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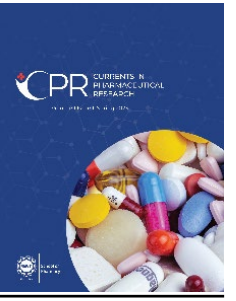

Title:	**Exploring Niosomes: A Comprehensive Review of their Structure, Formulation, and Biomedical Applications**
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Exploring Niosomes: A Comprehensive Review of their Structure, Formulation, and Biomedical Applications

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ABSTRACT

Niosomes are a novel class of non-ionic surfactant vesicles. They have emerged as promising vesicles for the delivery of a diverse range of therapeutic agents. Niosomes are implied for the improvement of stability and solubility of molecules used in pharmaceutical components. The current study delved into the formulation methods, applications, and recent advancements in niosomal technology. They offer various benefits over other drug delivery systems due to their biocompatibility, biodegradability, and versatility. The first section of this study outlined the background, detailed structure, and characteristics of niosomes. Niosomes are quite distinct in their characteristics as they have the ability to encapsulate both hydrophilic and lipophilic drugs. The second section of the current study highlighted various methods employed for niosome preparation, such as film hydration, reverse-phase evaporation, and microfluidic techniques. By modifying the lipid composition and surfactants, specific physicochemical properties, such as size, lamellarity, and surface charge can be achieved. The final section discussed applications of niosomes across pharmaceutical, cosmetic, and biotechnological fields. These include targeted drug delivery, gene delivery, cosmetic ingredient encapsulation, and vaccine adjuvant systems. Additionally, the recent advancements in niosome research have been discussed as well.

Keywords: niosomes, niosomes applications, niosome classification, targeted drug delivery

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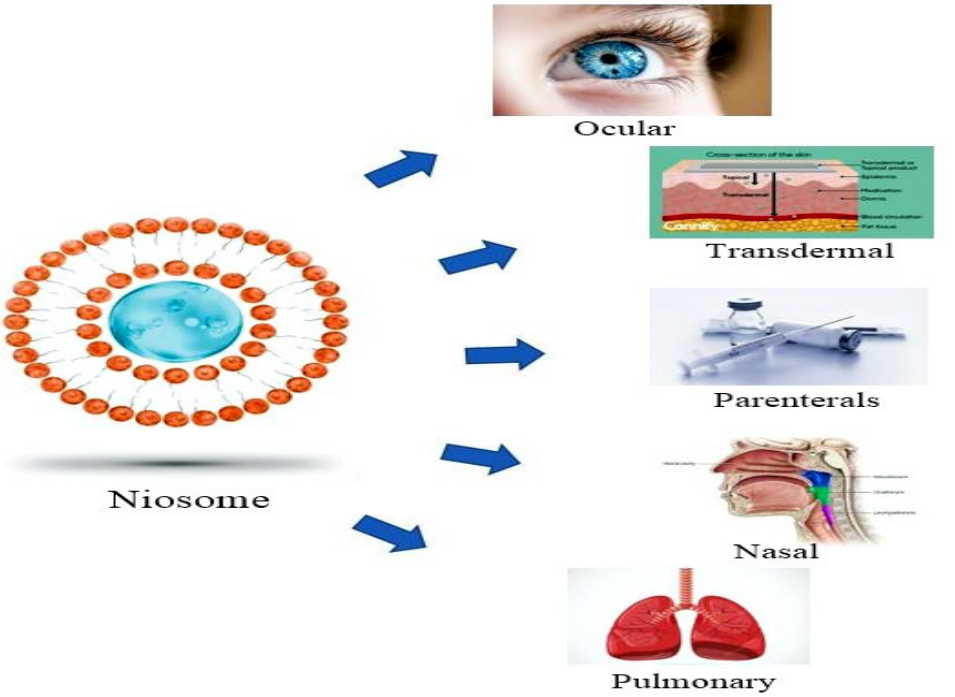
GRAPHICAL ABSTRACT



1. INTRODUCTION

Niosomes are minute vesicles built on non-ionic surfactants. They differ from liposomes in composition by primarily comprising non-ionic surfactants, cholesterol, and occasionally dicetyl phosphate while sharing a similar structural resemblance.

Niosomes have undergone extensive scientific investigation within the pharmaceutical realm for their potential in conveying pharmaceuticals, genetic material, vaccines, and nutraceuticals. This is owed to their adaptability in altering surface characteristics, enabling targeted delivery, controlled discharge, and improved therapeutic effectiveness. Their utility extends across diverse domains, however, not limited to cancer treatment, vaccine administration, dermatology, and other related fields.

1.1 Background of Niosomes

Niosomes were introduced for the first time as a feature of cosmeceutical industry [1]. It has been reported that the first non-ionic surfactant vesicles were devised by L'Oreal for cosmetic applications [2]. They were introduced as an alternative to liposomes in the 1970s by Lasic and Papahadjopoulos. The non-ionic surfactants comprise both polar and non-polar segments, possessing a high interfacial activity that forms bilayer upon hydration, hence entrapping both hydrophilic and hydrophobic drugs [3]. In 1909, Paul Ehrlich started off an era of establishment of targeted drug delivery systems when he anticipated a mechanism that might deliver the drug to a diseased cell directly [4].

The concept of targeted drug delivery system is associated with administration of active compounds, at a predetermined rate, for the achievement of a therapeutic effect at diseased site in a human or an animal body, reducing the interaction of medication in non-targeted tissues. To state precisely, drug targeting means to aim a therapeutic entity directly to a specific area where the action is desired, without any interaction of that entity with other surrounding tissues [5].

In case of niosomes, the drug or the active ingredient is placed in a vesicle, thus encapsulating it. The vesicle comprises a non-ionic surfactant bilayer. These vesicles usually contain non-ionic surfactant and cholesterol as an excipient. The vesicle forming an amphiphile is a non-ionic surface-active agent, for instance Span – 60. This surface active agent is usually stabilized by means of adding cholesterol and anionic surfactant [6].

2. CHARACTERISTICS OF NIOSOMES

2.1.Dual Encapsulation of Drugs

Niosomal formulations can be used to encapsulate both hydrophilic and hydrophobic drugs. For instance, drugs like paclitaxel and doxorubicin can be encapsulated by niosomes [7].

2.2. Improved Stability

Niosomes can be used to encapsulate drugs, such as ascorbic acid to improve their stability and protect them from degradation. They are highly resistant to degradation by hydrolysis [8].

2.3. Reduced Toxicity

Niosomes are generally biocompatible and biodegradable in nature. Drugs having a toxic nature, such as acyclovir can be encapsulated in niosomes to reduce their toxicity [9].

2.4. Targeted Drug Delivery

These types of vesicular formulations can also be used for targeted delivery of drugs, such as antifungal drugs, that is, clotrimazole that are aimed at a specific site of body [10, 11].

3.ADVANTAGES AND DISADVANTAGES OF NIOSOMES

3.1.Advantages

1. Niosomes can encapsulate a variety of drugs quite easily, such as hydrophilic, lipophilic, and amphiphilic drugs.
2. The characteristics of vesicles can be controlled by changing composition of vesicles of niosomes as well as their size lamellarity and also surface charge, concentration, and tapped volume.
3. Drug can be released in sustained/controlled manner from niosomes.
4. for easy handling and storage of surfactants, no special conditions are required.
5. Niosomes increase the bioavailability of the drugs which are poorly soluble.
6. Surfactants possess certain response including biodegradable, biocompatible, non-toxic, and non-immunogenic.

3.2. Disadvantages

1. Niosomes can cause aggregation.
2. There can be leakage of entrapped drug from niosomes.
3. Sometimes niosomal formulations can have physical instability.
4. The preparation methods of niosomes are time consuming [12].

4. STRUCTURAL COMPONENTS OF NIOSOMES

Figure 1. illustrates the components that constitute the niosomes.

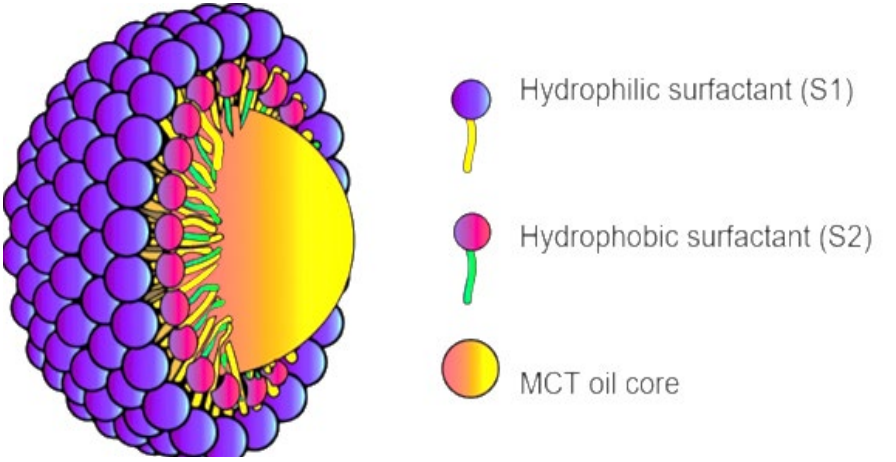


Figure 1. Structural Components of Niosomes [13].

4.1. Surfactants

Various surface-active agents and their combination have been used to entrap drugs (in niosomes). Following are some of the surfactants used in niosomes**.**

4.2. Ether-Linked Surfactants

Ether-linked surfactants are polyoxyethylene alkyl ethers comprising both hydrophilic and hydrophobic moieties which are linked with ether. The general formula of ether linked surfactant group is (CnEOm), in which 'n' ranges from 12 to 18 and 'm' ranges from 3 to 7. An example of this class of surfactants is C16 mono alkyl glycerol ether (single alkyl chain surfactant) which contains 3 glycerol units. Other ethers that can be used in the formation of niosomes include Polyoxyethylenecetyl ethers and Polyoxyethylenestearyl ethers [14].

4.3. Ester-Linked Surfactants

These are the surfactants in which hydrophilic and lipophilic groups are linked by ester groups. These surfactants have been studied for its application in the preparation of sodium stibogluconate and its delivery to marine visceral leishmaniasis [15].

4.4. Sorbitan Esters

A more widely used group is sorbitan esters. These find application in food industry. The combination of partial esters of sorbital plus its mono

and di-anhydride forms with the oleic acid are used to form sorbitan esters. An example of the sorbitan ester usage is the drug entrapment of Clindamycin Phosphate [16].

4.5. Alkyl Amides

Alkyl amides are the alkyl glucosides and galactosides that have been incorporated with amino acid spacers. The alkyl groups consist of fully or partially saturated hydrocarbons. The amide compounds usually have fluorocarbon chains.

5. TYPES OF NIOSOMES

5.1. Multilamellar Vesicles (MLV)

The multilamellar vesicles (MLV) consist of an aqueous lipid compartment that is surrounded by various bilayers separately. These vesicles are usually 0.5 to 10µm in diameter. They have the advantage of being mechanically stable, thus providing a longer shelf life [17].

5.2. Large Unilamellar Vesicles (LUV)

Large unilamellar (LUVs) are usually prepared by detergent solubilization method or reverse phase evaporation method. The diameter of LUVs is approximately 0.10µm in size. They have a high aqueous to lipid compartment ratio resulting in entrapment of larger amounts of bio-active materials in a lipid membrane rather economically.

5.3. Small Unilamellar Vesicles (SUV)

Small unilamellar vesicles (SUVs) are also known as sonicated lamellar vesicles due to the method of their preparation, that is, sonication. The diameter of SUVs ranges from 0.025-0.05µm. They are usually prepared by sonication, electrostatic stabilization or extrusion from multilamellar vesicles (Figure 2).

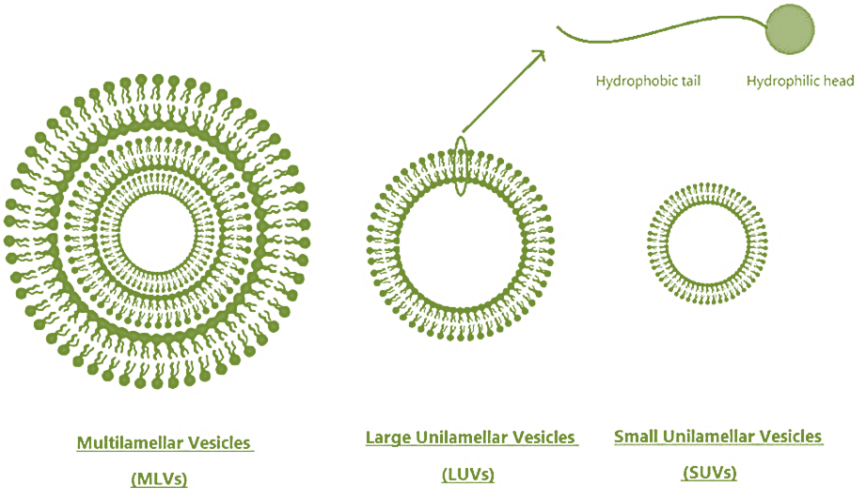


Figure 2. Types of Niosomes [18].

Other types of niosomes that are mentioned in literature include:

i. Proniosomes
ii. Discomes
iii. Elastic niosomes
iv. Surfactant ethosomes.

5.4. Proniosomes

The first type is dry niosomes, an aqueous niosomal dispersion after being hydrated immediately before use. Due to their dry nature, they eliminate various demerits linked with the physical stability which include leakage, aggregation, and fusion. Additionally, they provide significant benefits, such as ease of transportation and distribution, handling and storage, and intervals of dosing. The proniosomes, if applied topically, hydrate to form niosomes on the skin bypassing the occlusive barriers. In comparison to niosomes, they efficiently transport the drug in gel form by transdermal route [19]. Anti-fungal drugs, such as Econazole and Miconazole have been formulated as niosomes and have a greater efficacy than conventional dosage forms [20]. Contraceptive proniosomal gels containing agents, such as levonorgestrel, ethinyl estradiol, and estradiol aide in programs of population control [21]. Some anti-cancer drugs have

also been formulated as niosomes and studies have suggested their potential efficacy in the treatment [22].

5.5. Surfactant Ethosomes

The first ethosomes were prepared by Touitou which was synthesized by incorporation of high concentrations of ethanol to form a lipid vesicular system. Ethosomes are composed of un-ionized surface-active agents, water and isopropyl alcohol or ethanol (in high concentrations). They are different from other vesicular systems as they can permeate through the skin layer, that is, stratum corneum and in that they possess higher levels of transdermal flux (as compared to liposomes or niosomes). However, it remains unclear that exactly how do they permeate deeper into skin layers and have such enhanced permeation. Various studies have suggested that this enhancement is due to the synergism of ethanol and surfactants that constitute these ethosomes [23]. These lipid-based vesicular systems have some limitations, such as complex formulation and manufacturing, instability and risk of encapsulated drug leakage [24].

5.6. Elastic Niosomes

They enhance the permeation of drug through the pores (even smaller than the vesicles) of skin into stratum corneum. They can even pass though areas ten times smaller than the diameter due to their elasticity. This is the reason that they are capable to deliver compounds or therapeutic agents of varying molecular weights, that is, low or high. They also have the benefit of providing longer duration of action and higher biological action in contrast to conventional dosage forms. The transport of elastic niosomes is driven by means of trans-epidermal hydration and is independent of their concentration. Deformable elastic niosomes were the first detergent-based nanosized vesicles developed by Van den Bergh, containing two types of surfactants; sucrose laurate ester and the micelle forming octaoxyethylene laurate ester [25]. These deformable niosomes can provide enhanced skin permeability when encapsulate anti-inflammatory drugs, such as diclofenac and indomethacin [26]. Furthermore, enhanced skin permeation has been seen in case of lidocaine niosomal formulation in comparison to traditional drugs [27].

5.7. Discomes

Discomes are another type of niosomes which come under the phase diagram of vesicles made of nonionic surface-active agents. They are

characterized by large discoid structures. Niosomes containing hexadecyl diglycerol ether, dicetyl phosphate, and cholesterol were prepared by Uchebu and coworkers by mechanical shaking technique and sonication. After that, incubation was done with solulan C24 and soluble polyoxyethylene cholesteryl ether [28]. Four phases were indicated in the constructed partial phase diagram which included micellar phase, uncharacterized phase, lamellar phase, and another phase that was then called as 'discome' phase. This phase contained large vesicles having diameter between 12 to 60mm and their size increased after sonicating. Discomes entrapped the solutes that were water soluble solutes. 5(6)-carboxyfluorescein (CF) discomes retained 50% of the entrapped CF at room temperature for 24 hours. Vyas et al. also highlighted discomes as potential carriers for drugs in ophthalmology after they experimented and analyzed that discomes containing timolol maleate showed three times more ocular absorption than the solution form [29]. Drug delivery through discomes have some limitations, such as they are complex to formulate. When formulated, it is a challenge to maintain their structural integrity due to temperature variations and exposure to light. Another area of concern in case of discomes is their toxicity or immunogenicity [17]. Limited research in this field also limits understanding about their behavior, optimized formulation, and potential applications.

6. FACTORS AFFECTING THE FORMATION OF NIOSOMES

The formation or development of niosomes depends upon various factors that are as follows:

6.1. Type of Surfactants

The type of surfactant used in a niosome can affect its stability, efficiency of encapsulation, and toxicity. In the formulation of first niosomes, cholesterol and alkyl oxyethylene surfactants were used. The chain length of the alkyl group usually ranges between C12–C18. A good indicator for the detection of ability of vesicle formation is hydrophilic-lipophilic balance (HLB).

6.2. Cholesterol

The most important component of cell membranes is steroids. They bring about different changes in membranes that are significant in regard to the stability of bilayer, the permeability, and also the fluidity of the bilayer. One of the most commonly used natural steroid is cholesterol. Although, it

does not form the bilayered vesicles, it causes the transition liquid phase from the gel phase in niosomal systems [30].

6.3. Other Additives

Other additive compounds, such as charged phospholipids, for instance, stearyl amine (SA) and dicethylphosphate (DCP) have also been used for the production of charge in the niosomal formulations. Stearyl amine is used to form positively charged niosomes, that is, cationic, while DCP is used for the formation of negatively charged (anionic) niosomes.

6.4. Nature of Drug

The nature of encapsulated drug is one of the most ignored factors that can influence the vesicle formation. Studies have reported changes in the electrophoretic mobility of the hexadecyl-di-glycerol ethers when an amphipathic drug doxorubicin is encapsulated. These changes are pH dependent, thus indicating the incorporation of amphipathic drug in the vesicle membrane [14]. The effect of drug nature on niosome formation is shown in Table 1.

Table 1. Effect of the Nature of Drug on Niosomes and their Evaluation Parameters [31]

Sr. No	Effect of The Nature of Drug on Niosomes			Methods of Evaluation	
	Nature of drug	Leakage from the vesicle	Stability	Evaluation Parameter	Method
1	Amphiphilic drug	Decreased	Decreased	Permeation study	Franz diffusion cell
2	Hydrophobic drug	Decreased	Increased	Morphology	TEM, Freeze fracture technique, SEM
3	Hydrophilic drug	Increased	Decreased	*In-vitro* release study	Dialysis membrane
4	Macromolecule	Decreased	Increased	Size distribution, Polydispersity index viscosity	Dynamic light scattering (DSC)
				Entrapment efficacy	Centrifugation, Chromatography
				Membrane thickness	X-ray scattering analysis
				Turbidity	UV-Visible diode array spectrophotometer
				Thermal analysis	DSC

The drug being amphiphilic in nature for being encapsulated is also a significant factor that effects the formation of niosomes. Doxorubicin depicts the best example of such drugs with amphiphilic nature. Encapsulation in niosomes results in aggregation which was resolved by adding a steric stabilizer [32].

6.5. Effect of Temperature

Another factor that plays a major role in the development of vesicles and their size and shape is the temperature of hydrating medium. The temperature of medium must be above that of gel to liquid transition phase of the system. The major factors influenced by temperature include surfactant assembly and alterations in the shape of vesicles [33]. For instance, a change in shape of polyhedral vesicles into spherical ones was seen when temperature was increased from 25˚C to 48˚C. As the temperature reduced, these niosomes changed into polyhedral shape again. In comparison, vesicles made of solulan and cholesterol showed no transformation on either heating or cooling [34].

6.6. Stability

The main problems encountered in the storage of niosomes include leakage, aggregation, and fusion of the encapsulated drug (Figure 3). Stable formulation of drug shows high retention and entrapment efficiency over a longer period of time (months) in the case of tenoxicam. Only stable formulations were chosen in the stability studies at the end of each month. Although, the entrapment efficiency decreased by 10%, no other significant changes were found in the mean vesicle size after 2 months as compared to freshly formed niosomes of sucrose stearate. The stability testing of niosomes also involves their exposure to fluorescent light and UV radiations to check the vulnerability to photo degradation. For this purpose, the niosome preparations were first kept at room temperature and then exposed to ultraviolet radiations at 25 C for about 1 hour. Literature shows such preparations of niosomes loaded with tretinoin (Vitamin A metabolite) [35].

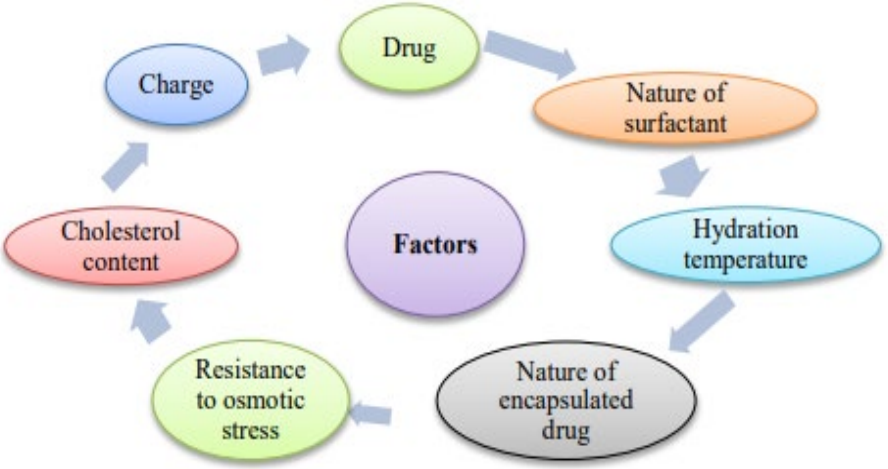


Figure 3. Factors Affecting Formation of Niosomes [36].

7. Characterization of Niosomes

Niosomes can be characterized by the following evaluation parameters (Table 1).

7.1. Measurement of Angle of Repose

The flow properties of dry powder of niosomes and angle of repose can be determined by funnel method. This is done by pouring the niosome powder in the funnel set at a fixed position in such a way that outlet orifice of 13mm of funnel remains 5cm above the lower surface. When the powder is poured, it flows down the funnel and forms a cone at the surface. The angle of repose can be calculated by the diameter of the base and the height of cone [37].

7.2. Vesicle Morphology

The structure and shape of vesicle of niosomes may be characterized by several types of microscopy including optical microscopy, freeze fracture microscopy, electron microscopy, fluorescence, scanning electron, confocal, cryo-electron, and negative staining transmission electron microscopy. Scanning electron microscopy can be used to check the size and surface morphology including the aggregates formation, roundness of the particles, and their smoothness. For this purpose, the niosomes are sprinkled on the top of a double-sided tape fixed on an aluminum stub. This

assembly is then placed in a vacuum chamber of SEM and samples are observed using a detector (gaseous secondary electron detector) [38].

7.3. Measurement of Vesicle Size

To measure the size of the niosome vesicle, its dispersion is diluted about 100 times using the same medium that was used to prepare them. Particle size analyzer is used to measure the size. This apparatus usually contains He-Ne laser beam with a wavelength of 632.8 nm which is focused using a Fourier lens R-5 (power 5mW). Sample is placed in a sampling handling cell and a detector measures the size [34].

7.4. Niosomal Recovery and Entrapment Efficiency

The capacity of niosome to load the drug and its efficiency to entrap is measured by the ultracentrifugation of its aqueous suspension and removing the supernatant. The sediment that is formed underneath is washed two times with the distilled water to remove the entrapped drug. The recovery of niosomal drug can be calculated by:

*% Recovery of Niosomes = (Amount of niosomes recovered/Amount of drug + surfactant + excipients) * 100*

The entrapment of the drug in niosomes can be measured by taking a sample of the vesicles and digesting it using triton X 100 or other organic solvent, such as isopropanol for the complete disruption of the vesicle [39]. The resulting solution is then analyzed and the drug entrapment percentage is determined by the formula:

*Entrapment Efficiency % = (Amount of drug in niosomes/Amount of drug used) * 100*

7.5. *In-Vitro* Release of Drug from Niosomes

The current study was conducted by the dialysis of the drug through membrane which is semi permeable. Niosome sample is added in a receptor compartment which contains a buffer and transfer through the dialysis membrane is checked. This release is measured by collecting the samples at periodic intervals and analyzing them with suitable method [40].

7.6. Zeta Potential Analysis

The surface charge present on the niosome determines their behavior and characteristics within the human or animal body. The charge density

and zeta potential of niosomes can be calculated by the process of micro electrophoresis. This can be done by various techniques including laser Doppler velocimetry and electrophoretic light scattering technique. The conditions are maintained such that temperature is 25°C.

7.7. Stability Studies

The stability studies of niosomes can be conducted by storing the optimized niosome batch at varying temperature in the vials which are sealed air tight. After storing them for a predetermined period either of 6 months or 12 months or other, they are taken out of the stability chamber. Afterwards, different tests are performed on them to determine the retained percentage of the drug and surface properties of the niosomes. The samples are usually checked at different intervals of time, such as for 0, 1, 2, and 3 months and observed for different evaluation characteristics. This analysis can be done by UV spectroscopy and HPLC methods. These methods detect any morphological changes and determine the drug content that remained encapsulated in the niosomes. The percentage content of niosomes is usually evaluated after hydration [41]. The stability studies are performed at specific conditions that include temperature, humidity, light exposure, pH changes, and multiple freeze-thaw cycles might be used.

8. METHOD OF PREPARATION OF NIOSOMES

Different methods of preparation of niosomes are as follows:

8.1. Ether Injection Method

This method uses a solution of surfactant that is made by mixing the surfactant (Span80/Tween80) in diethyl ether (Figure 4). This mixture is then added into warm water or an aqueous medium (containing the drug or therapeutic entity) by means of an injection having a 14 gauge needle (This is done very slowly as diethyl ether is highly flammable). The aqueous medium is maintained at a temperature of 60° Celsius. Single layered vesicles are then formed by vaporizing the ether. The size of these vesicles or particles ranges from 50 to 1000 µm depending on the conditions of preparation used [42].

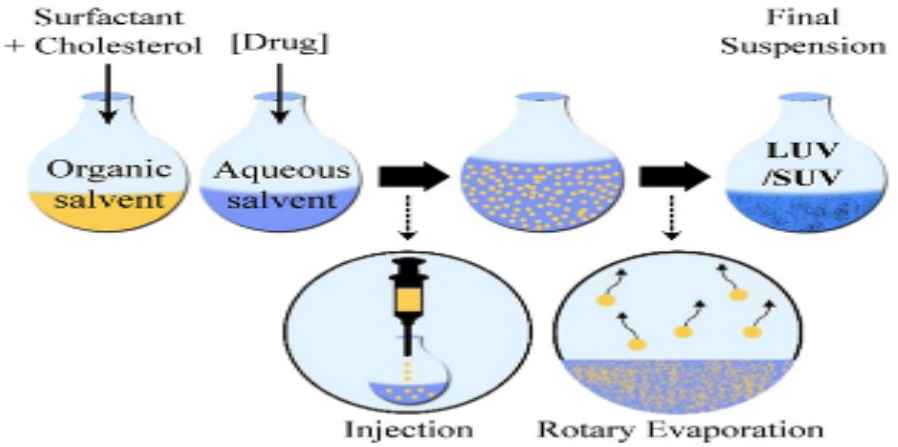


Figure 4. Preparation of Niosomes through Ether Injection Method [43].

8.2. Hand Shaking Method (Thin Film Hydration Technique)

Hand shaking technique is also called as 'thin film hydration technique'. It involves the dissolution of vesicle forming agents (surfactant<Tween80> and cholesterol) in a volatile organic solvent (diethyl ether or chloroform) in a round bottom flask (Figure 5). The organic solvent is then removed using a rotary evaporator at room temperature, thus leaving thin film of solid mixture deposited on the walls of the flask. Multi-lamellar niosomes can then be generated by rehydrating this surfactant film and gently agitating this mixture [36].

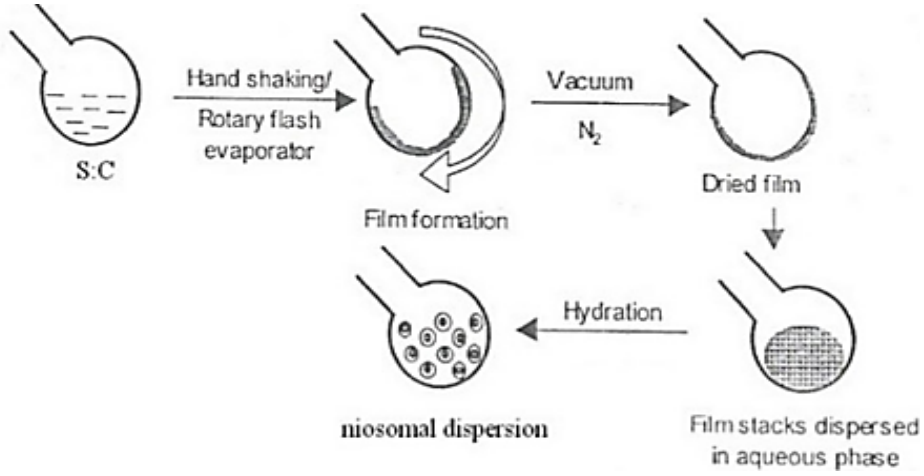


Figure 5. Hand Shaking Method [44].

8.3. Reverse Phase Evaporation Technique (REV)

In this method, a solution of surfactant and cholesterol in a ratio of 1:1 is formed by mixing ether and chloroform (Figure 6). To this mixture, the drug in an aqueous phase is added and sonicated at 4-5°C. Further sonication of the previously formed gel is done after adding PBS (phosphate buffered saline). After this process, the organic phase is removed by reducing the pressure and increasing the temperature to 40°C. A viscous niosome suspension is formed that can be diluted by adding PBS and heating at 60°C for 10 min at a water bath to yield niosomes [45]. Volatile compounds are being used, therefore good caution should be observed while preparing the Niosomes.

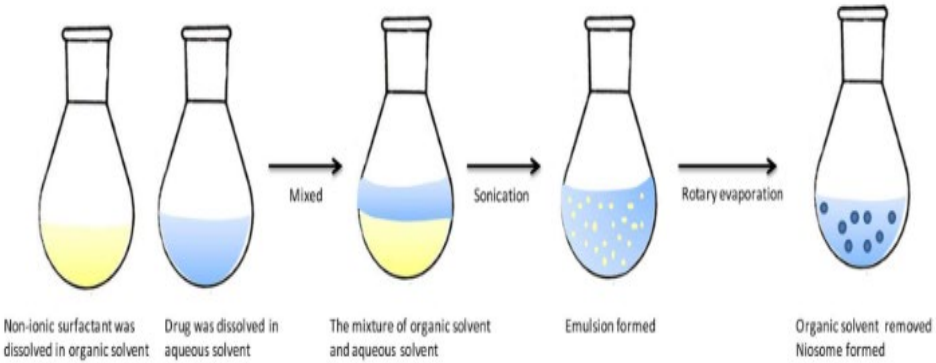


Figure 6. Reverse Phase Evaporation Method [31].

8.4. The "Bubble" Method

This method allows the formation of niosomes without using organic solvents (Figure 7). A round bottom flask with three necks is used as a bubbling unit. This unit is then positioned in a water bath to control the temperature. Water-cooled reflux is placed in the first neck, while a thermometer is positioned in the second neck and a nitrogen supply is placed in the third neck. A buffer with pH 7.4 is used for the dispersion of cholesterol and surfactant at 70°C. This is mixed for 15 seconds by means of a high shear homogenizer and nitrogen gas is used to bubble this mixture at 70°C, thus yielding niosomes [46]. This is the most effective and reproducible method as compared to other methods.

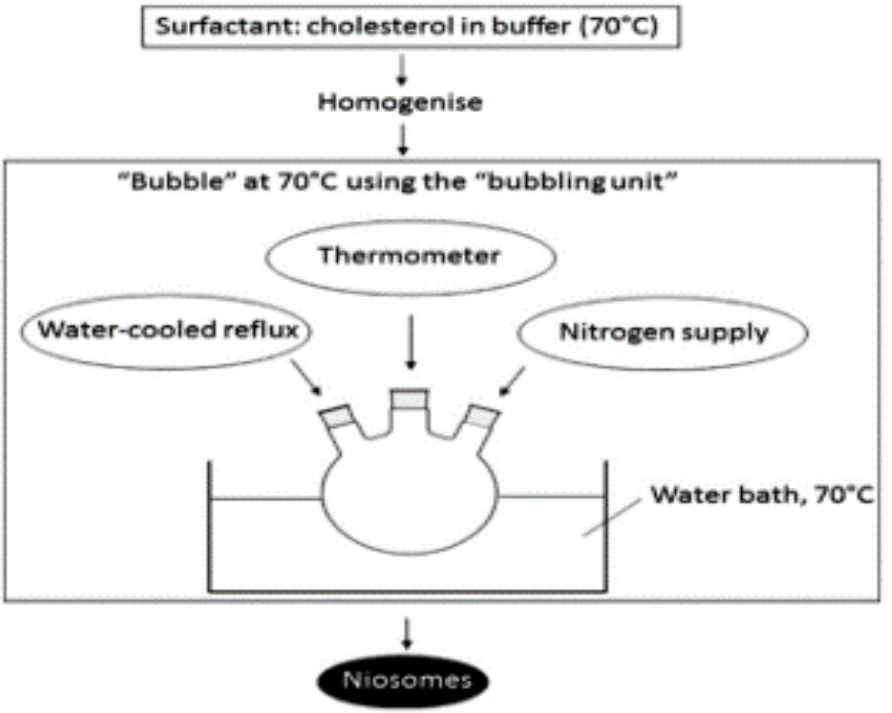


Figure 7. The Bubble Method for the Preparation of Niosomes [46].

8.5. Micro Fluidization

Another recent technique used for the preparation of unilamellar vesicles is micro fluidization (Figure 8). This technique yields vesicles of specific and defined size. The basis behind is the submerged jet principle which is based on the interaction of two fluid streams at very high velocities in micro channels that are precisely defined in an interaction chamber. A thin liquid sheet is impinged along a common front that keeps the energy of the system within the site of niosomes' formation. This results in niosomes with small size and greater uniformity [47]. The surfactants which can be used are Tween80/Span80.

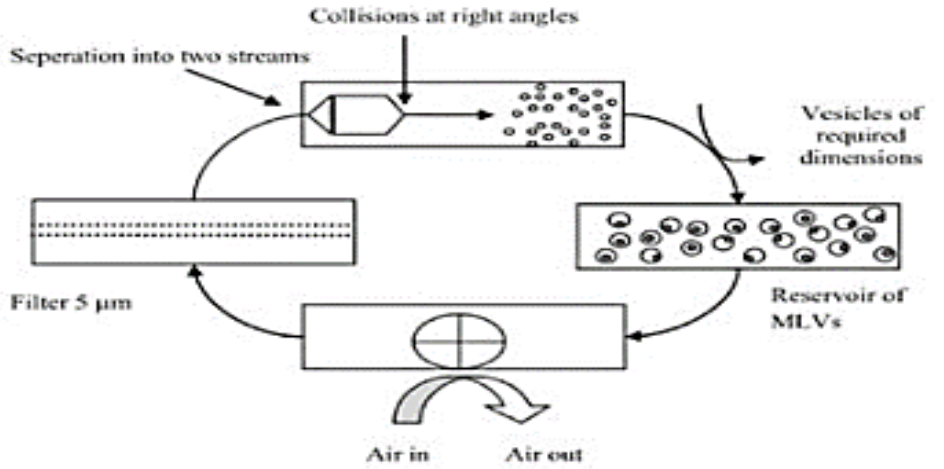


Figure 8. Micro Fluidization Method [48].

8.6. Multiple Membrane Extrusion Method

Multiple membrane extrusion method is used for the production of niosomes of desired size (Figure 9). A thin film of a mixture of surfactant, cholesterol, and dicetyl phosphate in chloroform is formed by evaporation. This film is subjected to hydration with polycarbonate membranes' solution of an aqueous drug. The extrusion of resultant suspension is carried out and placed in a series 8 passages [49].

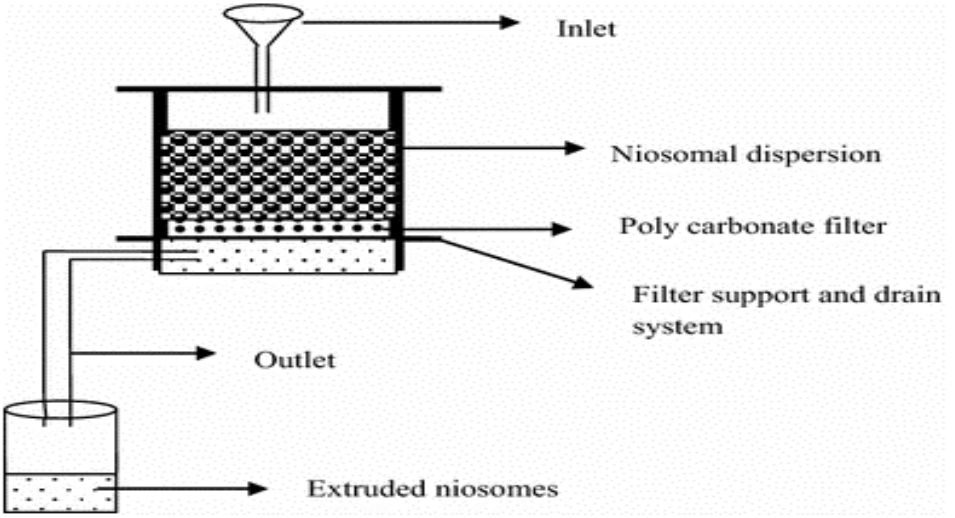


Figure 9. Membrane Extrusion Method [49].

8.7. Sonication

An aliquot of drug solution is used in this method (Figure 10). A10 ml glass vial is taken and used to put in buffer and surfactant/cholesterol mixture. Probe sonication of this mixture is carried out by a sonicator at 60°C for 3 minutes. A titanium probe is used to yield the niosomes [49].

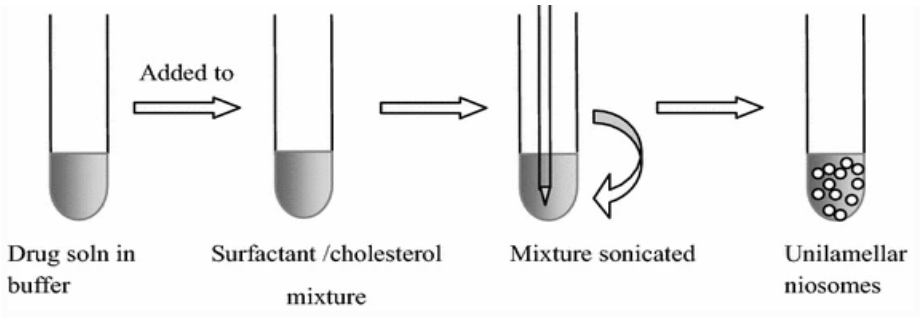


Figure 10. Sonication Method to Prepare Niosomes [49]

9. DELIVERY STRATEGIES

The review of various published literature shows that niosomes can be delivered by different routes and the route of administration is quite important when a vesicular formulation is being designed (Figure 11).

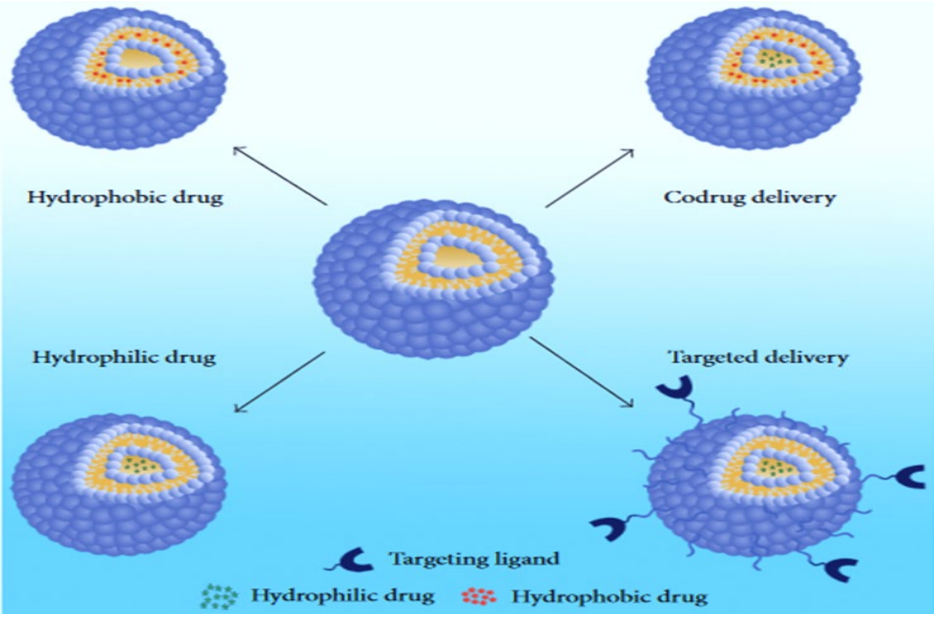


Figure 11. Drug Delivery Strategies through Niosomes [50].

9.1. Oral route

An in-vivo study was performed on rabbits to assess the acyclovir encapsulated in niosomes which showed a Higuchi release of the drug that resulted in improved and sustained effect of the drug. In comparison with the tablet form, 2 folds increase was seen in the mean residence time and oral bioavailability of acyclovir. Same was the case in a fluconazole formulation as niosomes showed a high encapsulation efficiency. An IVIVC study was performed for niosomes loaded with griseofulvin. The results showed enhanced bioavailability of the drug in the subjects and sustained effect by oral route. All of these studies concluded a single point that niosomes are a promising carrier system for drugs that require a sustained release [51].

9.2. Ocular Delivery

The delivery of drug to the eye by its permeation is dependent on the drug and vesicle's physicochemical properties. That is why niosomes have become popular in researches about ocular niosomal drug delivery in diseases, such as glaucoma and many other eye conditions. A study reported the entrapment of acyclovir anti-viral niosomes in keratitis caused by herpes simplex which can even cause blindness if not treated [52].

9.3. Transdermal Delivery

The main obstacle encountered in the delivery of topical drugs is stratum corneum's barrier function. Niosomes can be the solution of this problem as well as they can permeate directly through the skin and go into the systemic circulation. They provide the advantage to enhance the permeation into skin and also act as reservoir for drugs prolonging their time period. Niosomes of estradiol, in addition to the cholesterol, were found to facilitate the transdermal permeation of the drug. In comparison to a plain gel, aceclofenac gel made up of niosomes provides steady transdermal flux and a cumulative high penetration of drug. Niosomal meloxicam gel reduced edema more effectively in rats in comparison to the meloxicam conventional gels. The drug penetrates in the deep layers of the skin [50].

Table 2. Route of Administration of Niosomal Drugs [53]

Route of Administration	Examples of Drug
Intravenous route	Doxorubicin, Comptothecin, Insulin, Zidovudine, Cisplatin, Rifampicin

Route of Administration	Examples of Drug
Inhalation	All trans-retonic acids
Transdermal route	Piroxicam, Estradiol, Nimesulide
Ocular route	Timolol maleate, Cyclopentol
Nasal route	Sumatriptan, Influenza vaccines

10. APPLICATIONS OF NIOSOMES

A very common application of niosomes is seen as carriers of therapeutic or diagnostic agent. An example of a compound being loaded in niosomes is Iobitridol which is used as a diagnostic agent in X-ray imaging. Niosomes can also be used to produce sustained release topical dosage forms of dermally active agents serving as a solubilizing matrix. Other ways to use niosomes in drug delivery include penetration enhancers or in modulation of systemic absorption of drugs (Figure 12).

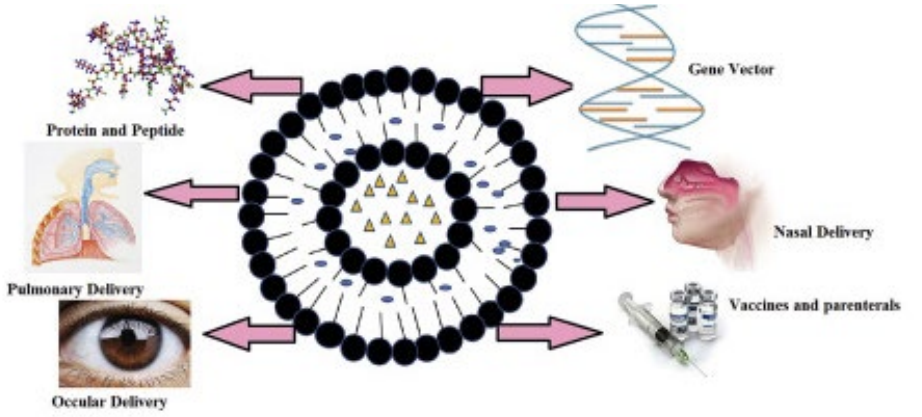


Figure 12. Applications of Niosomes [7].

10.1. For Transport of Therapeutic Agents

As a typical vesicle, niosome consists of an amphiphile which is used to form vesicles, such as an uncharged surfactant (span 60), cholesterol, and an anionic surfactant in small amounts. These vesicles are stable in nature and can be used to encapsulate a variety of drugs. Niosomes are excellent carriers of drugs. They can be used to carry the drugs to the target site and prevent them from biological environment. Many drugs, such as Rifampicin, Gatifloxacin, Acyclovir, Fluconazole, and Griseofulvin are loaded in the niosomes and used for therapeutic purposes. They have enhanced oral bioavailability, targeted effects, and sustained release for

long periods of time after their oral administration. One of the approaches to achieve localized therapeutic action by a drug is through using niosomes. This is because they have reduced tissue penetrability that keeps the drug agents localized at the specific site [19]. Some marketed formulations of niosomes have been discussed in Table 3.

Table 3. Some Marketed Formulations of Niosomes [54]

Brand	Name of The Product
Lancome - Foundation & Complexion	Flash Retouch Brush on Concealer
Helena Rubinstein - HR - Golden Beauty - Body Care	Golden Beauty After Sun Soothing Moisturizer 150ml
Lancaster - Suractif - Night Care	Suractif Non-Stop Lifting Advanced Night Cream 50ml
Givenchy - Blanc Parfait - Day Care	Blanc Parfait W4-L Universal Brightening Spots Corrector SPF 45 1.6ml
Guinot - Night Care	Deep Action Whitening Serum 30ml

10.2. Drug Targeting

Another useful aspect of niosomes is their drug targeting ability. They can help in delivering the drugs specifically to the Reticulo-endothelial System (RES) which takes up niosomal vesicles. Opsonins are the molecules that control the uptake of niosomes by marking them for clearance. The tumors that metastasize to organs, such as spleen and liver, can be treated by localizing of drugs. In addition to targeting the drugs to RES, niosomes can also aid in targeting therapeutic agents to other organs. Antibodies can be attached to niosomes as a carrier system [55]. Certain drugs are delivered as niosomes for targeted delivery to brain, such as Vasoactive intestinal Peptides [14].

10.3. Pulmonary Delivery

The asthmatic patients require an inhalation therapy frequently but they encounter difficulty due to drug's limited penetration through the mucus membrane (hydrophilic). Terzano et al. introduced a solution to this problem by developing niosomes of beclomethasone dipropionate in the presence of polysorbate 20 for pulmonary drug delivery in the patients

suffering from COPD. Four observations were made related to this development which included enhanced mucosal permeation, amplified therapeutic action, targeted delivery, and sustained effect of the drug [56].

10.4. Targeting of Bioactive Agents

Niosomes can also be used to deliver bioactive components to various parts of the body. They can target these components to different organs or tissues of the human body. Additionally, RES can be targeted by means of niosome formulations. For instance, hemoglobin is an iron-containing protein molecule that transports oxygen to the tissues. They can carry a red blood cell protein that is a transporter of oxygen to the tissues and carbon-di-oxide back to the lungs. Since the niosome vesicle can permeate oxygen, it is a good candidate to deliver hemoglobin in patients suffering from anemia [57].

10.5. Anti-neoplastic Treatment

Anti-neoplastic drugs are therapeutic agents that are effective against cancer [28]. Niosomes can be a good choice of entrapment of these drugs because they can provide a prolonged circulation of these drugs by altering their metabolism and half-life in turn, reducing the harmful side effects. Niosomes can be used for diagnostic purposes, such as they can carry iobitridol which is used in X ray imaging [58]. They can be used to treat tumors as they have been found to reduce the proliferation rate of the tumor. Moreover, they are also helpful to decrease the adverse side effects occurring from the tumor medications. Literature shows that drugs have been evaluated experimentally including vincristine, methotrexate, daunorubicin HCl, bleomycin, and doxorubicin [59].

10.6. Leishmaniasis

Studies have reported that niosomes can be used to administer the drugs for leishmaniasis in higher levels without causing side effects, thus allowing greater efficacy in the disease treatment. An anti-leishmanial drug known as ‘Sodium stibogluconate’ has also been loaded into niosomes which has shown lesser side effects, low doses, and improved efficacy in the anti-leishmanial therapy [60].

10.7. Delivery of Peptide Drugs

Different barriers, such as reduced epithelial permeability, pH gradients, and presence of proteolytic enzymes hinder the transport of proteins and

peptides, after administering drug by oral route, to the systemic circulation. An example is that of the niosomal formulation of recombinant human insulin which is a protein. The niosomes in the formulation were based on alkyl ethers. The *in-vitro* evaluation showed that the entrapment of insulin in niosome vesicle protected it from proteolytic enzymes, such as trypsin, pepsin, and a-chymotrypsin. The use of Brij 92/cholesterol in niosomes provided higher level of protection and the insulin released over a period of 24 hours was 26% in simulated intestinal fluid. These studies show that niosomes are a good choice for the sustained delivery of the oral dosage forms containing peptides and proteins [61].

10.8. Treatment of HIV-AIDS

Niosomes have also found applications in the treatment of viral diseases, such as HIV and AIDS. A drug commonly used for AIDS treatment, that is, Zidovudine, encounters obstacles, such as low potency and toxic effects. These problems can be solved by encapsulating this drug in the niosome vesicles. Various studies have suggested that zidovudine loaded in the niosomes can reduce toxicity, provide sustained release, and can be more efficient in AIDS therapy [18].

10.9. Vaccine and Antigen Delivery

Niosomes also have a superior effect in the preventive medicine, such as in the delivery of vaccines or antigens. Immuno-stimulatory characteristics have been seen in several surface-active agents and can be employed in immunology as vaccine adjuvants. 1-monopalmitoyl glycerol, cholesterol, and dicetyl phosphate used in a ratio of 5:4:1 for the preparation of niosomes can act as adjuvants. These niosomes were evaluated in mice by ovalbumin or a T-cell epitope containing peptide subcutaneous injection and bovine serum albumin [62]. Various surface-active agents also show immune stimulatory properties and may act as vaccine adjuvants. Therefore, it can be concluded that niosomes are a good carrier for vaccine which plays a significant role in immunization [63]. Niosome-based clorpheniramine gel has been used to treat mild allergy issues [64].

10.10. Transdermal Delivery

Some novel types of transdermal deliveries by vesicles are elastic niosomes and transfersomes. Out of these two systems, elastic niosomes provide the benefit of low manufacturing cost. Diclofenac diethylammonium containing elastic niosomes have been developed for the

topical delivery of analgesics and for no-invasive therapy of inflammation. Designs and modifications are made to formulate elastic niosomes with better penetrating properties [65]. A study conducted by Bayindir in 2015 investigated the use of paclitaxel-loaded niosomes as targeted drug delivery systems. The current study contrasted the delivery of this drug through niosomes with conventional formulations. The results illustrated that the niosomal delivery amplified the pharmacokinetic properties and tissue distribution of this drug, thereby enhancing its effectiveness [66].

10.11. Enhancement of Bioavailability

Niosomes have been found to play an effective role in increasing the bioavailability of drugs, such as Acyclovir, entrapped in niosomes prepared through fil hydration method show increase in bioavailability. A significant increase in griseofulvin bioavailability has been seen after the encapsulation in niosomes. Other studies have also showed that niosomal formulations of drugs, such as fluconazole, levofloxacin, cefixime, and doxorubicin enhance their bioavailability [49]. A research conducted by Vadlamudi. et al. in 2014 also showed an improvement in the bioavailability and pharmacokinetic profile of glibenclamide using niosomes [67].

10.12. Diagnostic Imaging

Niosomes are used in diagnostic imaging nowadays. Gadobentane niosomes are also used in diagnostic imaging these days [68]. Another study on the in-vivo effects of iopromide radiopaque niosomes has also been conducted. The study determined that iopromide niosomes concentrated on kidney when administered intravenously. Iobitridol, another diagnostic agent, used for X-ray imaging has been proved to be efficient when encapsulated in niosomes. Niosomes have the capability to contain diagnostic imaging agents, ensuring stability and controlled discharge of the imaging payload. This controlled discharge has the potential to improve imaging contrast and extend the duration of imaging [69].

11. COMPARISON OF NIOSOMES WITH LIPOSOMES

The following Table shows comparison of Niosomes with Liposomes:

Table 4. Comparison between Liposomes and Niosomes [12]

Parameter	Niosomes	Liposomes
Chemical Stability	Very good	Low

Parameter	Niosomes	Liposomes
Compound Purity	Good	Variable
Size	10-1000nm	10-3000nm
Structure	Uncharged single-chain surfactant	Double-chain Phospholipid
Stability	More stable	Instable even at room temperature
Biodegradable	Yes	Yes
Half Life	Long	Limited
Toxicity	Low	Low
Cost	Low	High

11. CLINICAL TRIALS OF NIOSOMES

The Table in the following figure overviews some of the clinical trials of Niosomes:

Disease	Caused by	Loaded drug	No of pts	Niosome preparation method	Outcome
Androgenetic alopecia	A variety of factors related to the actions of hormones	Aminexil	40	Hydration of the lipid film	In the hair growth formulations industry, niosomes can be employed as stable carriers for aminexil delivery, and niosomal aminexil is more therapeutically effective than traditional aminexil solution.
Acute cutaneous leishmaniasis	Leishmania parasite	Zinc sulphate (Plus, weekly treatment with intralesional Glucantime)	64	Hydration of the lipid film	Patients with leishmaniasis who do not have access to cryotherapy or do not respond to the standard protocol (cryotherapy plus intralesional Glucantime) can receive niosomal zinc sulphate and intralesional Glucantime as an alternative or second-line treatment because these methods are equally effective. The application of niosomal zinc sulphate is also painless and free of skin necrosis dangers.
- (Applied in healthy volunteers)	- (Applied in healthy volunteers)	Melatonin	14 healthy volunteers.	Sonication method	Topical administration of the melatonin niosomes (MN) gel leads to a substantial prolonged systemic delivery of melatonin which can be used as a sleep induction agent at daytime.
Verruca vulgaris	Human papilloma virus (HPV)	Zinc Sulphate	60	Hydration of the lipid film	Application of niosomal zinc sulphate beside cryotherapy leads to rapid remission of the lesions, higher percentage of clearance, and has no significant increase in adverse effects.

Figure 13. Clinical Trials of Niosomes [12]

12. CONCLUSION

Niosomes are colloidal vesicular carriers having a structure similar to that of liposomes. Thus, they can be seen as an alternative to liposomes. Niosomes are extensively applied in various DDS due to their unique and attractive properties. They have the ability to encapsulate various kinds of therapeutic agents, that is, drugs. Thus, they act as reservoirs for drugs. The technology utilized in the formulation of niosomes is developing progressively and is already showing promising results in different fields including treatment of cancer and other infectious diseases. Various cosmetic products are produced as niosomal delivery systems. Other fields in which niosomes can be used include ophthalmic, parenteral, and topical targeted drug delivery.

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