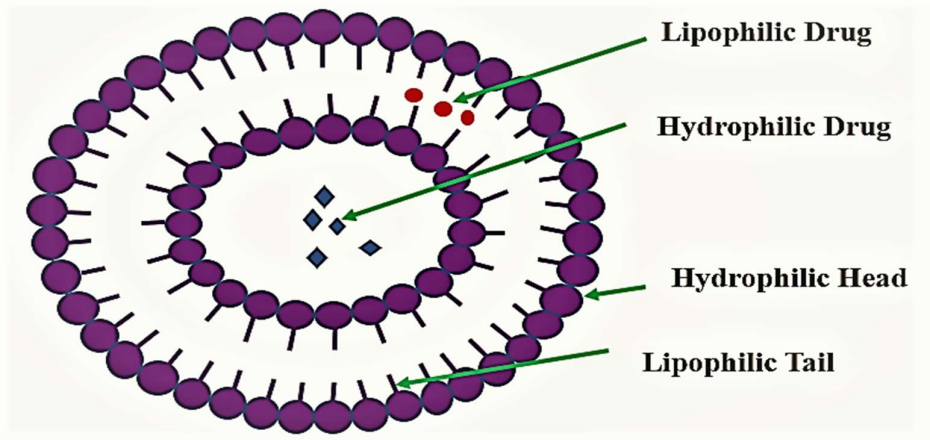


Figure 1- Structure of Niosomes

Components of Niosomes:

1. Non-ionic Surfactants **:** Due to the greater benefits they provide in terms of stability, compatibility, and toxicity compared to their anionic, cationic, and amphoteric counterparts, non-ionic surfactants are mostly used in the preparation of vesicles. Non-ionic surfactants are made up of both polar and non-polar parts and possess high interfacial activity. They tend to keep the pH of the solution close to physiological levels and are less poisonous, hemolytic, and irritating to cellular surfaces. They perform the functions of emulsifiers, solubilizers, wetting agents, and enhancers of permeability. The hydrophilic-lipophilic balance, critical packing parameter values, and CMC (Critical Micelles Concentration) all three factor determine which surfactant molecules should be used to create niosome[9].

Impact of HLB value of Surfacant on Niosome Development : If the HLB value is between 14 –16 then it's Fails to generate niosomes. 1.7-8.6 HLB value Reduces the entrapment efficiency, If HLB value > 6 then Cholesterol is required to be introduced for the production of bilayer vesicles. Lower Value of HLB then required the addition of cholesterol to promote stability of niosome. 8.6 HLB value Increases niosome entrapment efficiency[10].

Impact of CPP value on Production of Vesicle : A Critical Packing Parameter of non-ionic surfactant determines the shape of niosomal vesicles. CPP = V/lc x Ao Where, V = denotes the volume of the hydrophobic group, Lc = Critical Hydrophobic Group Length, Ao = Hydrophilic Head Group Area. CPP <1/2: Sphere-Shaped Micelles Develop, CPP 1/2 < CPP < 1: Bilayer micelles develop, CPP > 1: Inverted micelles develop[11].

Table I – Types of Non-Ionic surfactant used in the Preparation of Niosomes with their Examples[9]

Type of Non-ionic Surfactant	Examples
1) Alkyl ethers	
a. Alkyl glycerol ethers	Hexadecyldiglycerol ether
b. Polyoxyethylene glycol alkyl ethers (Brij)	Brij 30, Brij 52, Brij 72, Brij 76
2) Alkyl esters	
a. Sorbitan fatty acid esters (spans)	Span 20, Span 40, Span 60, Span 80
b. Polyoxyethylene sorbitan fatty acid esters (Tween)	Tween 20, Tween 40, Tween 60, Tween 80
3) Alkyl amide	
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 L 64, Pluronic 105

2. Cholesterol : Cholesterol incorporation influences niosome characteristics such as membrane permeability, rigidity, encapsulation effectiveness, toxicity, stability, and shelf life. The addition of molecules stabilizes the system against the development of aggregate via repellent steric or electrostatic force, which results in the transition from the gel to the liquid phase in the niosome system. It prevents vesicle aggregation, thus inhibiting leakage[12].

3. Charged Inducer : Diacetyl phosphate and phosphatidic acids are negatively charged inducers, and stearylamine and stearyl pyridinium chloride are positively charged inducers used in niosomal preparation. This improves the stability of the vesicle by inducing charge on the surface of the prepared vesicle, preventing fusion of the vesicle due to the repulsion of the same charge, and increasing zeta potential. The charged molecule is often added to the formulation of niosomes in the range of 2.5–5 mol %. However, increasing the number of charged molecules can prevent niosome formulation[9].

4. Drug : Both hydrophilic and lipophilic drug can be enclosed in niosomes[13].

ADVANTAGES OF NIOSOMES

- Targeted, controlled, and sustained drug delivery is possible with the help of niosomes.
- Niosomes are non-toxic, biocompatible, biodegradable, and non-immunogenic vesicles made of non-ionic surfactants.
- Drugs that are hydrophilic or hydrophobic can be enclosed in niosomes.
- Nearly all delivery methods, including oral, parentral, transdermal, ophthalmic, and pulmonary, are suitable for niosome administration.
- By modifying vesicle composition, size, lamellarity, surface charge, tapping volume, and concentration, vesicle properties can be altered.
- Niosomes have the capacity to hold drug molecules with a wide range of solubilities because the niosomal infrastructure contains hydrophilic, lipophilic, and amphiphilic moieties.
- Niosomes have the potential to enhance drug permeation through the skin.
- They improve the oral bioavailability of drugs that are not readily soluble[6,14]

DISADVANTAGES OF NIOSOMES

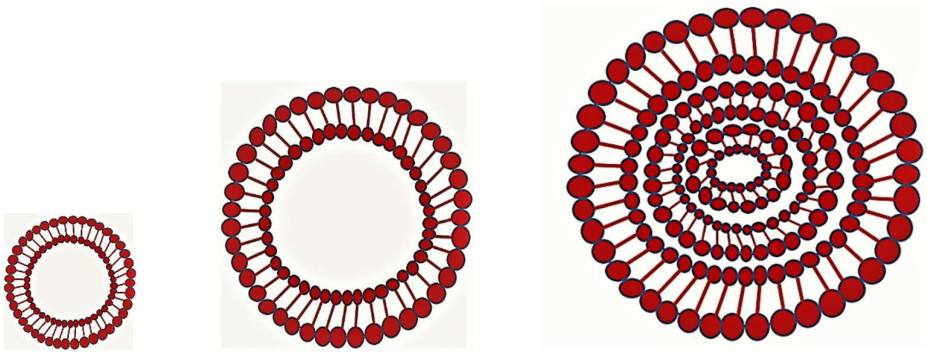
- Disadvantages associated with the aqueous suspension of niosomes, such as Physical instability, Aggregation, Fusion, Entrapped drug leakage, encapsulated drug hydrolysis reduces the shelf life of the dispersion.
- Niosomal preparation techniques like extrusion and sonication are time-consuming processes that require specialized equipment for processing[7].

CLASSIFICATION OF NIOSOMES

1. Based on Vesicle size, Number of bilayer, Method of preparation *:*

Table II - Types of Niosomes : Based on Vesicle, Number of bilayer, Method of preparation[15,16]

Parameters	**Multilamellar Vesicles (MLV)**	***Small Unilamellar Vesicles (SUV)***	***Large Unilamellar Vesicles (LUV)***
Vesicle Size	> 0.05μm	*0.025-0.05 μm*	*> 0.10μm*
Method of Preparation	Hand-shaking method	Sonication, French press, and Extrusion method, electrocapillary emulsification or Solvent dilution	Reverse phase evaporation and Ether injection method



a) b) c)

Figure 2- Types of Niosomes Based on Vesicle size – a) Small Unilamellar Vesicles b) Large Unilamellar Vesicles c) Multilamellar Vesicles

2. Based on composition :

- *Proniosomes :* A blend of water-soluble carriers and surfactants is used to create these dry niosomes. They have been hydrated to produce an aqueous niosome dispersion before use. Proniosomes are superior to niosomes in terms of stability[17].
- *Deformable Niosome :* Non-ionic surfactants, ethanol, and water are used to make elastic niosomes. **(**Mechanism of Deformation of Niosomal vesicle is described in Figure 3). Due to their ability to penetrate through pores in the stratum corneum that are smaller than vesicles, they are more effective than traditional niosomes. They can pass through pores in the stratum corneum of intact skin, thus improving penetration into the layer[18].

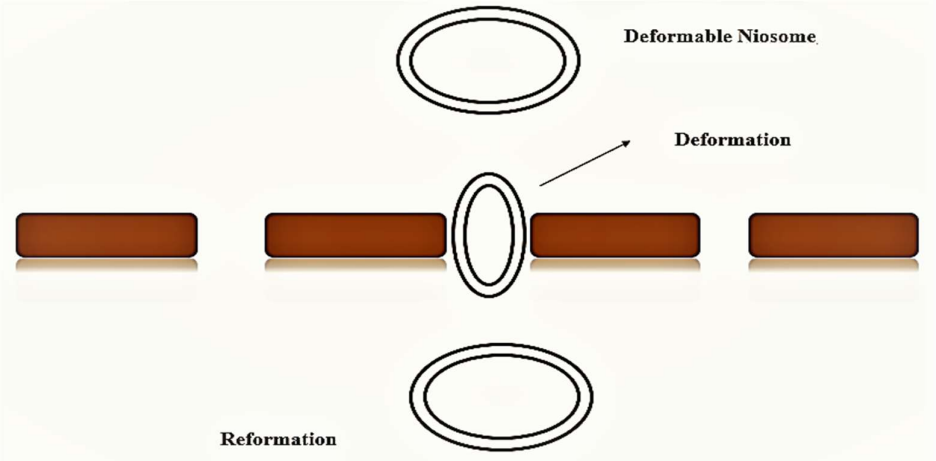


Figure 3 – Deformable Niosome

- *Aspasomes :* Aspasomes are vesicles created by combining carbyl palmitate, cholesterol, and a highly charged lipid called diacetyl phosphate. In order to obtain the niosomes, aspasomes must first be hydrated with water or another aqueous solution. The transdermal permeability of medication may be enhanced by aspasomes. Due to their inherent antioxidant properties, aspasomes have also been used to treat illnesses brought on by reactive oxygen species[19].

- *Bola Surfactant containing Niosomes :* Bola-form amphiphiles are made up of two identical aza-crown ether units that act as polar heads and are linked by a lengthy alkyl chain. Condensation of *N*-aza-18-crown-6 and alpha-omega-hexadecanedioic acid produced this bola surfactant (alpha-omega-hexadecyl-bis-1-aza-18-crown-6). This bola surfactant derived niosome has been discovered to be extremely effective for percutaneous medication administration. According to research, they increase percutaneous passage of 5-fluorouracil through the stratum corneum and epidermis[20]. Omega-headecyl-bis (1-aza-18 crown 6) (bola surfactant): Span-80 and cholesterol are included in this vesicle in a 2:3:1 molar ratio[19].
- *Discomes :* Discomes are disc-shaped niosomes under certain circumstances of the phase diagram of the non-ionic surfactant vesicle prepared from a hexadecyl ether, diacetyl phosphate, and cholesterol (69:29:2) by mechanical disruption, and then sonicated and incubated with various proportions of solulan C24 at 74 °C, and finally water-soluble solute entrapped in it. The disc-shape or large discoid structure was observed during the niosome to mixed micelles transition[21].

METHODS OF PREPARATION OF NIOSOMES

Ether Injection Method *:* In 1976, Deamer & Bangham reported about this technique[22]. The ether injection method basically involves slowly injecting a niosomal component dissolved in ether through a 14-gauge needle at a rate of about 0.25 ml/min into a heated aqueous phase kept at 60 °C. The slow vaporization of the solvent produces an ether gradient that extends towards the aqueous-non-aqueous interface (water-ether interface), which is likely to cause the development of large unilamellar vesicles. The diameter of the final vesicles varies depending on the circumstances, ranging from 50 to 1000 nm[9]. The method's drawbacks include that it is challenging to get rid of the trace levels of ether that are commonly found in the vesicle suspension[22].

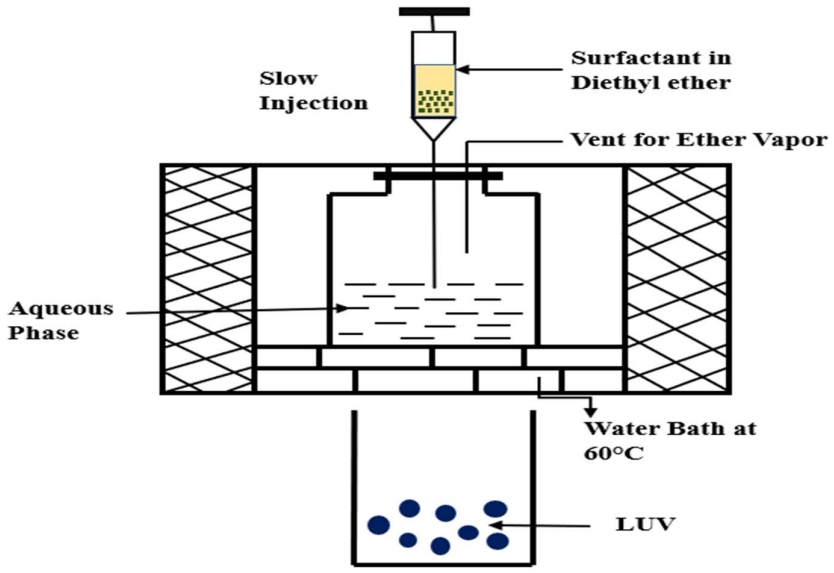


Figure 4 – Schematic Representation of Niosome formulation by Ether Injection Method

Reverse Phase Evaporation Technique (REV) : This method involves adding cholesterol and surfactant (1:1) to an ether and chloroform mixture. In addition, a drug-containing aqueous phase is used. Followed by 4-5 °C sonication of the combined two phases. The above-mentioned clear gel is then sonicated after a small addition of phosphate-buffered saline. The organic phase is eliminated at 40 °C and low pressure. A viscous niosome suspension is heated in a water bath at 60 °C for 10 minutes while phosphate-buffered saline is added to dilute. Niosomes are then produced. The preparation of large unilamellar vesicles is done using this technique[23].

Sonication : This procedure involves adding a drug solution dissolved in a buffer to the surfactant/cholesterol mixture. To produce niosomes, a titanium probe and sonicator are used to probe and sonicate the mixture for 3 minutes at 60 °C. The end product is small unilamellar vesicles[24]. When the sample is in a small volume, sonication can be done with a probe sonicator. However, bath sonicators are thought to be appropriate for large sample volumes[5].

Microfluidization Method : This method is based on the jet principle, which involves the interaction of two fluidized streams at extremely high speeds in microchannels inside an interaction chamber. It is ensured that energy supply to the system stays in the area of niosome production by placing the impigmented thin liquid sheet along a common front[24]. Formation of a niosome with a smaller size, better reproducibility, and ease of formulation were achieved using the microfluidization method[25].

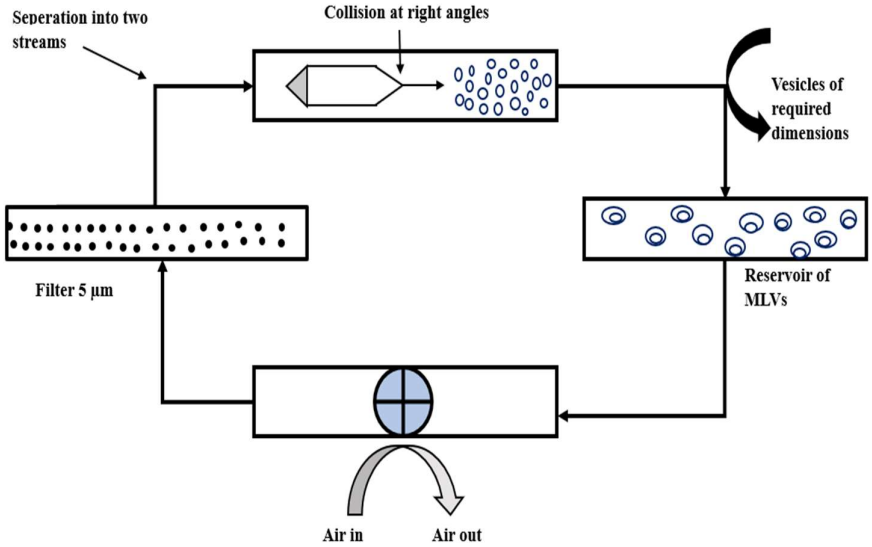


Figure 5 – Schematic Representation of formation of Niosome by Microfluidization / Microemulsifiation Method

Thin Film Hydration (THF) / Hand Shaking Method (HSM) : The first step is the dissolution of a mixture of surfactant and cholesterol in a round bottom flask containing volatile solvent. After that, the organic solvent evaporates using a rotator evaporator, leaving a thin film of a solid mixture at the bottom of the flask wall. Multilamellar niosomes are formed when the dried surfactant film is gently agitated in

the aqueous phase (water or buffer) at a temperature above the transition temperature of the surfactant. For further sonication, get unilamellar vesicles[26].

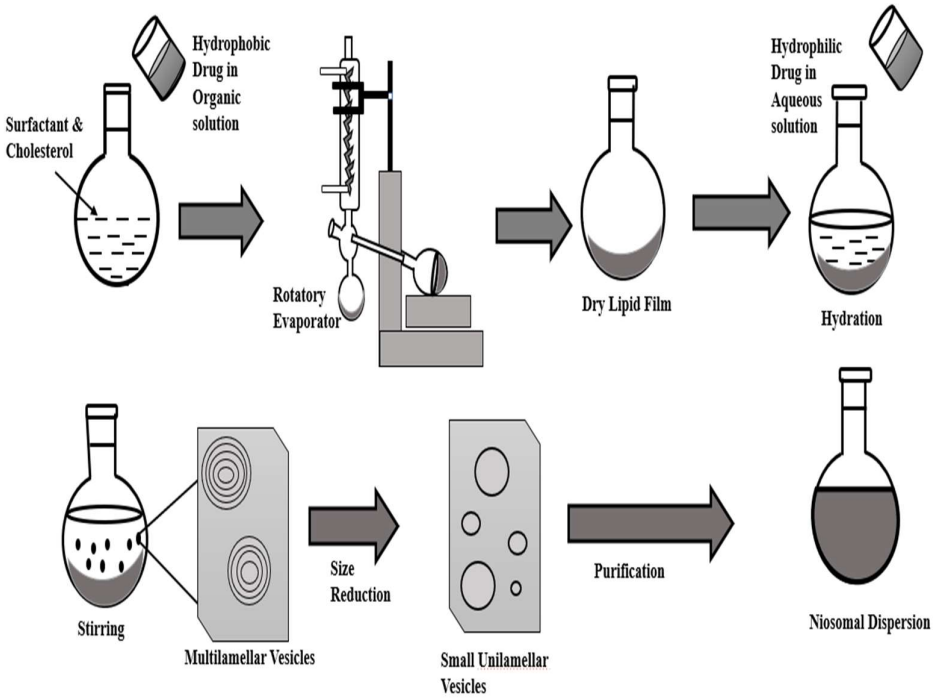


Figure 6 – Schematic Representation of Niosome formulation by Thin Film Hydration Method

Bubble Method : A round-bottom flask acts as the bubbling unit, with its three necks placed in a water bath to regulate temperature. The first and second necks are for water-cooled reflux and thermometers, while the third neck is used to provide nitrogen. In a buffer with a pH of 7.4, cholesterol and surfactant are combined and homogenized for 15 seconds at high shear before being bubbled at 70 °C with nitrogen gas[27].

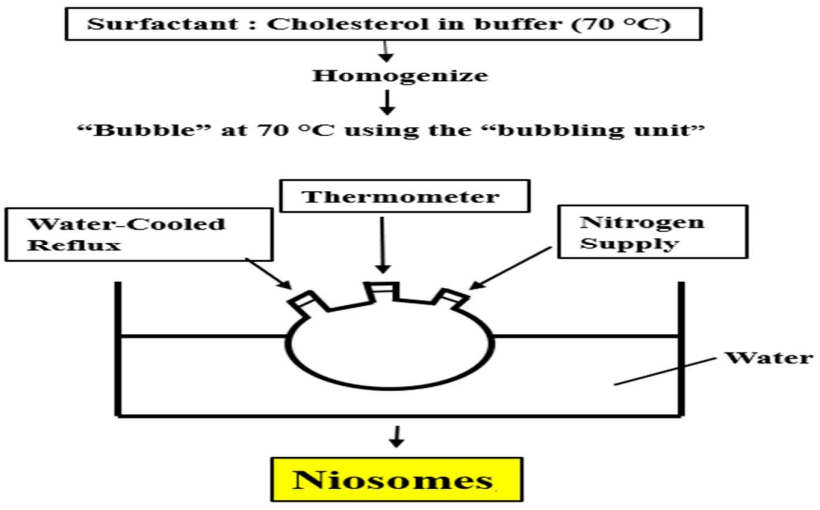


Figure 7 – Schematic Representation of Formation of Niosome by Bubble Method

Multiple Membrane Extrusion Method : After the surfactant, cholesterol, and dicetyl phosphate solution in chloroform evaporated, a thin layer was left behind. The resulting film is hydrated with the help of an aqueous drug solution. The solution and final suspension are extruded through a polycarbonate membrane in a series of up to eight passages. For adjusting niosome size, the multiple membrane extrusion approach is preferable[28].

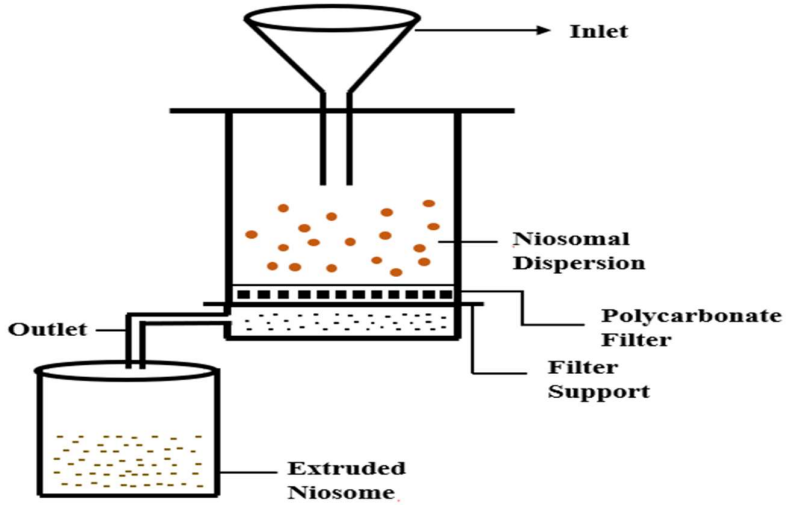


Figure 8 – Schematic Representation of Niosome formulation by Multiple Membrane Extrusion Method

Formation of Niosome from Proniosome : This method includes coating a water-soluble carrier, like sorbitol, with a non-ionic surfactant. This approach yields a dry formulation by protecting each hydrophilic particle with a thin coating of dry surfactant. By including the aqueous phase at (T > Tm), the niosomes are detected, and there is brief shaking simultaneously.

T = temperature, and Tm = mean phase transition temperature[29].

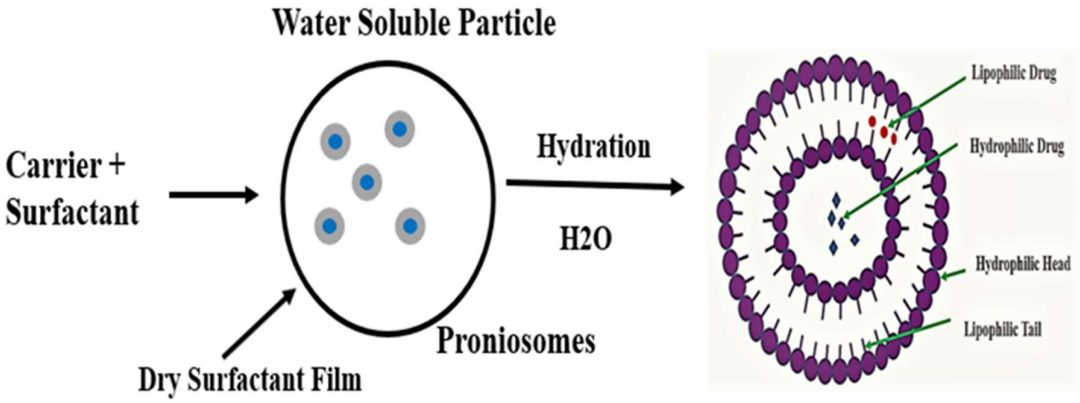


Figure 9 – Schematic Representation of Formation of Niosome From Proniosome

Transmembrane pH gradient (inside acidic) drug uptake process (remote loading) : Surfactant and cholesterol are dissolved using chloroform. Then, a thin layer is formed on the wall of the flask with a

circular bottom as the solvent evaporates under reduced pressure. Vortex mixing is used to hydrate the film with 300 mM citric acid at pH 4.0. The multilamellar vesicles are then sonicated after three cycles of freezing and thawing. A 10 mg/ml drug-containing water solution is added and vortexed to the niosomal suspension. The sample's pH is then increased to 7.0–7.2 using 1 M disodium phosphate. Niosomes are produced from this combination by heating it for 10 minutes at 60 °C [9].

FACTOR AFFECTING THE PHYSICOCHEMICAL PROPERTIES OF NIOSOMES

1. Concentration and Nature of Surfactant : Niosome size is increased by surfactants with higher HLB values because the increased hydrophobicity of the surfactants reduces surface free energy. The concentration of surfactant is directly proportional to the number of niosomes formed and entrapment efficiency, but it is applicable for limited concentrations[30]. Entrapment efficiency is also directly proportional gel transition temperature (Tc). For example, a span-60 with more Tc exhibits more entrapment.

Impact of the Surfactant on the Niosome Dispersion Characteristics : If a surfactant becomes more hydrophobic : Improves niosome stability and encapsulation. Increased phase transition reduced drug leakage from the aqueous compartment. If a surfactant becomes more hydrophilic : Reduces phase transition and niosome stability. enhances the transdermal delivery of water-soluble drugs[10].

2. Charge (Positive and Negative Charges) : Charge increases the intralamellar distance within the bilayer of multilamellar vesicles, which increases the drug's entrapment volume and stability[30].

3. Nature of Encapsulated drug : The type of drug being encapsulated affects the niosomal formulation. The drug is trapped in a vesicle due to the interaction of the surfactant head groups, which results in an increase in charge. The development of charge induces the surfactant bilayers to repel one another, which increases vesicle size[31]. Impact of nature of Drug on the property of vesicle : When Hydrophilic Drug is encapsulated in the niosome it leads to leakage of drug from the vesicles and reduces stability. If Hydrophobic Drug is encapsulated in the niosome it reduces the leakage of drugs from the vesicles, improves the stability of the vesicles, and enhances transdermal delivery. Amphiphilic Drug encapsulation Reduces the leakage of drug from the vesicles and improves encapsulation[32].

4. Resistance to Osmotic stress : Resistance to osmotic stress Vesicle diameter decreases when a hypertonic solution is added. Because of mechanical loosening of vesicle structure under osmotic stress in hypotonic solution, there is a slight swelling of vesicles, which causes a sluggish release at first, followed by rapid release[33].

5. Hydration Temperature : Geometry of vesicles also altered by Hydration Tempeature. Hydration should occur at a temperature above the gel-liquid phase transition temperature. Inappropriate hydration temperature, hydration medium volume, and time all contribute to an increase in the drug leakage problem[34]. At 25 °C, the polyhedral vesicle of C16G2: Solulan C24 (91:9) is formed, but this polyhedral

vesicle changes into a spherical vesicle at 45 °C, then cools to form a cluster at 55–49 °C, which forms a small spherical niosome[35].

6. Cholesterol Content : The rigidity of bilayers increases with an increase in cholesterol concentration and decrease in the release rate of drug. Entrapment efficiency, Stability and hydrodynamic diameter of niosomes are improved when cholesterol is used[36].

EVALUATION PARAMETERS OF NIOSOMES

Size, Morphology : Laser light scattering method, electron microscopy, molecular sieve chromatography, ultracentrifugation, and photon correlation are some techniques used to determine the mean diameter of the niosome, which are accepted to be sphere-shaped[37]. Transmission electron microscopy (TEM) *Morphology of niosomes estimated by transmission electron microscopy (TEM)* . For studying liquid samples, ice-fracture transmission electron microscopy (FF-TEM) methods are favored, whereas for studying solid samples, scanning electron microscopy (SEM) methods are utilized[28].

Bilayer Formation, Number of Lamellae, Membrane Rigidity : U*nder light polarization microscopy, an X-cross formation can be used to investigate bilayer vesicles made of nonionic surfactant. Small-angle X-ray scattering, nuclear magnetic resonance (NMR) spectroscopy, and electron microscopy are the techniques used for the detection of the number of lamellae*[38]. As a fluorescent probe, 1,6-diphenyl-1,3,5-hexatriene (DPH) was used. The technique of fluorescence probe mobility as a function of temperature can be used to estimate membrane rigidity[39].

Entrapment Efficiency *:* The first step in estimating the entrapment efficiency of the niosomal dispersion is the isolation of the unentrapped drug by dialysis, centrifugation, or gel filtration methods. By thoroughly disrupting the vesicles in 50 % n-propranolol or 0.1 % triton X-100 and then analyzing the resultant solution using the correct assay methods, the drug that remains trapped in the nucleus can be recognized. The Following formula is used for the estimation of percentage entrapment efficiency[40]:

Entrapment efficiency (% EE) = (Amount of drug entrapped / Total amount of drug) x 100

Measurement of Angle of Repose for dried niosome powder *: Funnel method is used for this test. Niosome powder was poured into a funnel that was set such that its 13 mm output aperture was 5 cm above a flat black surface.* Measurement of the height of the cone and the diameter of the base, these two parameters are used for the determination of the angle of repose after the powder fell from the funnel to create a cone on the surface[41].

Zeta Potential *:* This technique is employed to ascertain the colloidal characteristics of the fabricated formulations. The niosomes produced following hydration with phosphate buffer were measured using a Zeta potential analyzer based on laser droppler velocity and electrophoretic light scattering (Zeta Plus, Brookhaven Instrument Corporation, New York, USA). The temperature had been fixed at 25 °C. Charge on vesicles was measured directly, and their mean zeta potential values with standard deviation were calculated[42]. Niosomes that are stable are those whose zeta potentials are greater than +30 mv and greater than -30 mv[43].

In Vitro Release Study *: In Vitro* Release Study Dialysis tubing can be used to conduct these tests. Purified niosomal suspension is put into a dialysis bag, and the bag is then sealed. The donor compartment is a niosomal dispersion bag placed in a container containing phosphate buffer solution and continuously shaken at 37 °C. At laser points in time, the samples were removed and examined with a UV spectrophotometer to determine their drug content. Other methods, including Franz diffusion cells, are also used for these tests[44].

Stability Studies : The optimized batch was kept in airtight, sealed vials at a range of temperatures, including 4 °C, 25 °C, and 45 °C, to test the stability of the niosome. In order to determine the surface characteristics and percentage of drug retained in niosomes, samples were collected at certain intervals of time (0, 1, 2, and 3 months), examined for color change and surface properties, evaluated for the percentage of drug retained after being hydrated to niosomes, and then subjected to appropriate analytical techniques (UV spectroscopy, HPLC methods)[40,42].

APPLICATION OF NIOSOME

1. Niosomes serve as hemoglobin carriers.

The niosmal vesicle is used as a transporter for hemoglobin in patients who are anemic because it is permeable to oxygen. Haemoglobin Niosomes Produced by solvent vaporization, vesicles appeared as unilamellar, spherical red vesicles, according to research[45].

2. Drug delivery via Niosome

It has been discovered that niosomes carry iobitridol, a radiopaque contrast substance utilized in x-ray imaging[46]. Topical niosomes serve a variety of purposes, including penetration enhancer, local depot for sustained release of dermally active material, and solubilization matrix[47].

3. Opthalmic drug delivery

Aggarwal and Kaur in 2005 investigated a comparison study of marketed formulations and chitosan-coated niosomal formulations of timolol maleate (0.25 %). This chitosan-coated niosomal formulation has a greater impact on intraocular pressure reduction[48].

4. Delivery of a peptide drug

According to a pharmacokinetic study performed by[49], the niosome was investigated for the parentral and vaginal delivery of insulin and demonstrated a good ability to prevent insulin from degrading as well as prolong the life of the drug, increasing its therapeutic value.

5. Immunological application of the niosome

The characteristics of the immune response triggered by antigens have been studied using niosomes. Niosomes have been described as an effective adjuvant by Brewer and Alexander in terms of immunological selectivity, low toxicity, and stability[50].

6. Transdermal delivery of drugs by niosomes

Niosomes transdermal drug delivery method has increased penetration rate by improving therapeutic effectiveness and bioavailability[51]. Using confocal imaging and research on hairless mice, the topical

administration of erythromycin using different formulations, including niosomes, was examined. It was discovered that non-ionic vesicles might be made to target pilosebaceous glands[23].

7. Anti-neoplastic treatment

Niosomes can alter metabolism, prolong the effect of medication, half-live, and thereby decrease pharmacological side effects. Shah Hamid had developed a withaferin niosome for anticancer activity, and the result showed that it was three times more effective against Hela cells than alone[52].

8. In Leishmaniasis

Baillie et al. studied that the antileishmanic activity of drugs like sodium stibogluconate is increased when drugs are incorporated into the niosome[53].

TRANSDERMAL DRUG DELIVERY THROUGH NIOSOME : MEDIATORS OF PERCUTANEOUS PENETRATION

During the application of niosomes to the skin, it is essential to decide whether a localized impact inside the skin (dermal medicine conveyance) or a general impact followed by saturation through the skin (transdermal medication conveyance) is needed[54]. Many pharmaceutical research teams focusing on diseases like cancer, psoriasis, alopecia, acne, and inflammation are interested in transdermal targeting since it attempts to penetrate the bloodstream. The drug is distributed throughout the body after entering the systemic circulation through the blood vessels of the skin. Comparing the transdermal route to other drug delivery techniques reveals some advantages, like avoiding the risk and inconvenience of intravenous therapy, avoiding peak and trough serum levels, gastrointestinal degradation, and first-pass hepatic metabolism (pH, enzymatic activity, and interaction with food and orally administered drugs). This improves the efficacy of the drug and its bioavailability[55]. However, the low rate of skin penetration for transdermal medication delivery is one of the main challenges. Intercellular, intracellular, and transappendageal are the three probable transdermal delivery pathways for drug transfer over the stratum corneum. A drug that has crossed the epidermis may either be eliminated by the dermal circulation or transferred to deeper tissue[56]. Niosome approaches have been tested for their ability to circumvent the barrier function; one of these approaches involves the use of penetration enhancers. It involves three mechanisms. Enhancing diffusivity through modifying the lipid structure between corneocytes is the idea behind the lipid-protein partition theory. Change intracellular protein domains in the horney layer to improve drug partitioning into skin and tissue[57].

In 2011, a significant contribution was made to the assessment of niosomal vesicles as a penetration enhancer. The researcher wanted to know if the increased hydrophilic drug penetration across the skin that is always seen with the vesicular system depends on the structure of the niosomes that are used to transport active molecules or if it depends solely on the dual nature of the surfactant. Despite the appearance that surfactants do not permeate the deeper layer of the skin, successful drug delivery requires the simultaneous presence of both vesicular carriers and drugs, as well as direct contact between the vesicles and the epidermis[56].

MECHANISMS OF ACTION OF NIOSOMES AS PERMEATION ENHANCERS FOR TRANSDERMAL DELIVERY

The ability of the niosome to increase drug transfer through the skin is explained by various mechanisms, Mechanisms of action of Niosome for dermal and transdermal applications is Schematically Represented in Figure 10, which involves several steps. For hydrophilic drugs: 1) The surface of the skin exhibits a high level of niosome adsorption and/or fusion, in which the drug interface thermodynamic gradient functions as a driving force for drug penetration. 2) Sebum dissolution by the vesicles to aid follicular drug transport. 3) Large water-soluble compounds are transported via the pore pathway. 4) Alteration of electric charges that are present on the surface of ionic drugs. For lipophilic drugs: 1) Alteration of the stratum corneum's barrier function as a result of reversible disturbance of lipid organization. 2) Lowering trans epidermal water loss causes the stratum corneum to become more hydrated and loosen its tightly packed cellular structure, which enhances drug permeation. 3) Improvement of transdermal permeability through nanosizing. 4) Rerouting the transport of lipophilic substances through the permeation pathway to the follicular system On the other side, niosomes may merge with the cell membrane, causing the cytoplasm to completely mix with the contents of the niosomes. Finally, niosomes may be taken up by the cell (endocytosis), in which case lysozymes in the cytoplasm may break down or digest the niosomal membrane, releasing the material that was trapped inside into the medium[51].

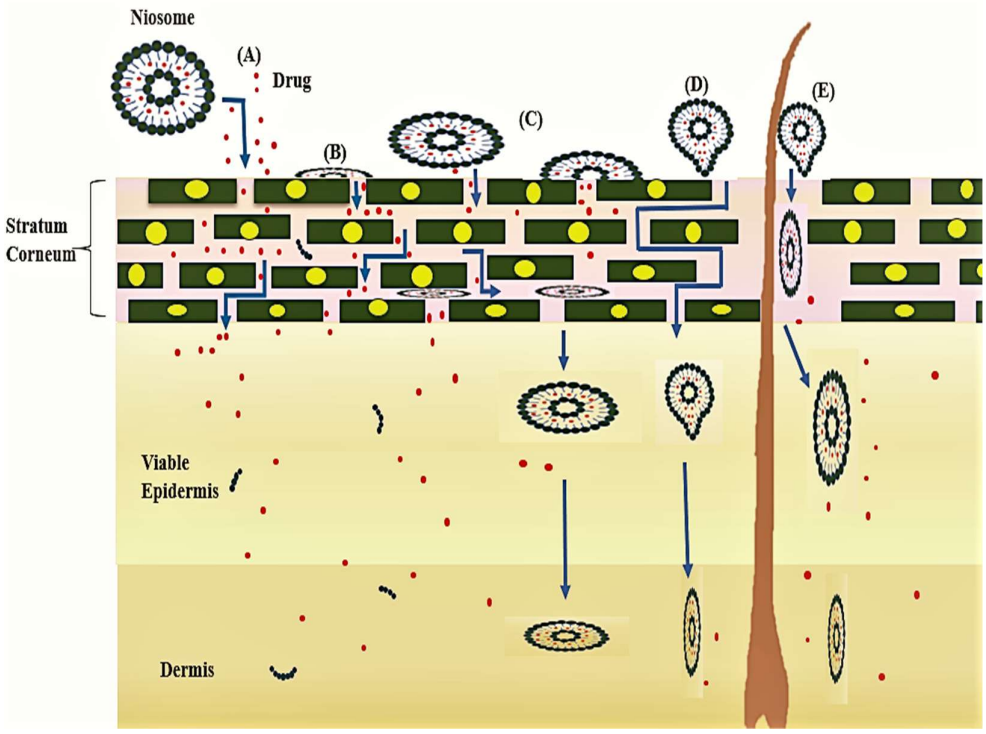


Figure 10 – Schematic Representation of Possible mechanisms of action of Niosome for dermal and transdermal applications: (A) released of drug molecule through niosomes; (B) niosome constituent serve as penetration enhancer; (C) niosome adsorption and/or fusion with stratum corneum; (D) intact niosome penetration through the intact skin; (E) niosome penetration through hair follicles and/or pilosebaceous units.

NIOSOMAL DRUG DELIVERY THROUGH VARIOUS ROUTES WITH ITS METHOD OF PREPARATION, EXCIPIENTS

Table III – Niosomal Drug Delivery through Various Routes its method of preparation, Excipients

Drug	Application	Method	Excipient	Outcome	References
Griseofulvin (Oral Route)	Antifungal	Ether Injection Method	Span-20, Span-40, Span-60, Cholesterol, Dicetyl Phosphate	Improved Oral Bioavailability & Prolonged drug Release	58
Tacrolimus (Ocular Delivery)	For Corneal allograft rejection	By Reconstituting the Proniosome	Poloxamer 188, Soybean, Phosphatidyl -choline, Cholesterol Hyaluronic acid	Enhances Opthalmic Bioavailability, Increase Corneal Permeability.	59
Minocycline (Coated implant)	For Peri implant Diseases	Thin Film Hydration	Span 60 & Cholesterol	Sustain & Prolong drug release for over 1 week, antibacterial activity.	60
Rifampicin	Antitubercular /Antimicrobial	Sonication Method	Span 60 & Cholesterol, dicetyl phosphate	Increase the drug release Profile of Poorly Soluble Drug	61
Vidagliptin	Hypoglyemic	Sonication Method	Cholesterol & Span 60, Potassium dihydrogen phosphate	It Shows Sustain release of drug upto 13 hr.	62
Bromocriptin Mesylate (Intranasal Brain Targeting Delivery)	For Parkinsons disease.	Ether Injection Method	Span 60 & Cholesterol	Better Brain relative bioavailability, Enhanced Pharmacokinetic effect, reduce oxidative stress.	63
Glimipiride (Oral Route)	Hypoglycemic	Thin Film Hydration	Cholesterol, Tween & Span(20,60,80,40), Methanol	Improves Bioavailability of Drug , Reduces adverse effect	64
Vinca Rosea	Anticancer, Antihypertensive	Thin Film Hydration	Tween 60, 80 and Span 20, 60, 80	Increases Bioavailability of drug	65
Luliconazole Transdermal Route)	Antifungal	Thin Film Hydration	Span 60, Tween 80, Cholesterol	Enhances drug effectiveness through niosomal transdermal delivery.	66
Simvastatin (Transdermal Route)	Antihyperlipidemic	Thin Film Hydration	Cholesterol, Tween 80, Span 60	Results in Prolong Drug Release & increased bioavailability.	67

Clarithromycin (Transdermal Route)	Antibiotic	Ether Injection Method	Span (40,60,80), Tween (60,80)	Greater permeability, greater flux than conventional patch.	68
Clozapine (Transdermal Route)	Antipsycotic	Thin Film Hydration	Span 80, Cholesterol Ethyl cellulose,	Improves drug release & effective delivery of drug was achieved	69

CONCLUSION :

Niosomes are composed of non-ionic surfactants that are more stable than liposomes, which undergo degradation and hydrolysis. That's why niosomes are superior to liposomes. Due to the arrangement of non-ionic surfactant in the vesicles and the amphipathic nature of non-ionic surfactant, it is possible to incorporate water-soluble and water-insoluble drugs. Niosomal drug delivery is possible through various routes, such as oral, parentral, ophthalmic, pulmonary, and transdermal. Less drug permeation is the drawback of transdermal drug delivery, which is overcome by using niosomes, which act as a permeation enhancer. Proniosomes and elastic niosomes are novel developments of the niosome. Various categories of drugs, such as antibiotics, antifungals, anticancer, anti-inflammatory, and anti-diabetic, are possible to deliver through niosomes. Therefore, niosomes function as therapeutic transporters for targeted, sustained, and controlled delivery.

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