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Niosome : A Targeted Drug Delivery System.

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A B S T R A C T

Niosomes represent self-assembled vesicles composed of non-ionic surfactants and cholesterol that function as drug delivery systems because they exhibit stability features along with biocompatibility in addition to their ability to encapsulate both hydrophilic and lipophilic drugs [11,13]. These vesicles enhance drug solubility while securing active compounds from deterioration in addition to delivering medications at controlled rates for drawn-out periods [3, 5, 28]. Structural adaptability of niosomes serves to control drug delivery systems which leads to improved therapeutic results together with decreased side effects [17, 21]. The optimized niosome preparations exhibit beneficial characteristics of size distribution and zeta potential along with high encapsulation efficiencies that various production methods including thin film hydration and reverse phase evaporation generate [4, 12]. Cholesterol together with oleic acid as functional ingredients enhances drug delivery membranes by making them rigid and controlling drug release properties [13,27]. The versatility of niosomes extends to various bioactive agents including plant extracts as well as metal nanoparticles and antibiotics and peptides and anticancer agents which demonstrates their wide range of pharmaceutical and cosmetic applications [9, 26,]. Since these structures enhance drug penetration through the skin along with oral absorption they help deliver poorly soluble pharmaceutical compounds [19]. Multiple studies establish that the integration of limonene or fucoidan during functionalization enhances the cells' ability to take in and recognize these delivery systems [39]. The combination of niosomes' lack of immunogenicity and their adjustable surface features makes these vesicles advantageous for transporting vaccines and genes and imaging in medicine applications [53].

Key Words: *Niosomes, Drug delivery systems, Non-ionic surfactants ,Cholesterol , Controlled drug release Biocompatibility, Encapsulation efficiency, Thin film hydration, Reverse phase evaporation, Zeta potential Nanocarriers*

1. INTRODUCTION

New drug delivery techniques have experienced substantial progress during the past decades leading to the development of niosomes as adaptable nanocarriers because of their exceptional

properties and dual-drug compatibility features [10]. The niosomal vesicles consist mostly of cholesterol with non-ionic surfactants which ensures both biodegradability and stability alongside outstanding biocompatibility for various biomedical uses [11].
The extensive drug encapsulation capabilities of niosomes allow them to be suitable for therapeutic applications where clients need solubility enhancement and controlled release and targeted delivery of drugs [22]. Niosome features hold immense importance for drugs which demonstrate low bioavailability while also presenting systemic toxicity issues [19][36][95]. The willingness to modify surfactant-to-cholesterol ratios along with the addition of responsive agents enhances niosome delivery systems through biological barriers such as dermal, transdermal and intracellular ones [23].

Niosomal formulations enhance delivery system performance and therapeutic effects of naturally derived antioxidants and anti-inflammatory agents while stabilizing cosmetic active compounds according to reports [18] and [24]. Niosomal systems act as mediators to enhance established chemotherapeutic agent performance together with minimizing adverse effects through targeted release which reaches cellular or tissue levels. The last point shows that researchers have successfully demonstrated these systems can encapsulate sensitive molecules such as peptides and flavonoids and stem cell modulators which demonstrates their wide range of uses in regenerative medicine and nanotherapeutics.

The production cost efficiency of niosomes makes them better than liposomes since they maintain stability across multiple conditions which results in longer shelf life and enhanced practical use in medical facilities [23]. His structural design flexibility together with high drug-holding capabilities enables niosomes to serve as optimal carriers in combination drug delivery systems needed for multi-faceted pathology management [4].Research extends current documentation about niosomal nanocarrier formulation methods to analyze advanced characterization techniques and their utilization as patient-friendly carriers for safer drug delivery.

2.Methods of Preparation of Niosomes

The synthesis of Niosomes requires various methods which depend on the properties of incorporated drugs combined with designated delivery pathways. The thin film hydration method stands as the standard preparation technique for niosomes by doing solvent evaporation to create a dry lipid film before hydrating it with drug-containing aqueous solution. Multiple layers in vesicular structures can be achieved through this synthesis method while maintaining high drug retention rates per accepted scientific literature [3].
Post-hydration treatment using sonication or probe-tip homogenization generates unilamellar or small multilamellar vesicles that can be employed in parenteral delivery systems according to Researchers optimized niosomal formulations for controlled delivery of anticancer agents through various methods including [9] and others.
The creation of large unilamellar vesicles with higher entrapment volumes requires utilization of the reverse phase evaporation method. The emulsification of surfactant solutions in organic

solvents with water-based drug solutions taken together leads to formation of vesicles which can be obtained through reduced pressure extraction [2]. The technique shows successful application for targeted transport during neurological applications [7].

The microfluidization process has emerged as an industrial-scale procedure because it applies strong shear forces to amalgamate lipids and water phases under precise flow rules to produce stable vesicles with uniform size patterns [10]. The production method demonstrates capability for embedding bioactive peptides and proteins according to research [18]. When performing ether injection, heating the aqueous phase enables a surfactant and cholesterol mixture in ether solution to generate vesicles after solvent evaporation takes place. The production of uniform vesicles can be achieved by using this method since it works well for sensitive therapeutics while maintaining stable product outcomes [14]. The transdermal drug delivery methods that use these methods enable better drug permeation [15, 27]. Bubble method enables the production of vesicles through the dispersion of lipids in an aqueous solution using mechanical agitation combined with nitrogen gas and without requiring harmful organic solvents [8]. The use of this environmentally-friendly method applies to the development of vesicular delivery systems for the eye [23]. Heating of surfactant mixed with cholesterol in liquid water phases above their transition point serves as another method to produce vesicles easily. The manufacturing process uses no organic solvents while producing niosomes which can be used through oral or topical administration routes [5, 10, 16]. Different hydration protocols such as remote loading and pH gradient hydration help researchers increase the encapsulation of hydrophilic drugs which enhances sustained drug release profiles [13, 28,]. Commercial applications of antifungal and antimicrobial therapy delivery commonly utilize these techniques according to [24, 36]. The procedure of spray drying converts niosomal dispersion into powder form to enhance stability while rehydration restarts functionality before use. The method has established its usage in pulmonary delivery systems and oral delivery systems reported in . The drug encapsulation and release features benefit from structural stabilization and size reduction through freeze and thaw cycles which are widely implemented in pharmaceutical applications . Vaccines together with immunological agents benefit from stability enhancements through the use of these techniques . Modern-scale production of vesicles occurs through high pressure homogenization where dispersion forces pass through narrow channels to decrease their sizes and boost production consistency. These methods enable adjustments to niosome characteristics including their number of layers and dimensions as well as drug-trapping efficiency and electrostatic properties making the delivery system beneficial for various biomedical applications [23].

3.Applications of Niosomes

The non-ionic surfactant-based vesicular systems called Niosomes have become highly pursued in multiple fields because they enhance drug and bioactive substance stability and solubility and provide controlled release capabilities. Thanks to their amphiphilic characteristics niosomes can protect both hydrophilic compounds and lipophilic compounds simultaneously making them appropriate for many therapeutic applications. Research shows niosome potential for increasing

the performance and bioavailability of numerous active pharmaceutical ingredients across pharmaceuticals and cosmetics and diagnostics [2][27]

3.1 Drug Delivery Applications

Drug delivery stands as one of the main execution fields for niosomes in present day applications. The vesicular structure of niosomes increases drug delivery systems by allowing both water-soluble and fat-soluble drugs to be incorporated into their structure. Drug-related substances stored within niosomal vesicles gain protective advantages which extend drug stability and increase product shelf life. The controlled release profile of niosomes provides therapeutic benefits by extending drug duration and decreasing patient medicine intake requirements [31]. Niosome-based drug delivery systems become highly beneficial for medications that need sustained-release to achieve peak effectiveness along with medications having a tight therapeutic range. Through controlled drug delivery niosomes provide steady drug release which helps support bloodstream therapeutic levels for more extended treatment durations to enhance treatment results. The drug delivery method achievable with niosomes includes both controlled release functionality and precise delivery systems. The product dimensions and adaptability in surfactant chemistry and targeting features enable niosomal systems for particular body area delivery that decreases systemic complications and strengthens medication effectivity at treatment locations [29]. Research demonstrates the effectiveness of focused drug delivery through niosomal technologies which now apply between cancer remedies and infectious disease and inflammatory site treatments. Pharmaceutical agents show enhanced stability through Niosomes because these carriers serve as effective delivery systems which control drug release. Therapeutic agents of diverse properties can be encapsulated by these carriers because of their dual compatibility with hydrophilic and lipophilic compounds. Niosomal-based drug delivery systems have demonstrated effectiveness as transdermal carriers for nimesulide and flurbiprofen because they enhance patient drug benefits and treatment duration [1][4]. The absorption and solubility properties of challenging compounds including quercetin improve with niosomal formulations due to its low solubility nature [1]. Through their ability to enhance drug delivery to the eyes niosomes provide more steady drug effects with better treatment stability in ophthalmic medicine. Within these systems drugs release through a controlled method that produces extended therapeutic benefits along with less frequent medicine application requirements. The delivery of diverse bioactive substances becomes possible through niosome systems due to their ability to work through oral, parenteral and topical routes [5].

3.2Transdermal and Topical Applications

The pharmaceutical community finds niosomes especially valuable for transdermal and topical drug delivery applications. Niosomal formulations achieve better skin penetration and these properties lead to their application in cosmetic and pharmaceutical preparations developed to improve skin conditions and appearance. The skin layers receive a better delivery of active ingredients through niosomal encapsulation technology that includes antioxidants with vitamins

and anti-aging agents. Niosome delivery improves skin penetration and increases active availability and minimizes irritant effects that conventional topical products commonly generate . The protective mechanisms of niosomes act as valuable assets for cosmeceuticals because they shield incorporated substances from degradative processes which include antioxidant degradation when exposed to light. Several studies demonstrate niosome application as a protective method for light-sensitive ingredients like lycopene and vitamin C and lutein through maintaining stability levels and extending their active effectiveness in skin care solutions [27]. The ability of niosomes to deliver precise sunscreen delivery and enhance the skin penetration of sunscreen ingredients currently makes them essential for UV protection formulations according to reports [19]. Niosome technology strengthens cosmetic formulations because it implements a powerful mechanism for maintaining difficult-to-stabilize or conventional delivery-resistant active compounds. Active compounds such as essential oils and herbal extracts reach maximum protection through niosomal systems through encapsulation because they shield the compounds from environmental elements and control their release pattern for extended durations. The controlled release mechanism of niosomal formulations decreases the requirement for regular topical application therefore making niosomal systems a suitable technology for skin care applications [29].

3.3 Diagnostic and Imaging Applications

The diagnostic sector accompanied by medical imaging applications represents another essential use of niosomes beyond their functions in drug delivery systems. Niosomes serve as carriers of imaging agents which includes X-ray and MRI and ultrasound contrast agents to enable improved medical imaging techniques. Niosomal carriers improve the stability along with performance of imaging agents thus ensuring better clinical suitability. Niosomal systems release diagnostic agents through controlled mechanisms which enhances precise disease detection methods as well as offering real-time tracking opportunities with better therapeutic planning prospective [35]. The field of diagnostics together with medical imaging utilizes niosomes as carriers for these purposes. Through their role as imaging agent carriers niosomes enhance the stability of contrast agents while improving their effectiveness for X-ray and MRI and ultrasound imaging thus helping medical personnel achieve better visualization of tissue structures and diagnose accurately [3][5]. The precise imaging capability of niosomes occurs because these vesicles create better contrast agent delivery which enhances their value for detecting diseases during real-time monitoring events [6]. Niosomes demonstrate enhanced capability in nuclear medicine because they provide effective radiolabeled agent encapsulation for drug encapsulation studies as well as biodistribution research. Enhanced drug permeability and retention studies at target sites are possible through this technology which delivers important information about how drugs penetrate sites via the enhanced permeability and retention (EPR) effect [4][5].

Researchers are currently investigating niosomal applications for theranostic purposes since these drug delivery vehicles can transport simultaneous diagnostic and therapeutic elements. The

two-way capability of these vehicles allows both therapeutic substance delivery and treatment monitoring through imaging tools at the same time. The combination of therapeutic and diagnostic features in niosomes design enables new precision medical options that allow doctor-relevant treatment decisions from real-time diagnostic feedback [15][18].

3.4 Industrial and Pharmaceutical Uses

Niosomal use extends to numerous industrial as well as pharmaceutical applications. These vesicular drug carriers work effectively with synthetic and natural drug substances because of their broad therapeuticatility. Exposure to niosomal formulations provides two advantages for pharmaceutical applications. The formulations assist with delivering poorly soluble drugs through the oral route leading to better gastrointestinal absorption . Niosomes find application in vaccine delivery systems because their encapsulation capacity for antigens enables vaccine compounds to release at controlled rates for improved immune response. Niosomes defend encapsulated antigens from enzymes to improve both vaccine durability and functional efficiency.

Niosome technology offers promising applications for gene delivery to scientific research. The delivery of small molecules alongside biological molecules including plasmids or siRNA is possible through their dual capacity. Researchers can optimize niosome designs to deliver genetic material either for processes that edit genes or silence particular genetic sequences [29]. Niosomes represent promising genetic medicine and therapy innovations because of their flexible design capabilities.

3.5 Computational Optimization and Future Directions

The optimization of niosomal systems happens through computational tools like molecular dynamics simulations which have improved their development process. The predictive techniques assist scientists to forecast how niosomal formulations react to distinct settings which enables them to optimize their design and functionality. Such tools enable the simulation of surfactant-drug-environment interactions which results in improved design of targeted and efficient niosomal delivery systems [14][26].

Nanoscale technology applications for niosome formulation development will grow through research that enhances their precision targeting capacity as well as drug carrying ability and stability properties. Studies explore different surface modification techniques that employ ligands and antibodies for increasing niosomal carrier specificity. Niosomal advancement will drive their significance in drug delivery and diagnostics and imaging fields alongside cosmetics to provide both superior performance and better therapeutic outcomes [33].

3.6 Protein, Gene, and Vaccine Delivery

The carrier function of Niosomes provides a method to transfer both protein compounds and genetic material into specific cells. Research demonstrates niosomes show value in optogenetic therapies for neuronal treatments specifically in cortical neurons by acting as non-viral vectors for plasmid delivery which bypasses the security concerns of viral vectors [3][4]. Research into

niosome technology explores gene therapies because they target both mesenchymal stem cells and retinal tissue to develop new treatment methods for genetic disorders [1][3].

The delivery system of vaccines also benefits from niosomal applications. Niosomal antigens offer protection which extends vaccine component stability and delivers sustained release and better vaccine efficacy. Research suggests that niosomal vaccines have the capability to improve immunization efficiency by delivering precise cells or tissues which reduces vaccine-associated side effects from conventional delivery pathways [5][6].

3.7 Antibacterial and Antimicrobial Applications

The exploitation of niosomal technology extends to antibacterial along with antimicrobial treatment applications. The combination of niosomal selenium nanoparticles (SeNPs) has proven effective as an antibacterial agent by inhibiting pathogenic bacteria while blocking biofilm development according to [1][3]. Niosomes loaded with SeNPs show improved antibiofilm properties which strengthens their potential as a treatment solution against antibiotic-resistant infections [2].

Niosomes demonstrate an effective capability for drug delivery that focuses on intracellular pathogens. Special agents incorporated into niosomes create a mechanism that directly delivers drugs to Mycobacterium abscessus pathogens thereby decreasing bacterial concentrations and improving therapeutic success [2][3].

3.8 Cosmeceuticals and Dermatological Uses

Niosomes have become a key subject of interest within the cosmeceutical industry for dermatological implementations. Anti-aging compounds such as vitamins and antioxidants use niosome carriers to both control their release rate and improve skin absorption of bioactive substances [3][4]. Sensitive compounds including lycopene vitamin C and lutein receive protection from niosomes because these compounds show susceptibility to degradation when exposed to environmental stressors such as light and air [3][4].

Through better stratum corneum penetration niosomes facilitate enhanced effective skin condition and wound healing treatments. The gradual time-based delivery of medications from these formulations improves their effectiveness while reducing typical topical treatment side effects [5][6].

3.9 Future Directions and Emerging Applications

Scientists currently focus their research on niosome development to achieve improved performance through nanotechnology. New surface modifications that include moieties or ligands enable niosomes to be developed for precise targeted drug delivery to specific areas. Researches will gain the ability to predict and customize niosomal formulations through advances in computational simulations and modeling work.

Through encapsulation of chemotherapeutics and antioxidants together with bioactive compounds Niosomes demonstrate great potential for various fields including cancer research and cosmetic sciences and infectious disease therapy in upcoming investigations [6][7].

3.10 Targeted Delivery and Therapeutic Optimization

The key strength of niosomes lies in their exact tissue or organ targeting ability. The drug delivery process can benefit from melatonin-loaded niosomes due to their ability to modify bilayer properties which enhances drug bioavailability at destination sites [2][3]. Niosomal carriers deliver drugs precisely to different body areas including brain, liver, lungs and skin which creates a better therapeutic option by reducing unwanted drug effects [1][2].

Niosomes serve as drug delivery carriers in cancer treatment because they enhance combination medicine effects which leads to better tumor responsiveness and site-specific distribution capability without the negative systemic complications [2]. Niosomes provide an encapsulation method which enhances curcumin bioavailability alongside therapeutic outcomes while decreasing its adverse effects. Scientific studies indicate that niosomes containing curcumin show promising results for inhibiting cancer cell growth.

S/N	Drug Name	Preparation Method	Niosome Composition	Route of Administration	Entrapment Efficiency (%)	Ref
1	Doxorubicin	Thin film hydration	Span 60:Cholesterol (2:1 molar ratio)	Intravenous	78.3	[12]
2	Curcumin	Ether injection	Tween 80:Cholesterol (1:1)	Oral	65.7	[25]
3	Amphotericin B	Reverse phase evaporation	Span 20:Cholesterol:Dicetyl phosphate (7:3:1)	Topical	84.1	[33]
4	Ibuprofen	Thin film hydration	Span 60:Cholesterol (1:1)	Transdermal	70.2	[14]
5	Ciprofloxacin	Microfluidization	Span 40:Cholesterol (2:1)	Intravenous	80.5	[32]
6	Paclitaxel	Ethanol injection	Span 80:Cholesterol (3:2)	Oral	76.9	[25]
7	Fluconazole	Reverse phase evaporation	Span 60:Cholesterol (2:1)	Topical	82.0	[18]
8	5-Fluorouracil	Sonication	Span 20:Cholesterol:PEG (1:1:0.2)	Intralesional	68.4	[12]
9	Insulin	pH-gradient + microfluidization	Span 60:Cholesterol (4:1)	Oral	74.6	[34]
10	Methotrexate	Thin film hydration + sonication	Span 40:Cholesterol (3:1)	Intravenous	77.2	[10]
11	Rifampicin	Ether injection	Span 60:Cholesterol (1.5:1)	Oral	66.8	[13]
12	Acyclovir	Thin film hydration	Span 80:Cholesterol (2:1)	Topical	72.1	[13]
13	Nifedipine	Reverse phase evaporation	Span 60:Cholesterol (3:2)	Oral	81.3	[19]

14	Zidovudine	Microfluidization	Span 40:Cholesterol:Dicetyl phosphate (2:2:1)	Intravenous	79.5	[128]
15	Tamoxifen	Ethanol injection	Span 60:Cholesterol:PEG 400 (2:1:0.5)	Oral	75.0	[34]

Fig1.1 Observation of Niosomal Formulation's of different drugs,with different methods of preparation

4.Evaluation and Characterization of Niosomes

Niosomes, a type of non-ionic surfactant-based vesicles, have gained significant attention in drug delivery systems due to their potential to encapsulate both hydrophilic and lipophilic drugs. Their characterization is crucial for evaluating their stability, size distribution, drug encapsulation efficiency, and drug release profiles, all of which influence their efficacy in therapeutic applications. The evaluation of niosomes generally includes the assessment of parameters such as particle size, zeta potential, polydispersity index (PDI), morphology, encapsulation efficiency, and drug release behavior. Various analytical techniques, including dynamic light scattering (DLS), zeta potential measurement, transmission electron microscopy (TEM), and field emission scanning electron microscopy (FESEM), are employed to provide detailed insights into the properties of these vesicles.

4.1 Particle Size and Size Distribution

One of the most critical characteristics of niosomes is their particle size, as it influences their stability, drug release, and cellular uptake. Particle sizes in niosomal formulations typically range from 45 to 150 nm. For instance, formulations containing PEG-b-PCL nanoparticles were found to have an average particle size of approximately 45 ± 10.07 nm, whereas other formulations exhibited sizes around 150 nm[2][3]. The particle size is determined using DLS, which provides valuable information on the distribution of particles in the formulation. Additionally, the polydispersity index (PDI), which reflects the uniformity of the particle size distribution, is generally between 0.02 and 0.23. Lower PDI values indicate uniform size distribution, which is essential for consistent drug delivery and optimal therapeutic effects[4][5].

4.2 Zeta Potential and Surface Charge

Zeta potential is a key indicator of the stability of niosomes. A higher zeta potential, typically around 24.6 ± 3.2 mV, suggests good stability due to electrostatic repulsion between particles, which prevents aggregation. For example, niosomal formulations with a zeta potential of −28.2 ± 3.68 mV demonstrate stable dispersions, while formulations with less negative charges, like PEG-b-PCL niosomes at −9.29 ± 3.68 mV, may be less stable[2][4]. Zeta potential measurements are crucial not only for determining the long-term stability of niosomes but also for understanding their biological interactions, such as cellular uptake. Positive or negative zeta potentials can influence the rate of niosome absorption by cells, affecting their overall therapeutic efficiency.

4.3 Morphology and Structural Integrity

The morphology of niosomes is evaluated using advanced imaging techniques like TEM and FESEM. These techniques allow researchers to observe the vesicular structure and confirm the spherical shape typical of niosomes. Niosomes are often found to have single-layered vesicular structures, although some formulations may exhibit multilamellar vesicles depending on the method of preparation[7][8]. The structure of niosomes is influenced by the composition of surfactants, cholesterol, and other excipients, which impact their shape and lamellarity. Morphological analysis is crucial for understanding how niosomes will interact with biological tissues and how they will deliver their payload to the target site.

4.4 Encapsulation Efficiency and Drug Loading

Encapsulation efficiency is another important parameter that indicates how effectively the drug is incorporated within the niosome structure. Niosomes have shown high encapsulation efficiencies, typically exceeding 80%, which makes them suitable carriers for a wide range of bioactive compounds, including both hydrophilic and lipophilic drugs[6]. The method of preparation, such as solvent evaporation or thin-film hydration, can influence the encapsulation efficiency by affecting the drug's interaction with the niosome matrix. Higher encapsulation efficiencies are often achieved with surfactants that promote better interaction between the drug and the vesicular structure, allowing for enhanced drug loading and sustained release profiles.

4.5 Release Profiles and Drug Release Kinetics

The ability of niosomes to release drugs in a controlled and sustained manner is one of their key advantages in drug delivery applications. In vitro drug release profiles are evaluated to determine the rate and extent of drug release over time. For example, curcumin and cisplatin-loaded niosomes have shown cumulative release profiles of 51% and 48%, respectively, over a period of 48 hours, demonstrating their potential for sustained drug delivery[3][4]. Release kinetics are typically studied using dialysis bag experiments, which simulate the release of drugs under biological conditions. The release behavior can be influenced by factors such as niosome size, surface charge, and the method of drug encapsulation. Controlled release allows for prolonged therapeutic effects and reduced dosing frequency, making niosomes an attractive option for various therapeutic applications.

4.6 Stability Studies

Stability is a critical factor for ensuring the long-term efficacy of niosomes as drug delivery systems. Niosomal formulations undergo stability studies to assess changes in particle size, PDI, and zeta potential under different conditions, such as storage at varying temperatures or during freeze-thaw cycles. Formulations that maintain their size and charge over time are considered stable and suitable for clinical use. For instance, niosomes that underwent cold-hot cycling showed no significant changes in their size, indicating their potential for stability under fluctuating environmental conditions[2][5]. Stability studies are also important for evaluating the retention of encapsulated drugs, as formulations that exhibit high stability will be able to maintain their drug content over longer periods.

4.7 Method of Preparation and its Influence

The method of preparation plays a vital role in determining the characteristics of niosomes, including their size, morphology, and drug encapsulation efficiency. Common preparation methods include thin-film hydration, microfluidization, and solvent evaporation. These methods

affect the structural integrity, size distribution, and encapsulation efficiency of the niosomes. For instance, formulations prepared using microfluidic methods have been shown to exhibit better stability compared to those prepared by traditional thin-film hydration techniques[2][3]. Additionally, the choice of surfactant and the concentration of cholesterol can impact the size and morphology of niosomes, with higher cholesterol concentrations typically leading to smaller vesicles[4]. These factors must be optimized to achieve the desired properties for a specific drug delivery application.

4.8 Biodegradability and Biocompatibility

The biocompatibility and biodegradability of niosomes are crucial factors for their safety and effectiveness in therapeutic applications. Niosomes are designed to be non-toxic and biodegradable, allowing them to break down safely within the body without causing harmful side effects. Studies have demonstrated that niosomes can encapsulate a variety of bioactive compounds, protecting them from oxidative stress and enzymatic degradation while enhancing their therapeutic efficacy[5]. In addition, niosomes have been shown to exhibit favorable skin permeation, making them suitable for topical drug delivery applications. Ensuring the biocompatibility of niosomes is essential for their widespread clinical use, especially in long-term drug delivery systems.

5.Expanded Evaluation and Characterization of Niosomes

5.1 Entrapment Efficiency Calculation

Entrapment efficiency (EE) is a crucial parameter in the characterization of niosomes, as it reflects the ability of niosomes to encapsulate the active pharmaceutical ingredient (API) efficiently. The calculation of EE typically involves a specific formula where the percentage of the drug encapsulated in the niosomes is determined by measuring the difference between the total drug amount and the free drug in the supernatant [1]. This measure of efficiency is vital as it directly impacts the therapeutic potential of niosomal formulations, indicating the extent to which the drug is protected within the vesicular structure and can be effectively delivered to the target site.

5.2 Encapsulation of Hydrophilic and Lipophilic Drugs

One of the advantages of niosomes is their versatility in encapsulating both hydrophilic and lipophilic drugs, which enhances their bioavailability and stability. This dual capacity allows niosomes to be used for a wide range of drugs, expanding their potential applications in drug delivery systems. For example, niosomes have been shown to improve the stability and controlled release of drugs like quercetin, which are typically unstable or poorly soluble in aqueous environments[2][3]. This capability is attributed to the structure of the niosomes, which creates a suitable environment for both types of drugs to be encapsulated effectively.

5.3 Organoleptic and Morphological Characterization

The organoleptic properties of niosomal formulations, such as color, texture, and odor, play a role in their physical appeal and stability. For instance, quercetin-loaded niosomes were evaluated for their organoleptic characteristics, revealing a yellow color, distinctive odor, and thick consistency[2][3]. These properties provide insights into the formulation's stability and

physical state. Additionally, morphological characterization is essential to confirm the niosomal shape and structure. Particle size measurements showed that formulations had varying sizes, such as 2.13 µm for F1, 2.99 µm for F2, and 3.31 µm for F3[3][1], which are indicative of the dispersibility and stability of the niosomal formulations. A range of particle sizes ensures that niosomes can be tailored for different routes of administration and therapeutic targets.

5.4 pH and Encapsulation Efficiency

The pH values of niosomal formulations are also critical, as they need to be within a physiologically acceptable range for effective skin application. For example, pH values of 6.10, 6.13, and 6.16 were recorded for quercetin niosomes, remaining within the skin's physiological pH range[4][3]. This ensures that the formulations will not cause irritation or adverse reactions upon application. Furthermore, encapsulation efficiencies of 81.86%, 84.02%, and 88.24% for F1, F2, and F3 formulations, respectively, demonstrate the high capability of niosomes to encapsulate the active ingredient, ensuring a sustained release and improved therapeutic outcome[3][1].

5.5 Molecular Dynamics and Drug-Niosome Interactions

In more advanced studies, molecular dynamics simulations have been employed to study the interactions between drugs like melatonin and niosome bilayers. This approach helps in understanding the structural orientation of lipids within the bilayer and the influence of cholesterol on bilayer stability[1][2][4]. Cholesterol has been shown to significantly influence the bilayer's properties, enhancing both the structural integrity and stability of the niosomal formulation. Additionally, lateral diffusion coefficients provide a measure of the mobility of both the surfactant (Span60) and the encapsulated drug within the bilayers, offering insights into how drug release is governed[5][6].

5.6 Structural and Biophysical Characterization

The physical and chemical properties of niosomes, including size, shape, and encapsulation efficiency, are typically evaluated using techniques such as SEM, DLS, and FTIR. These techniques offer comprehensive characterization of the niosomal formulations, ensuring that they meet the desired criteria for drug delivery systems[1][2]. In particular, FTIR is used to study the interactions between surfactants, cholesterol, and drugs within the niosome structure, revealing any chemical changes that may occur during the encapsulation process[6]. The stability of the niosomal formulations is also assessed under various conditions, including temperature fluctuations and storage over extended periods.

5.7 Characterization of Nanoparticles and Drug Loading

When niosomes are combined with nanoparticles, such as selenium nanoparticles (SeNPs), the characterization process becomes even more intricate. SeNPs are often characterized using UV-Vis spectroscopy, XRD, and TEM analysis to confirm their size, shape, and crystalline structure[3][4]. For instance, the SeNPs in the study had an average size of 41.2 nm, indicating their spherical shape[5]. The incorporation of SeNPs into niosomes can enhance the therapeutic properties of the drug by improving the overall stability and bioactivity of the formulation. Additionally, encapsulation efficiency (EE) for SeNP-loaded niosomes was found to be 37.58%, which is lower than traditional niosomal formulations, indicating the challenges involved in loading inorganic nanoparticles into the bilayer[6].

5.8 Drug Release and Stability Studies

The release of drugs from niosomes is a vital part of evaluating their suitability as controlled release systems. Drug release is typically studied using dialysis bags or Franz diffusion cells, which simulate the conditions in the human body and allow for the measurement of drug diffusion over time[3][4]. The niosomal formulations, especially those loaded with SeNPs, demonstrated effective drug release profiles over an extended period, contributing to sustained therapeutic action. Stability studies revealed that storing niosomes at different temperatures and humidity levels allowed researchers to assess their long-term viability and drug retention capabilities[5].

5.9 In Vivo and Anti-Arthritic Activity

Niosomes have also been tested for their in vivo bioactivity, particularly in the case of anti-arthritic drugs like ursolic acid. The optimized ursolic acid niosomal formulation (UANF) demonstrated significant anti-arthritic effects when evaluated in animal models, highlighting the potential of niosomes in targeted and controlled delivery of therapeutic agents[1]. Similarly, rosmarinic acid niosomes exhibited anti-inflammatory effects, with a significant difference in inflammation suppression between the niosomal gel and the solution form. In vivo bioactivity tests provide valuable data on the effectiveness and safety of niosomal formulations, ensuring that they can be used for the intended therapeutic applications[2][3].

5.10 Cell Viability and Cytotoxicity

The cytotoxicity of niosomes is a critical factor in evaluating their safety for human use. Cell viability assays, such as the MTT assay, are commonly used to assess the toxicity of niosomes on various cell lines. In a study involving oleanolic acid-loaded niosomes, cell viability was measured on HepG2 cells, demonstrating the formulation's safety profile[5][6]. Furthermore, niosomes are also evaluated for their ability to deliver genetic material, where the niosome-to-plasmid ratio plays a crucial role in optimizing gene expression[5]. These studies emphasize the importance of assessing both the therapeutic efficacy and biocompatibility of niosomal formulations.

5.11 Microbial Studies and Antimicrobial Properties

Niosomes also show promise in antimicrobial therapy, as demonstrated by formulations targeted at Mycobacterium abscessus. These formulations exhibited antimicrobial properties, making them a potential tool for treating infections caused by resistant microorganisms[9]. Similarly, studies involving niosomes loaded with curcumin or other antimicrobial agents have demonstrated enhanced activity against biofilms, including multidrug-resistant Staphylococcus aureus. These studies underscore the versatility of niosomes in various therapeutic areas, ranging from anti-inflammatory to antimicrobial applications. morphology [13]. For example, selenium-loaded niosomes exhibited average sizes of 177.9 nm with an EE of 37.58% [15][16].

7.Biological Evaluation and Applications

7.1 In Vivo and Cytotoxicity Studies

Animal studies and cell-based assays are essential for assessing therapeutic potential. Ursolic acid and rosmarinic acid niosomes exhibited enhanced anti-inflammatory responses in rat models compared to free drug solutions [12][14]. Cytotoxicity studies using the MTT assay demonstrated effective inhibition of HepG2 and KB cancer cell lines by oleanolic acid and

curcumin niosomes, respectively [15][200].Melittin-loaded niosomes were evaluated through SEM and TEM for uniformity and size (~121.4 nm) and showed better bioactivity than free melittin [18][22]. Transfection efficiency in gene delivery studies was improved by optimizing the niosome-to-plasmid ratio [13][27].

7.2. Antimicrobial and Antibiofilm Properties

Niosomal formulations have shown promising antimicrobial activity. For example, tetracycline-loaded niosomes maintained size stability and antimicrobial activity under refrigeration [11][19]. Curcumin-loaded niosomes were effective against biofilm-forming *Staphylococcus aureus*, enhancing its antibacterial spectrum [13].

7.3. Predictive Modeling and In Silico Analysis

In silico studies aid in predicting pharmacokinetics and docking performance. ADME predictions revealed solubility and permeability limitations in free curcumin, which were overcome via niosomal encapsulation [15][15]. Protein-ligand docking simulations validated binding mechanisms using tools like Ramachandran plots and Z-score analysis [14].

8. Limitations of Niosomes in Drug Delivery Systems

8.1 Rapid Clearance and Limited Circulation Time

The growing research interest in niosome drug delivery faces major obstacles from their behavior within the human body. One significant drawback in niosome usage is their quick removal process by the mononuclear phagocyte system in blood circulation. The short life span of drug delivery establishes a barrier against effective accumulation throughout their passage within bodily tissues particularly inside tumor areas where sustained drug presence is necessary [1,2,]. Scientific studies show that niosomes experience poor tumor penetration which remains an essential barrier to therapeutic effectiveness since these vesicles struggle to penetrate deep tissues [3,36].

8.2 Barriers Across Different Routes of Administration

The approach through which a niosomal formulation is administered creates multiple impediments for its effectiveness. The degradation of medications by gastrointestinal enzymes together with first-pass hepatic metabolism limits oral administration of drugs to produce below-average systemic drug levels [12,26]. Medical transdermal treatments encounter obstacles because the stratum corneum of the skin maintains high resistance against drug diffusion. The effectiveness and acceptance rate of skin treatments are negatively influenced by diverse skin moisture amounts and the possibility of skin discomfort [22,27,28]. Insufficient drug absorption occurs through nasal and pulmonary administration because of rapid mucociliary clearance along with alveolar macrophage uptake that reduces drug bioavailability [33,23,17].

8.3 Instability During Storage and Use

The main drawback of niosomal formulations is their susceptibility to both physical and chemical instabilities. The shelf life and therapeutic effects suffer deterioration when storage-related vesicle fusion and aggregation cause drug material to escape from the vesicles [1,14,34].

The structural quality of niosomes gets damaged due to surfactant breakdown that occurs under specific combinations of temperature and pH [15,34]. Light exposure and oxidative stress together with high humidity act as environmental factors to compound existing issues with niosomal storage and packaging requirements [4,27].

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Conclusion

Niosomes have emerged as a promising and flexible platform for drug delivery, offering considerable advantages due to their biocompatibility, ability to encapsulate both hydrophilic and hydrophobic agents, and capacity for controlled drug release. A wide array of studies has underscored their potential in overcoming limitations associated with conventional delivery systems [12, 18, 27, 35,]. The fundamental appeal of niosomes lies in their amphiphilic nature, which allows for high encapsulation efficiency and protection of therapeutic molecules against enzymatic degradation and harsh environmental conditions [26, 28, 33]. Multiple formulation methods have been evaluated for niosome synthesis, with the **thin film hydration technique** consistently demonstrating high versatility and reliability. This method, often combined with sonication or extrusion, has been shown to yield vesicles with desirable size distributions and significant entrapment efficiencies, especially when surfactants like Span 60 or Span 80 are combined with cholesterol in appropriate molar ratios [15, 24, 18, 24, 35]. Other preparation approaches, such as **reverse phase evaporation** and **ethanol injection**, have proven beneficial in producing more uniform vesicle structures with enhanced drug retention [20, 33, 14, 35]. In more recent developments, **microfluidization** and **pH gradient loading methods** have allowed for the fine-tuning of vesicle properties and loading capacity, particularly for peptides and proteins like insulin and interferons [31, 36].

The route of administration significantly influences the design and expected behavior of niosomal formulations. Niosomes designed for **oral delivery** have demonstrated improved drug bioavailability by enhancing mucosal adhesion, delaying gastric degradation, and facilitating sustained release across the gastrointestinal tract [26, 34]. **Intravenous formulations** have benefitted from PEGylation strategies and surface charge manipulation to prolong circulation time and facilitate passive targeting, especially in anticancer therapy [14, 29, 11,]. Meanwhile, **topical** and **transdermal routes** have capitalized on the deformability of niosomal membranes to improve dermal penetration, leading to better therapeutic effects in localized infections, inflammation, and dermatological conditions [17, 33]. The **composition of niosomes** plays a critical role in determining their physical stability, drug release kinetics, and biological interaction. Cholesterol serves as a membrane stabilizer, reducing vesicle permeability, while additives like dicetyl phosphate or stearylamine help modulate surface charge for improved interaction with target tissues [21, 28]. Surfactants from the Span and Tween series have been widely used, and their hydrophilic-lipophilic balance (HLB) values directly influence vesicle size, rigidity, and encapsulation potential [19, 22]. More advanced designs include the incorporation of polyethylene glycol (PEG) or bile salts to improve circulation longevity and targeting capabilities [36,23,29]

Characterization studies have confirmed the reproducibility and robustness of niosomal formulations using analytical techniques such as dynamic light scattering (DLS), transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FTIR), and zeta potential

analysis [23, 32]. These evaluations ensure control over critical parameters like vesicle size, polydispersity, entrapment efficiency, and surface charge, which are essential for predictable in vivo performance. Despite substantial advancements, certain **limitations** persist in the development and application of niosomes. Concerns regarding long-term stability during storage, batch-to-batch reproducibility during scale-up, and potential immunogenicity of non-ionic surfactants need to be systematically addressed [26]. Moreover, the translation from bench to clinic is often hindered by regulatory challenges and the complexity of ensuring large-scale consistency in particle size, drug loading, and sterility [25,27].

Nevertheless, innovative technologies such as **lyophilization**, **spray-drying**, and **microfluidics-based continuous production** offer solutions for industrial-scale formulation and preservation of niosomal systems [23,26]. Research efforts focused on co-delivery systems, stimuli-responsive vesicles, and ligand-mediated targeting are also reshaping the potential applications of niosomes in personalized medicine [13, 25]. In summary, niosomes represent a dynamic and adaptable drug delivery system with the capacity to address various pharmaceutical challenges, from solubility enhancement to targeted therapy. The ongoing innovations in formulation design, vesicle engineering, and scale-up techniques continue to strengthen their position in the landscape of nanomedicine. Future research should prioritize clinical evaluation, toxicological profiling, and regulatory standardization to facilitate broader implementation of this promising platform [21,34].

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