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# NIOSOMES: A NOVEL DRUG DELIVERY SYSTEM

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**Keywords:**

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**ABSTRACT:** Drug-delivery systems designed for specific targets allow drugs to be precisely delivered to areas affected by diseases. Various carriers are used to deliver drugs, including immunoglobulins, serum proteins, synthetic polymers, liposomes, niosomes and microspheres. In the last decade, there has been a considerable amount of interest directed towards the advancement of surfactant-based vesicles (known as Niosomes) for the purpose of improving drug delivery. Niosomes are self-assembled vesicular nanocarriers that are produced when cholesterol, non-ionic surfactant, or other amphiphilic compounds are hydrated & having a range of applications, including brain-targeted delivery and cutaneous delivery. Similarly to liposomes, niosomes can carry lipophilic and hydrophilic cargoes due to their bilayer structure. A vast number of research articles have been published on their manufacturing methods and applications in pharmaceuticals and cosmetics. Furthermore, niosomes may be created using simple procedures, need lower production costs, and are viable for extended periods of time, thus eliminating the fundamental limitations of liposomes. This review provides an overview of the present status of niosomal research, including the development of niosomes, various types of niosomes, the physical analysis of niosomes, and current usage in the pharmaceutical industry.

**INTRODUCTION:** A system of drug delivery involves delivering pharmaceutical compounds at specific rates to produce a therapeutic effect in humans or animals at weakened sites while decreasing the concentration of the medication in surrounding tissue [1]. There are some significant challenges associated with conventional drug delivery systems, including unfavorable pharmacokinetics and distribution, which can lead to undesirable side effects.

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The reticuloendothelial system can degrade drugs in the blood circulation, while inadequate drug uptake can reduce their effectiveness.

Over the past decades, nanocarriers have been extensively investigated to due to their following benefits over conventional drug delivery systems: (a) they enable targeted drug delivery to the sick location; (b) they increase absorption, as surface area increases, increasing bioavailability; (c) they optimize the way drugs are processed and distributed in the body, resulting in improved pharmacokinetics and bio-distribution; and (d) they prolong the drug's effectiveness by increasing its retention within biological systems. For effective nano drug delivery systems, the ultimate goals are: formulation using biodegradable ingredients;

attaining the desired delivery to the diseased spot without interfering with the organs or healthy tissues around; no early release (premature or burst release); loading system cells with enough high-dose medications to provide the intended therapeutic impact; prolonged period of time for a controlled medication release so that dose not exceed recommended safe dosage and patient compliance. Out of the various drug delivery systems available, niosomal delivery systems successfully accomplish most of the objectives mentioned above [2].

In the year 1909, Paul Ehrlich introduced the idea of delivering treatment specifically to the affected cell, while leaving the healthy cells unharmed. This method has been referred to as the "MAGIC BULLET" ever since. Various drug carrier systems, such as immunoglobulins, serum proteins, synthetic polymers, liposomes and microspheres have been produced since then. Liposomes and niosomes are two of the most well-documented vesicular drug delivery systems in these systems [1]. The niosome is a vesicle composed mainly of non-ionic surfactants and, in many instances, cholesterol (CHOL). As a result of its unique structure, niosomes can encapsulate both hydrophilic and lipophilic substances. Hydrophilic substances can be entrapped in vesicular aqueous core so adsorbed on bilayer surfaces while lipophilic substances are encapsulated by partitioning into the lipophilic domain of the bilayer.

In recent times, Niosomes have gained significant attention as potential vehicles for delivering drugs through various routes of administration. They have emerged as prominent vesicles amidst all vesicular systems. Niosomes possess numerous advantages compared to other drug delivery systems, making them highly valuable for a wide range of applications. One notable benefit of niosomes is their capability to encapsulate various drugs, genes, proteins, and vaccines [3].

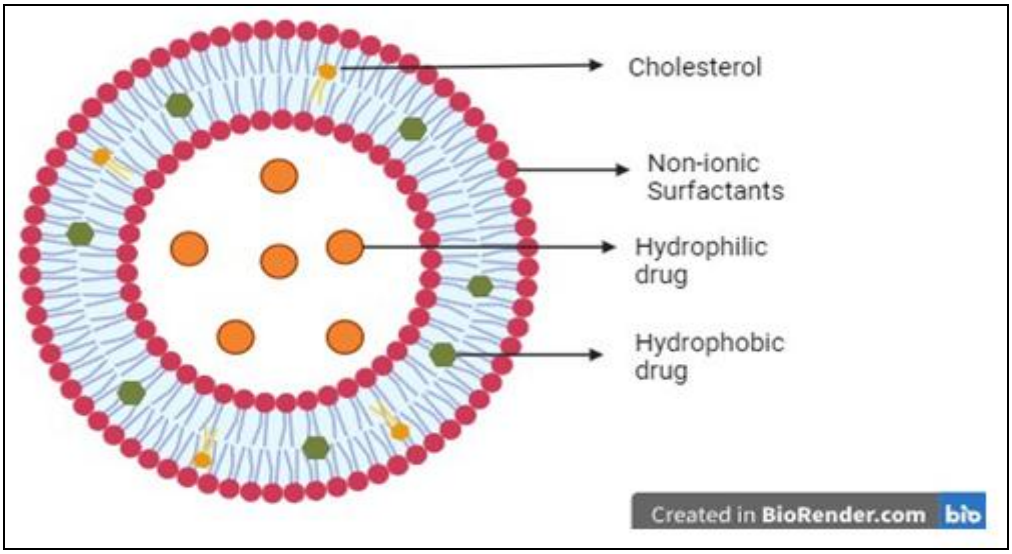



**FIG. 1: NIOSOME STRUCTURE "CREATED BY BIORENDER.COM" (SOURCE: PERSONAL COLLECTION)**

**Advantages:**

1. In comparison with liposomes, niosomes have a longer storage life and are osmotically active and chemically stable.
2. Patient compliance is higher than that of alternative delivery systems.
3. In order to achieve the desired effect, only a small amount of medicine is needed.
4. The drug is gradually and consistently released as a depot formulation.
5. This drug is not affected by first-pass metabolism or gastrointestinal degradation.
6. Due to their non-ionic nature, they are highly compatible with biological systems and are low in toxicity.
7. Niosome scan be administered intravenously, topically, or orally.
8. Various types of drugs, including hydrophilic, lipophilic, and amphiphilic, can be incorporated into niosomes.

9. Continuous and controlled release of the drug is possible.
10. They have the ability to enhance the absorption of medication through the skin, which is made possible by their extended release from the bloodstream [4-9].

❖ **Disadvantages:**

- The process is time consuming.
- Specialized equipment is needed for processing
- Limited shelflife
- Cohesion
- Compilation
- Drug leakage from vesicles
- Encapsulated drugs undergo hydrolysis [10-12].

**Types of Niosomes:** Niosomes are classified as Small unilamellar vesicles (SUV), large unilamellar vesicles (LUV), or multilamellar vesicles (MLV) based on their size and number of layers [13].

**Small Unilamellar Vesicles (SUV):** SUVs come in various sizes, ranging from 10 to 100 nm, and can be manufactured through methods such as high-pressure extrusion, sonication or high-shear homogenization. SUVs have a tendency to combine and are not thermodynamically stable. Additionally, they have limited entrapment efficiency for hydrophilic drugs [14].

**Large Unilamellar Vesicles (LUV):** LUVs, with a size ranging from 100 to 1000 nm, possess a significant amount of water in relation to surfactants. These niosomes can be created through various methods like the transmembrane pH gradient technique (known as remote loading), reverse phase evaporation, heating, solvent injection, dehydration, and rehydration processes. Due to the minimal utilization of non-ionic surfactants, LUVs are a highly effective option for producing them on a large scale [15].

**Multilamellar Vesicles (MLV):** MLVs range in size across 0.5 to 10 µm, with individual bilayers encapsulating the aqueous medium. MLVs are the most often utilized niosomal carriers with sufficient mechanical stability, perfect for embedding lipophilic bioactive chemicals via a simple manufacturing procedure [16].

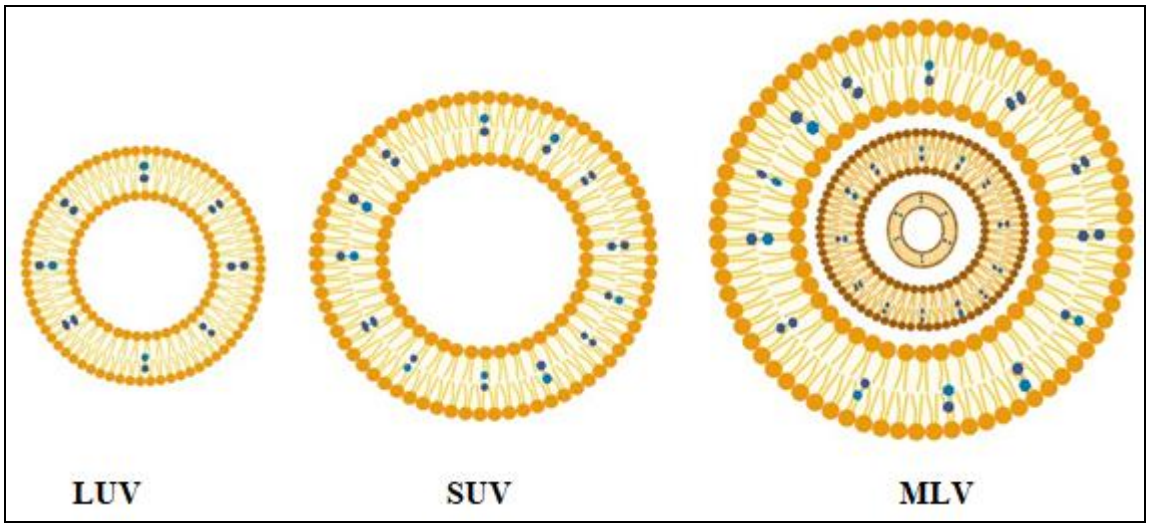



**FIG. 2: NIOSOMES ARE CLASSIFIED ACCORDING TO THEIR NUMBER OF LAYERS AND SIZE, i.e., SMALL UNILAMELLAR VESICLES (SUV), LARGE UNILAMELLAR VESICLES (LUV), MULTILAMELLAR VESICLES (MLV).** "Created by Biorender.com" (Source: Personal Collection).

Additionally, niosomes are classified based on the type of non-ionic surfactant and other ingredients used in their production, as well as their diverse medical uses [17].

**Proniosome:** These preparations are water soluble, dry powders that have been surfactant coated. At the moment of their use, these substances are replenished with water, which helps to address the drawbacks of niosomes such as clumping, leakage of therapeutic substances, and vesicle fusion [18].

**Aspsome:** A mixture of cholesterol, ascorbyl palmitate (ASP), and other lipids with a greater negative charge, like diacetyl phosphate, is used to produce these vesicles. This formulation serves to

increase transdermal medication administration and minimizes the adverse effects generated by reactive oxygen species (ROS) [19].

**Bola Niosomes:** The niosomal preparations have been formulated by combining Bola surfactants α, ω-hexadecyl-bis-(1-aza-18-crown-6) (Bola C16) with span 80 and cholesterol. These preparations are commonly utilized to improve permeability in the delivery of drugs through the skin [20].

**Discomes:** These MLVs are created by combining Solulan C24, a type of cholesteryl poly-24-oxyethylene ether, with a small quantity of cholesterol. These mixtures are utilized to produce a controlled release formula for delivering medicine to the eyes. The size of these formulations can vary from 11 to 60 μm [21].

**Elastic Niosomes:** Elastic niosomes have the ability to be flexible without destroying their structure, and they pass through pores smaller than their size. The vesicles consist of nonionic surfactants, water, and ethanol. Because of their structural flexibility, they can more effectively penetrate layers of intact skin [22].

**Components of Niosomes:** The formulation, pharmacokinetic behavior, and use of drug-loaded niosomes are all influenced by the composition of the niosomes. Generally speaking, a niosome is made up of lipids like cholesterol, charge- inducing substances, and non-ionic surfactants. These components are generally harmless and biocompatible [23].

**Non-ionic Surfactants:** The basic components needed to prepare niosomes are non-ionic surface-active compounds. These molecules have a non-polar tail and a polar head, making them amphiphilic. These uncharged surfactants are less harmful and more stable than anionic, cationic, and amphoteric surfactants. These non-ionic surfactants, have various types of functions, such as reducing hemolysis and inflammatory responses to the surfaces of cells, enhancing the ability to pass through, and enhancing the ability to dissolve. They can also inhibit p-glycoprotein. Research has documented the application of non-ionic surfactants in cardiovascular, HIV protease inhibitor, anticancer, and steroid medications with enhanced absorption and targeting. Non-charged non-ionic surfactants have the potential to be employed in drug delivery systems, offering a means to achieve sustained release in terms of rate, duration, and location. Key parameters influencing entrapment efficiency (EE) include the critical packing parameter (CPP), gel liquid transition and hydrophilic-lipophilic balance (HLB). Research has shown that an increase in HLB levels will result in longer alkyl chains and larger vesicles. It has been noted that HLB values between 14 to 17 are not considered ideal, while an HLB value of 8 resulted in the maximum EE. For example, the use of a surfactant with a low HLB value has the potential to enhance the EE of a lipophilic drug. One more important component in EE is the phase transition temperature. Span 60 is a biodegradable surfactant that offers excellent EE because to its high transition temperature [24-29].

**Cholesterol:** It is commonly recognized that cholesterol (CHOL) interacts with non-ionic surfactants to affect the shape and physical characteristics of niosomes. A number of surfactants only (up to 30–50 mol %) generate vesicles upon the addition of CHOL. The HLB value of the surfactants indicates how much CHOL is needed. In order to offset the impact of the bigger head groups on the critical packing parameter (CPP), the CHOL concentration must be increased as the HLB value rises over 10 [13]. Niosomes are frequently prepared by combining cholesterol and a non-ionic surfactant in a 1:1 M ratio. Cholesterol can impact medication absorption effectiveness, membrane permeability and stiffness, stability, storage conditions, toxicity, and the capacity of dried niosomes to be rehydrated. Cholesterol not only prevents the medications from degrading too quickly but also blocks undesirable pharmacological and immunological consequences. However, the kind of non-ionic surfactant used will determine this effect.

Cholesterol may increase the hydrophobicity of bilayers, resulting in a decrease in surface free energy. There are two general impacts of cholesterol- in liquid-state bilayers, cholesterol improves chain order; in gel-state bilayers, cholesterol decreases chain order. Because cholesterol slows down the release of the material it encapsulates and so slows down the rate of breakdown, it makes bilayers more rigid. The

charge in multilamellar vesicles raises the interlamellar distance between succeeding bilayers, which in turn increases the volume of the entrapped material. Additionally, the niosome vesicle structure can be impacted by cholesterol. By creating hydrogen bonds between its hydroxyl groups and the alkyl chains of surfactant molecules, cholesterol increases the stability of bilayers. As a result of these interactions, bilayer acyl chain movement is restricted and membrane cohesion is enhanced. By altering the flexibility of chains within bilayers, it enhances the stability of vesicles by elevating their transition temperature [30-33].

**Hydration Medium:** Hydration medium is a synthesis medium is required for the Production of niosomes in addition to the previously listed ingredients. Niosome synthesis requires hydration, and phosphate buffer is frequently used since it can help with both drug loading and niosome synthesis. As well as the composition and hydration conditions of the medium, including pH, temperature, and the duration of niosome nanoparticle entrapment, niosome nanoparticles are affected by the size, distribution, and entrapment efficiency.

The medium's pH level is essential to the drug encapsulation process as well as the synthesis process. The solubility of the drugs being encapsulated dictates the applied pH of the buffer; it has been reported that phosphate buffer at pH 7.4 produces stable vesicles with tiny particles. Studies have shown that the media volume and duration of hydration can also affect the final properties of drug-loaded niosomes, such as drug leakage and entrapment efficiency. It is clear that more acidic environments typically result in increased drug release, while longer hydration durations lower niosome size, increase entrapment efficiency, and increase stability [34-37].

**Methods of Preparation:**

**Reversed Phase Evaporation Method [REV]:** The method involves dissolving surfactant and cholesterol in an organic solvent (e.g., chloroform and ether), followed by adding an aqueous solution of the drug. To create an emulsion, the two immiscible phases are homogenized and sonicated. subsequently the organic phase is removed at a lower pressure, resulting in the formation of large unilamellar niosomes distributed throughout the aqueous phase [38].

**Ether Injection Method:** In this method, a mixture of surfactant and cholesterol is dissolved in diethyl ether and gradually inserted (0.25ml per min) through a 14-gauge needle into a beaker filled with an aqueous solution consisting of phosphate buffer saline pH 7.4, in which required amount of drug were dissolved which maintained at 60 °C. Large unilamellar vesicles are usually formed after the organic solvent evaporates [39].

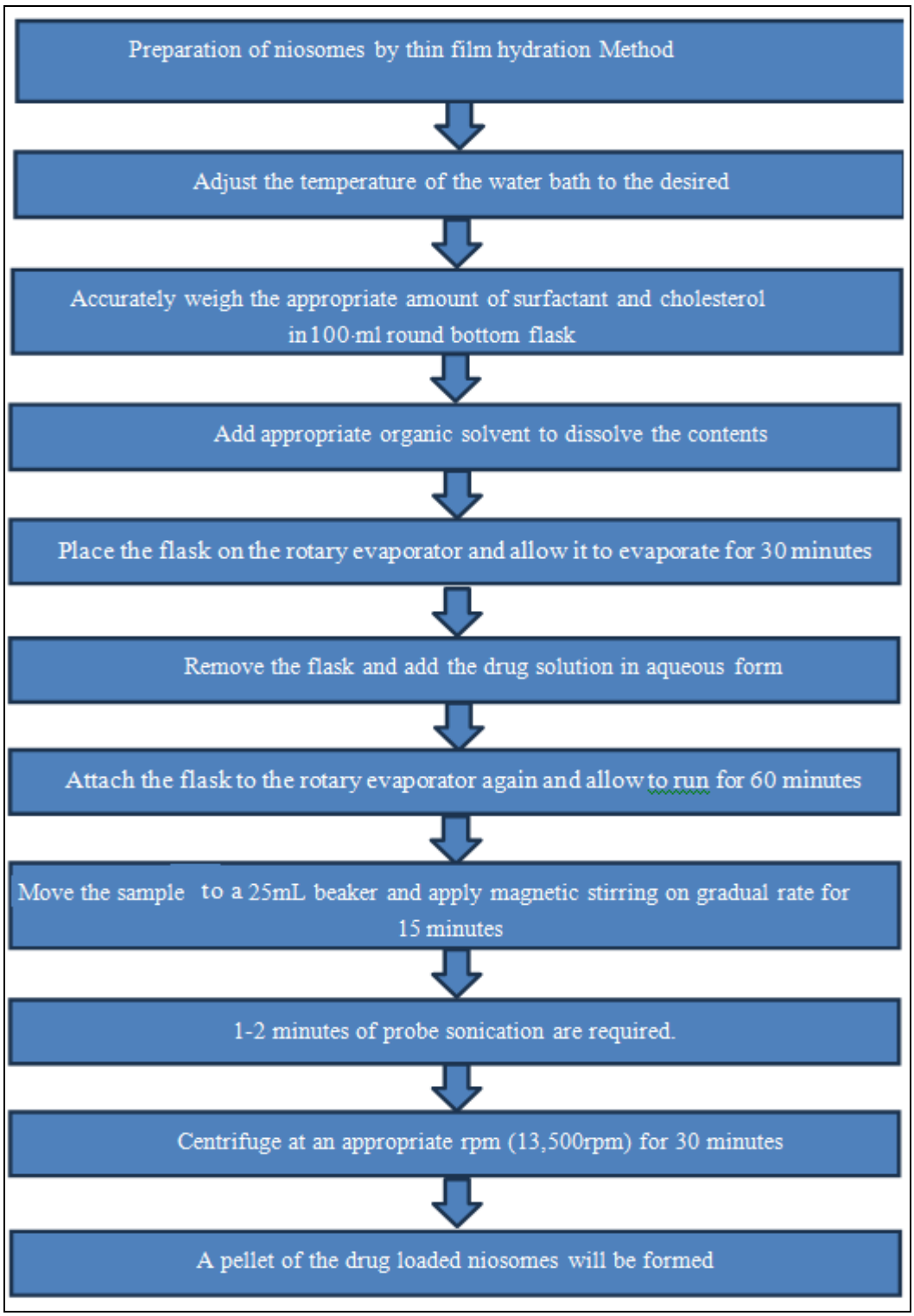
**Hand Shaking Method:** Thin-layer hydration is a similar technique that follows. Hereby, an organic solvent is used to dissolve surfactants, cholesterol, and other lipophilic ingredients. As the organic solvent evaporates, a thin layer form, upon hydration and mild mechanical shaking, a milky mixture containing niosomes is formed [13].

**Micro Fluidization:** This method is based on the submerged jet principle, which describes how two fluidized streams interact in microchannels inside the interaction chamber at extremely high velocities. A shared front between thin liquid sheet impingements ensures that energy supplies in the niosome formation area stay consistent, leading to the development of niosomal vesicles that are more uniform, smaller, and more reproducible [4].

**Sonication Method:** The drug-containing buffer solution is first added to a glass vial containing a mixture of surfactants and cholesterol. To produce niosomes, the mixture is then probe-sonicated using a titanium probe sonicator for three minutes at 60 °C. It is possible to create unilamellar vesicles in addition to multilamellar vesicles (MLVs) [13].

**Thin-film Hydration Method:** The method of thin-film hydration is a simple approach frequently employed in the creation of niosomes. In this process, a mixture of surfactant and cholesterol, which are substances that help form membranes, is dissolved in an organic liquid in a round-bottomed flask attached to a rotary evaporator. The organic liquid is then evaporated, leaving behind a thin, dried film on the flask's bottom. Afterwards, water or buffer is introduced to the film at a temperature higher than the transition temperature of the surfactant.

It is then agitated gently for a set amount of time to create multilamellar vesicles. These vesicles can be further processed by sonication to produce unilamellar vesicles. Aqueous or organic phases are used to dissolve the drugs to be encapsulated, depending on their solubility. Sonication is typically used after this procedure to enable the creation of niosomes with a uniform size distribution [38].




**Characterization of Niosomes:**

**Vesicle size and Shape:** Niosomal vesicles are assumed to have a spherical form, and the laser light scattering method can be used to measure their mean diameter. The diameter of these vesicle scan also be ascertained by electron microscopy,

optical microscopy, molecular sieve chromatography, ultracentrifugation, photon microscopy, and freeze fracture electron microscopy. Frozen thawed niosomes have larger vesicles, which could cause vesicle fusion during the cycle [40].

**Zeta Potential:** The surface charge, commonly referred to as the zeta potential, offers crucial information about the physical stability of niosomes. The laser doppler anemometry technique allows for the measurement of surface potential, while the zeta potential magnitude indicates the level of electrostatic repulsion between neighbouring particles. Niosomes that exhibit a zeta potential more than +30 mV or less than −30 mV is deemed to possess satisfactory stability [2].

**Encapsulation Efficiency (EE):** The percentage of drug captured within niosomes is known as the entrapment efficiency. By using the provided equation (indirect evaluation of the entrapment efficiency), it is possible to calculate the amount of free drug in the supernatant after centrifuging the loaded niosomal solution.

Entrapment Efficiency % = $Total\ amount\ of\ initially\ added\ drug - Untrappeddrug / Total\ amount\ of\ initially\ added\ drug$ X 100

As an alternative, niosomal membranes can be Break by organic solvent (such as methanol) or Triton™ X-100, releasing the drug that has been entrapped. A spectrometric detection can then be made at relevant λ max [38].

**Stability Study:** The stability of niosomes can be assessed by measuring mean vesicle size, size distribution, and entrapment efficiency. This assessment is conducted by observing the niosomal suspension under different temperature conditions. Niosomes are sampled periodically throughout storage, and UV spectroscopy or HPLC techniques are used to determine the amount of medication retained in the niosomes [41].

***In-vitro* Release:** The dialysis membrane technique is commonly used in *in-vitro* release investigations. In this method, a little amount of niosomes is placed into a dialysis pouch and tightly fastened at both ends. Another beaker with appropriate dissolving medium is kept at 37°C, and the dialysis bag is placed inside and stirred with a magnetic stirrer. At regular intervals, a sample solution is taken from the beaker and replaced with new dissolving medium. The drug concentration in the samples was determined at the given wavelength using UV spectrophotometry [42].

**Number of Lamellae:** The number of lamellae present in niosomes can be ascertained by employing electron microscopy, NMR spectroscopy, or X-ray scattering techniques [43].

**Applications of Niosomes:**

**Targeting of Bioactive Drugs:**

**To Reticulo-endothelial System [RES]:** RES cells have a particular affinity for vesicles. This characteristic can be utilized for the treatment of animal tumors that have spread to the liver and spleen, as well as for the treatment of liver parasitic infestations.

**To Organs Other than RES:** The idea has been put forth that antibodies could be employed by the carrier system to reach specific locations within the body. Immunoglobulin proves to be a practical approach for targeting drug delivery [44].

**For the Treatment of Leishmaniasis:** Leishmaniasis is a condition that arises when the parasite invades cells and the liver. Antimonial drugs are frequently utilized for treatment. A study on mice demonstrated that the effectiveness of sodium stibogluconate in niosomal form was enhanced. Administering two doses on consecutive days had an additive effect. As drug-loaded liposomes, niosomes are also useful in experimental leishmaniasis [45].

**Anti Neoplastic Treatment:** Most antineoplastic medications have serious negative effects. Drug metabolism can be changed by niosomes, which prolongs the half-life and circulation of medications while lowering their adverse effects. Niosomes slow down the growth of tumors and raise plasma levels by delaying clearance [46].

**Study of Immune System:** Niosomes have been employed for the examination of the immune response triggered by antigens. Their ability to selectively target the immune system, along with their minimal toxicity and enhanced stability, make them an ideal choice [47].

**Niosomes as Carrier for Hemoglobin:** Hemoglobin is transported *via* niosomes. Similar to non-capsulated hemoglobin, vesicles are easily permeable to oxygen and can have their hemoglobin curve modified. It is possible to overlay the visible spectrum of niosomal suspension with that of free hemoglobin [48].

**Antibiotics:** Niosomes, which are non-ionic surfactant vesicles, can be utilized to transport a water-soluble local antibiotic for ophthalmic administration. The research focused on Gentamicin sulphate, and the findings indicated that niosomes hold great potential as carriers for the topical use of Gentamicin sulphate in the eyes [49].

**Delivery of Peptide Drug:** Niosomes are being investigated by researchers as a viable means of shielding peptides from peptide breakdown in the gastrointestinal tract. The oral administration of a vasopressin entrap derivative in niosomes was used in an *in-vitro* investigation to show that drug entrapment increases the stability of the peptide [50].

**Transdermal Delivery:** Niosomes were studied for their potential to improve medication penetration and lessen skin irritation through the intact stratum corneum, as well as for use as a transdermal drug delivery method.

Researchers examined the penetration of ketorolac, a strong nonsteroidal anti-inflammatory drug, into excised rabbit skin from different proniosome gel formulations using Franz diffusion cells. The drug penetration and lag time were greatly enhanced by the produced proniosomes [51].

**Cosmetics:** Non-ionic surfactant vesicles were initially reported in relation to cosmetic uses by L'Oreal. In the 1970s and 1980s, L'Oréal invented and patented niosomes. In1987, Lancôme introduced "Noisome," their debut product. In cosmetic and skin care applications, niosomes' capacity to boost the stability of medications that are entrapped, enhance the bioavailability of substances that are poorly absorbable, and improve skin penetration are all advantageous [52].

**CONCLUSION:** Recent years have seen an increase in interest in vesicular drug delivery methods including niosomes and liposomes. It is clear that niosomes seem to be a more preferred drug delivery method than liposomes. Niosomes, which can load both hydrophilic and lipophilic medicines, offer an easy, extended, targeted, and efficient drug delivery mechanism.

Niosomes potential can be increased by the use of innovative loading, modification, and preparation techniques. In conclusion, niosomes are an effective tool for drug administration in the treatment regimen of many diseases and may be able to treat patients more effectively than conventional drug- delivery platforms.

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