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Exploring Niosomes: A Versatile Platform for Targeted Drug Delivery and Therapeutics

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A B S T R A C T

Drug delivery systems are made to move therapeutic agents to certain places in the body where they will work. An effective carrier is a crucial component of these systems because it prevents the drug from degrading too quickly or being removed too soon, increasing its concentration at the intended location. Because niosomes are immunologically innocuous, biodegradable, and biocompatible, they have emerged as effective drug carriers. Niosome is a novel drug delivery system in which drugs are enclosed in vesicles that are made from the self-assembly of non-ionic surfactant and cholesterol in the presence of a hydration medium. More and more scientific papers are saying that niosomes could be a good way to deliver a wide range of drugs. This article highlight the structure, methods of preparation and various applications of niosomes.

Keywords: Niosomes, drug delivery, non-ionic surfactant, controlled release

1. INTRODUCTION

A drug delivery system is the way that drugs are given to people or animals at a controlled rate to have a therapeutic effect at the site of disease while keeping the concentration of the drug low in healthy tissues nearby [1]. In 1909, Paul Ehrlich developed the concept of treating only diseased cells without harming healthy ones. This concept was known as "magic bullet." [2]. Since then, a number of drug delivery systems have been developed, such as immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, and niosomes. [1]. For a long time, researchers have been trying to find new and better ways to deliver drugs than the ones we already have. This goal will keep going until a system is made that works the best for treating people without causing any side effects. A number of drug delivery and targeting systems are being developed right now to lower the risk of drug degradation and loss, avoid side effects, and improve the drug bioavailability and concentration at the target site [4]. Some of these systems use carriers like niosomes, liposomes, and transferosomes [3].

Niosomes are small vesicles made from non-ionic surfactants. They are often mixed with cholesterol or other lipids that help keep them stable to make a bilayer structure. Synthetic surfactants like Span, Tween or polyoxyethylene ethers are used to make niosomes. Compared to other vesicular systems, these surfactants make the chemicals more stable, lower the cost of production, and make the products last longer on the shelf [5]. The bilayer structure happens because surfactants are amphiphilic, which means they naturally group together into unilamellar or multilamellar vesicles when they are in water. Adding cholesterol to the mix makes the membrane more stable, stops water-soluble drugs from leaking out, and changes the vesicle's flexibility and phase properties. Niosomes are especially good at delivering drugs that can be broken down by water or air because they are more chemically stable than regular liposomes [6].

Advantages [7]:

- It gives a prolonged therapeutic effect with fewer side effects.
- Enhances the drug's absorption in the body.
- It provides better patient adherence as compared to other delivery systems.
- The bilayer structure protects the active ingredient from external factors.
- They provide sustained and controlled drug release.
- Prevents the drug from degradation in the gastrointestinal tract and bypasses first-pass metabolism.
- Maintains structural stability even in emulsion form.
- Can be administered through oral, topical and parenteral routes.
- Helps protect the drug from enzymatic degradation.
- Offers multiple administration routes, such as intravenous and oral delivery.

Disadvantages [8]:

- May decrease their shelf life
- Include physical and chemical instability.
- Aggregation or fusion of vesicles
- Leaking or hydrolysis of the encapsulated drug.

2. STRUCTURE AND COMPOSITION OF NIOSOMES

Niosomes are spherical structures formed of non-ionic surfactant and cholesterol.
1. Non-ionic surfactant.
2. Cholesterol.
3. Hydration medium.

1. Non-ionic surfactant:
The absence of charged groups in their hydrophilic head regions is a characteristic of nonionic surfactants. Compared to amphoteric, cationic, or anionic surfactants, they are less toxic, more stable, and have better biocompatibility. Nonionic surfactants, like the Span series (Span 20, 40, 60, 80, and 85) and the Tween series (Tween 20, 40, 60, 80, and 85), are frequently used to prepare niosomes. The niosomal formulations' increased stability and efficacy are facilitated by these surfactants [9]. Nonionic surfactants have been successfully used in the delivery of HIV protease inhibitors, steroids, anticancer agents, and cardiovascular medications, according to studies. This has improved drug absorption and allowed for targeted delivery to particular bodily locations [11].
2. Cholesterol: An essential component of niosome formation is cholesterol. It has a major impact on the vesicle membrane's permeability, stiffness, and entrapment efficiency, among other characteristics. Additionally, cholesterol improves the stability and shelf life of freeze-dried niosomes by improving their capacity to rehydrate. Furthermore, adding cholesterol makes the niosomal formulation more viscous, which reinforces its structural integrity [10]. In addition to safeguarding drugs from premature degradation, cholesterol also helps suppress undesirable immunological and pharmacological responses, thereby enhancing the overall safety and effectiveness of the niosomal formulation [11].
3. Hydration medium:
Along with other necessary components, a hydration medium is necessary for the formation of niosomes. Phosphate buffer is frequently used for hydration, which is an essential step in the synthesis of niosomes. It is a preferred medium in the preparation process because it not only makes niosome formation easier but also helps with effective drug loading [10].

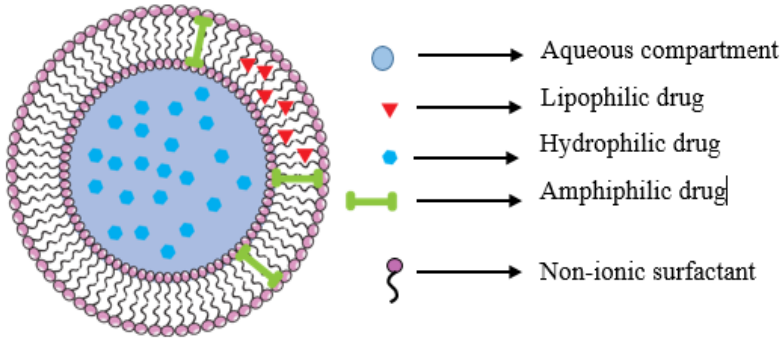

Fig. 1–Structure of Niosomes

3. METHODS OF PREPARATION

Niosomes' vesicle size, size distribution, entrapment efficiency, number of bilayers, and membrane permeability are all directly influenced by their preparation technique. Therefore, choosing the best approach for niosome formulation requires a thorough understanding of these techniques [12]. Numerous methods for niosome preparation have been reported in the literature. These techniques include the bubble method, reverse-phase evaporation, ether injection, thin-film hydration, transmembrane pH gradient drug uptake, and microfluidization [13].

3.1. Thin film hydration method [13]:

One popular and simple method for making niosomes is the thin-film hydration method. This method involves first dissolving cholesterol and surfactants, which act as membrane-forming agents, in an organic solvent inside a round-bottom flask that is connected to a rotary evaporator. Following the solvent's evaporation, a thin layer is left on the flask's interior surface. Multilamellar vesicles are created by adding an aqueous phase (such as water or buffer) to this film at a temperature higher than the surfactant's transition temperature and gently stirring it for a predetermined amount of time. Drugs are added to

either the organic or aqueous phase, depending on how soluble they are. The resulting suspension is usually sonicated to produce unilamellar vesicles with a uniform size distribution.

3.2. Ether injection method:

Surfactant dissolved in diethyl ether is slowly injected into warm water kept at 60°C, this technique enables the creation of niosomes. A 14-gauge needle is used to introduce the surfactant solution into the aqueous phase. Single-layered vesicles are created when the ether evaporates. Depending on the particular conditions used during the process, the final vesicles' sizes can range from 50 to 1000 nm [14].

3.3. Sonication method:

A widely used technique for creating vesicles is sonication. This method involves combining a surfactant and cholesterol mixture with a portion of the drug solution made in buffer in a 10-ml glass vial. After that, a titanium probe is used to subject the mixture to probe sonication at 60°C for three minutes, which causes niosomes to form [15].

3.4. Micro-fluidization method:

The principle of this method is based on the submerged jet principle, which produces small, uniform unilamellar niosomes. This process uses pneumatic pumps to force the aqueous and lipid-dispersed phases through a membrane and pressurized vessel at high pressure and velocity. The two streams collide inside the pressurized vessel's continuous micro-channel, producing a uniform pressure profile and intense turbulent mixing. The method has a number of benefits, including increased production output, reduced vesicle size, enhanced uniformity, and high aqueous phase encapsulation efficiency. However, because of the high pressure inside the interaction chamber, there is a chance that lipids will degrade [16].

3.5. Bubble technique:

This unique one-step process eliminates the need for organic solvents and prepares niosomes, especially large unilamellar vesicles. In this method, a three-neck round-bottom flask is filled with cholesterol, a buffer solution, and a nonionic surfactant. A thermometer and a water-cooled reflux system are used to carefully control the temperature, and the third neck is used to introduce nitrogen gas. The mixture is subsequently placed in a water bath that is kept at 70°C, which causes niosomes to form [17].

4. CHARACTERIZATION OF NIOSOMES

4.1. Vesicle size:

Niosomal vesicles are generally spherical in shape, and their average size can be determined using several analytical methods. Electron microscopy, ultracentrifugation, molecular sieve chromatography, laser light scattering, optical microscopy, freeze-fracture electron microscopy, and photon correlation spectroscopy are methods for determining the size of niosomes [18].

4.2. Size Distribution:

Polydispersity, or simply dispersity as IUPAC recommends, is the variation in particle size within a distribution. Using two fitting parameters, the Polydispersity Index (PDI), also known as the Heterogeneity Index, is a numerical value obtained from the cumulants analysis of correlation data. Because this measurement is scale-free (dimensionless), systems with PDI values less than 0.05 are usually highly monodisperse [19].

4.3. Osmotic Shock:

Osmotic studies can be used to assess changes in vesicle size. This technique involves incubating niosomal formulations for three hours in hypotonic, isotonic, and hypertonic solutions. Optical microscopy can be used to observe any changes in vesicle size following incubation [20].

4.44. Stability studies:

By examining metrics like average vesicle size, size distribution, and entrapment efficiency, one can evaluate the stability of niosomes. The niosomal suspension is stored at various temperatures, and samples are taken at predetermined intervals to perform this assessment. Next, high-performance liquid chromatography (HPLC) and UV spectroscopy are used to measure the amount of drug retained within the niosomes [9].

4.5. Entrapment Efficiency:

Centrifugation was used to assess the drug-loaded niosomes' entrapment efficiency. A 1.5 ml Eppendorf tube containing 1 ml of the niosomal dispersion was centrifuged at 17,000 rpm for 30 minutes at 4°C in order to extract the unentrapped medication. Following centrifugation, the drug-containing supernatant was extracted, diluted with PBS, and examined with a UV spectrophotometer [21].

Entrapment efficiency = (Total amount of drug – The amount of drug in supernatant liquid) / Total amount of drug × 100

4.6. Zeta potential:

Instruments like a Zetasizer and dynamic light scattering (DLS) can be used to measure the surface zeta potential of niosomes. Niosome stability and behavior are strongly influenced by their surface charge. The niosomes having charge either positive or negative on their surface are more stable and agglomeration-resistant than uncharged vesicles [22].

5. APPLICATIONS OF NIOSOMES

Pharmaceutical applications:

1. Anticancer drug delivery:

Chemotherapy is frequently used as the standard treatment for cancer. However, the limited penetration of tumor tissues and the detrimental effects on healthy cells limit the effectiveness of many anticancer medications. Researchers have looked into different approaches to deal with these issues, like using niosomes as a cutting-edge system for delivering drugs. [22].

1.1 Breast cancer:

When compared to their free drug forms, niosomal formulations of anticancer medications like 5-FU, cantharidin, and tamoxifen have shown noticeably improved cytotoxicity, cellular uptake, and antitumor efficacy. These studies demonstrate how niosomes may enhance cancer treatment by boosting therapeutic efficacy while lowering dosages and minimizing adverse effects [23].

1.2 Ovarian cancer:

Hexadecyl diglycerol ether (C16G2) and Span 60 were used by Uchegbu et al. to create doxorubicin-loaded niosomes. The Span 60 niosomal formulation demonstrated a slight improvement in overcoming drug resistance when tested against a human ovarian cancer cell line and its doxorubicin-resistant subline. This was demonstrated by a slight reduction in IC50 when compared to the free drug [24].

1.3 Lung cancer:

When compared to their free drug counterparts, niosomal formulations of pentoxifylline and adriamycin showed improved therapeutic results. While niosomal pentoxifylline dramatically decreased lung tumor nodules, indicating effective drug accumulation at distant metastatic sites, niosomal adriamycin prolonged tumor growth delay in lung cancer models, suggesting improved efficacy. These results lend credence to niosomes' potential to enhance medication delivery and therapeutic efficacy in the treatment of cancer [25].

2. Targeted drug delivery:

Bragagni et al. developed a brain-targeting formulation of niosomal doxorubicin by using a glucose derivative as a targeting ligand. Early rat tests showed promising results for the product, which contains Span, cholesterol, Solulan, and N-palmitoylglucosamine. Compared to the commercial form, the customized niosomes significantly reduced drug accumulation in the heart, prolonged blood circulation time, and enabled effective delivery of doxorubicin to the brain [26].

3. Antibiotic drugs:

When it comes to administering antibiotics and anti-inflammatory drugs, niosomal carriers have demonstrated considerable promise, particularly in terms of improving drug retention and skin penetration. Research has shown that ciprofloxacin-loaded niosomes have enhanced antibacterial activity influenced by cholesterol content and surfactant characteristics, whereas rifampicin-loaded niosomes offer sustained drug release. Gentamicin-loaded niosomes successfully extended drug release in ocular applications; charge inducers, cholesterol, and surfactant type are important formulation elements that affect drug entrapment and release behavior. All things considered, niosomes present a viable strategy for enhancing the therapeutic efficacy and regulated administration of antibiotics [27].

4. Antiviral drugs:

Antiviral drug delivery using niosomes has demonstrated promising results. Using Tween, Span, and cholesterol, Ruckmani and Sankar created zidovudine-loaded niosomes that showed excellent entrapment efficiency and prolonged drug release. Prolonged release was offered by Tween 80-based niosomes, particularly those that contained dicetyl phosphate. However, stability was greatly impacted by storage conditions; over a 90-day period, more drug leakage was seen at room temperature as opposed to 4°C. The significance of formulation and storage parameters in antiviral niosomal delivery was highlighted by pharmacokinetic studies conducted on rabbits, which showed that these formulations were eliminated from the bloodstream in five hours [28].

Applications of Niosomes in Cosmetics:

1. Niosomes for delivery of antioxidant and whitening ingredients:

Ellagic acid (EA) is a very powerful antioxidant but its low permeability and poor solubility limit its use. Studies have investigated the transdermal delivery of EA using niosomal formulations made with Span 60 and Tween 60 in order to get around these restrictions. The niosomal formulation considerably increased EA penetration and distribution within the epidermis and dermis layers when compared to EA in solution form, according to the findings, suggesting better skin delivery potential [29].

2. Niosomes for delivery of anti-aging ingredients:

In a com parison of niosomal formulations with entrapped rice bran and formulations with unentrapped rice bran particles, Manosroi et al. (2012) examined the anti-aging properties of rice bran-based niosomes. The findings demonstrated that these formulations improved a number of skin characteristics, such as hydration, decreased hyperpigmentation, increased elasticity, and improved skin thickness and smoothness. They also helped to prevent skin aging by safeguarding collagen. Interestingly, formulations with both entrapped and unentrapped rice bran were more effective than those with just entrapped ingredients, indicating a potential synergistic anti-aging effect. Niosomes also helped prolong the shelf life of the active compounds when added to gel- or cream-based formulations, which are more stable than unentrapped particles alone. Overall, the study found that niosomes made from rice bran offer substantial synergistic advantages for anti-aging skincare in cosmetic formulations [30].

Applications of Niosomes in Gene Therapy:

The study shows that the recently created niosomal formulation—which is based on a cationic lipid along with polysorbate 80 and squalene—is a promising gene delivery method for retinal therapy. The mixture successfully delivered genetic material in vivo with targeted expression in various retinal layers, demonstrated high transfection efficiency in retinal cells without sacrificing cell viability, and efficiently condensed and protected DNA. These results point to its great potential for non-viral gene delivery in the treatment of inherited retinal disorders [31].

Applications of Niosomes in Ocular Drug Delivery:

1. Treatment of glaucoma:

To increase ocular retention time and boost the bioavailability of this antiglaucoma drug, Jain et al. created a niosomal gel formulation with pilocarpine hydrochloride. Their results demonstrated that the niosomal gel had a 2.64-fold higher bioavailability than the commercially available Pilopine HS gel, suggesting that it has a greater potential for treating glaucoma [32].

2. Treatment of Fungal Keratitis:

Fungal keratitis, also called keratomycosis, is a dangerous corneal infection that can be brought on by contact lens wear, topical corticosteroid use, corneal damage, or long-term ocular surface conditions. Commonly used antifungal drugs include fluconazole, voriconazole, natamycin, and ketoconazole; however, their low bioavailability frequently poses a problem. Elmotasem et al. used a fluconazole–hydroxypropyl-β-cyclodextrin (FL-HP-β-CD) complex encapsulated within Eudragit nanoparticles to study fluconazole-loaded niosomes for ocular drug delivery. The results showed that applying cationic chitosan to the niosomes improved their mucoadhesive qualities, increased corneal permeability, and prolonged the duration of the drug's action, all of which helped to effectively treat fungal keratitis [33].

6. CONCLUSION

Niosomes are an exciting advancement in drug delivery, with the potential to change the way we approach treatments in various fields, including pharmaceuticals, cosmetics, eye care, and gene therapy. Their unique bilayer structure, made from non-ionic surfactants and cholesterol, allows them to effectively encapsulate both water-loving and fat-loving drugs. This capability enhances their stability, bioavailability, and ability to target specific areas in the body. What sets niosomes apart from traditional delivery systems are their impressive advantages, such as controlled release of medication, lower toxicity, and the ability to improve how well patients stick to their treatment plan. Research has shown their effectiveness in treating cancer, addressing eye diseases like glaucoma, and even in innovative cosmetic products. Plus, their potential in gene therapy is particularly promising, as they can efficiently deliver genetic material. While there are challenges to overcome, like scaling up production and gaining regulatory approval, tackling these issues is essential for making niosomes a reality in everyday healthcare. Their ability to reshape drug delivery strategies is incredibly hopeful and could lead to better outcomes for patients everywhere. In summary, niosomes represent a highly promising nanocarrier platform, offering innovative solutions to complex therapeutic challenges and holding great potential for shaping the future of targeted, effective, and patient-friendly drug delivery systems.

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