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Niosomes in Improving Bioavailability and Reducing Toxicity Through Vesicular Carriers

REVIEW

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Abstract

Niosomes are non-ionic surfactant-based vesicular drug delivery that were created to address the drawbacks of traditional dosage forms, specifically their poor bioavailability, instability, and systemic toxicity. It is constituted mostly of non-ionic surfactants, cholesterol, and charge inducers, niosomes are capable of encapsulating both hydrophilic and hydrophobic medicines within their water core and lipid bilayer, respectively. This review comprehensively discusses the composition, methods of preparation, and functional characteristics of niosomes, with a particular focus on their role in enhancing bioavailability and reducing drug-induced toxicity. Various preparation techniques, including ether injection, thin-film hydration, sonication, microfluidization, and transmembrane pH gradient methods, are highlighted. Examples including griseofulvin, anthocyanins, tretinoin, calcein, and antiviral medications support the critical examination of the use of niosomes in the administration of antifungal, antiviral, anticancer, anti-inflammatory, neuroprotective, and dermatological treatments. Additionally, the effectiveness of niosomes in targeted drug delivery, controlled release, brain targeting, and reduction of organ-specific toxicity is emphasized. Clinical translation is still hindered by issues including stability, largescale manufacturing, sterilization, and regulatory concerns, notwithstanding its benefits. Further perspectives focus on stimuli-responsive, ligand-targeted, and combination drug-loaded niosomes to improve therapeutic outcomes. Overall, niosomes represent a promising and versatile vesicular carrier system with significant potential in improving drug bioavailability, safety, and patient compliance.

Keywords: *Niosomes, Vesicular Drug Delivery, Bioavailability, Reducing Toxicity, Preparation, Applications.*

1. Introduction

Niosome was first created in 1975 by the L'Oreal corporation for use in cosmetics. They were used as medication delivery devices in 1980 following five years of development [1]. They are drug delivery technologies that use a vesicle to encapsulate the medicament. The vesicles bilayer of nonionic surface active ingredients is what gives them their name [2]. When non-ionic surfactants from the alkyl or dialkyl polyglycerol ether class are combined with cholesterol, tiny lamellar structures known as niosomes are created. The enclosed interiors of these structures frequently contain a buffer solution with the appropriate pH. Because of their special structure, they can contain both hydrophilic and hydrophobic medications in their watery inner core and lipid bilayer, respectively, while also sheltering the drug from harzardous circumstances [3]. They are a kind of vesicular surfactant-based nanoparticles that provide enhanced

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bioavailability, biocompatibility, non-immunogenic and targeted drug delivery have overcome many of the drawbacks of traditional drug delivery systems. Niosomal carriers are liposomes, since they are easier to handle, have greater chemical stability, and are less expensive to produce it. Non-ionic surfactants have a few advantages over phospholipids, including being more cost-effective and chemically more stable due to their resistance to hydrolysis and oxidation during storage. This review explains how niosomes provides improved bioavailability and reducing the toxicity through vesicular carriers in treatment of various diseases. Additionally, a few studies have looked into how well niosomes work as a topical treatment. Chlorhexidine loaded niosomes in situ gels increases the retention time in root canal system [4]. It is a potential strategy that improves therapeutic efficacy and reduces side effects in the encapsulation of antimicrobial drugs in various nanovesicular systems. The optimized niosomal formulations increased antibacterial activity against the bacteria by enhancing the inhibition zone and lowering MIC and MBC values when compared to free medications [5]. The creation of nanocarriers that pass through the brain endothelium and range in size from 1 to 100 mm is the most promising non invasive method of brain delivery [6]. Niosomes enhance bioavailability by allowing M cells of peyer's patches to pass over the anatomical barrier of the gastrointestinal tract by transcytosing them in the intestinal lymphatic tissues. The niosomal vesicles are absorbed by the reticulo-endothelial system. Such localized medication buildup is used to treat diseases such as leishmaniasis, where parasites infiltrate the liver and spleen cells [7]. Innovative niosomes enriched with retinol are utilized to treat a variety of illnesses, including psoriasis, icthyosis, and acne vulgaris [8]. They are stable and osmotically active, and they are also utilized as a depot to supply it as a regulated release [9]. Ethylene injection, hand shaking, sonication, microfluidization, multimembrane extrusion, reverse phase evaporation, transmembrane pH gradient drug updating, bubble method, and niosome synthesis from proniosomes are some of the preparatory techniques used to create niosomes.

2. Components of Niosomes

2.1. Non-Ionic Surfactants

In terms of their potency, toxicity, and resemblance to cationic and anionic surfactants niosome development requires non-ionic surface active agents. They are less harmful and hemolytic while stimulating cell surface [10]. The primary kinds of nonionic surfactants employed in the synthesis of niosomes include alkylethers, alkylamide and fatty acids. When selecting surfactant molecules for the formation of niosomes. Values for the Critical Packing Parameter (CPP) and Hydrophilic Lipophilic Balance (HLB) are essential. The foundation for describing the niosome formulations is the solubility of the medicine present and the HLB number of the surfactant used [11]. They are therefore favored for the synthesis of stable niosomes for both in vivo and in vitro uses [12].

2.2. Cholestrol

Steroids, such as cholesterol, play a crucial role in the development of niosomes because they support the actual structure and characteristics of non-ionic vesicles. It has been demonstrated that cholesterols have a significant impact on inflexibility, porosity, leakage, and loading efficiency. The cholesterol is amphiphilic. In the bilayer structure of niosomes, cholesterol and the hydophilic head of a surfactant create hydrogen bonds. Thus, niosome designs and physical characteristics like entrapment efficiency, stablility over time, payload release and biostability are influenced by niosome cholesterol concentration. In order to protect niosomes from the destabilizing effects of plasma and serum components, cholesterol increases vesicle rigidity. Additionally, it prevents leaking by reducing vesicle permeability for trapped molecules.

2.3. Charge Inducers

Positive and negative charge inducers are the two categories of charged inducers. Through the induction of charge on the produced vesicles surface, it improves their stability. It works by giving larger zeta potential values and prevents vesicles with the same charge from fusing together due to repulsive forces. Lipoamine acid, dicetyl phosphate, and dihexadecyl phosphate are commonly used negative charge inducers, whereas common positive charge inducers cetylpyridinium chloride and sterylamine [13]. However, niosome production can be inhibited by increasing the quantity of charged molecules. Their stability and the encapsulation effectiveness of the integrated medications may be decreased by an increase in the concentration of charge-inducing substances.

3. Niosomes in Improving Bioavailability in Treatment of Various Diseases

3.1. Griseofulvin

Griseofulvin is a medication that dissolves poorly in water. Here, niosomes are made using the ether injection and thin film methods. Diacetyl Phosphate (DCP) is utilized as a surfactant in Span 20, Span 40, and Span 60 to stabilize the system and prevent vesicle agglomeration and aggregation. In niosomes made using both techniques, Span 60 consistently demonstrated the maximum entrapment of any surfactant type on rising total lipid concentration. Compared to the normal griseofulvin, which showed slow absorption, the niosomal formulation showed noticeably quicker absorption and reached a peak concentration in plasma (Cmax) more quickly. However, when taken orally, the straightforward drug had a greater tmax and failed to achieve a increased blood concentration because to its poor solubility and absorption profile. It shows the comparative mean vesicle size of niosomes made utilizing various techniques, surfaces, and compositions. Nonetheless, the findings demonstrate a correlation between the surfactant-lipid ratio, preparation method, and loading efficiency as well as vesicle size. The mean vesicle size increases when the surfactant / cholesterol ratio falls (formulations I to III), but it continuously declines from Span 20 to Span 60 in both the thin film and ether injection methods. According to the loading efficiency result, the loading efficiency rises within each formulation approach from Span 20 to 60 (the opposite trend to the size) and from I to III (the same trend as size). The maximal Concentration (Cmax) of the niosomal formulation was approximately double that of the free drug. The plasma drug profile suggests that the innovative niosomal system may also be able to maintain the therapeutic level of griseofulvin for a longer period of time than free griseofulvin.

3.2. Anthocyanin

A class of phytochemicals known as anthocyanins gives plants their purple or crimson coloration. Their antibacterial, neuroprotective, anti-cancer, anti-cardiovascular, anti-thrombotic, anti-diabetic, and eye-protective qualities have also been demonstrated. Anthocyanins limited effectiveness and distribution within the body are due to their poor stability and bioavailability. This work demonstrated the most recent state-of-the-art techniques for developing complexes based on lipids, polysaccharides, and proteins, as well as nano-encapsulation and exosomes, to overcome anthocyanin constraints. Diethyl ether was used as the coating medium to dissolve cholesterol and Tween 20, a non-ionic surface active agent. The resultant solution was gradually injected using a needle into phosphate buffer (pH 7.4) containing anthocyanin while being stirred steadily. At 60°C, the organic solvent evaporated, forming the anthocyanin niosome complex. Before stabilizing, the dialysis membrane's nio-somal anthocyanin release rate was rather high for the first half hour of the in vitro release test. After 10 hours, 90% of the anthocyanins were released. Researchers have demonstrated that the amounts of cholesterol and surfactants can alter the membrane's stiffness, hence regulating the anthocyanin efflux from the niosomal vesicles. To boost anthocyanin bioavailability, the niosomal anthocyanin

complex managed to strike a compromise between the targeted cell membrane's affinity and encapsulation effectiveness. Another study used the thin-film approach to create an anthocyanin noisome gel. In short, a thin film was created by dissolving particular amount of Span 60 and of cholesterol in 100% ethanol, which was then evaporated for 30 minutes at 60˚C. To create anthocyanin niosomes, the resulting thin film was combined with two millilitres of anthocyanins in isotonic phosphate buffer saline. Lastly, a gel containing sodium polyacrylate was thoroughly mixed with the produced anthocyanin niosomes. It further increased the topical delivery and also enhanced the wound healing property in rat model. Because of its unique properties, including increased stability and bioavailability, nano-encapsulation is thought to be an efficient means of delivering bioactive substances. The stability, releasing rate, and encapsulation effectiveness of the loaded substance were all strongly correlated with different nano-encapsulation coating material compositions. The phospho-lipids or cholesterols found in liposomes and niosomes facilitate anthocyanin's passage through cell membranes, increasing its bioavailability [14].

3.3. Tretinonin

Niosomes loaded with tretinoin, dicetyl phosphate, and cholesterol were prepared using polyoxyethylene lauryl ether, sorbitan esters, and a commercial blend of octyl / decyl polyglucosides. It uses a variety of ingredients, including Brij®30 (Br30), Triton® CG 110 (TrCG110), improved soy phosphatidylcholine (Phospholipon®90, P90), hydrogenated soy phosphatidylcholine (Phospholipon®90H, P90H), and Span®40 (Sp40). This study examined the vesicle structure of Large Unilamellar Vesicles (LUV), Small Unilamellar Vesicles (SUV), and Multilamellar Vesicles (MLV), as well as their size distribution, entrapment efficacy, and in vitro release of encapsulated tretinoin. At the end of the trials, tretinonin content and vesicle stability were assessed in donor phase samples. Tretinonin consistently retrieved more than 95 – 96% of the given dose from both the donor and receptor compartments. Transmission Electron Microscopy (TEM) and Dynamic Light Scattering (DLS) studies revealed no discernible changes in the size or form of the vesicles. Vesicle stability and tretinonin content were assessed in donor phase samples at the conclusion of the experiments. More than 95 – 96% of the prescribed amount was regularly recovered by TRA from the donor and receptor compartments. Span 80 used in preparation of niosomes showed a decreased stabiity and increased tretinonin leakage. The size of the niosomal formulations is found to be decreased when the cholesterol / surfactant ratio decreases. In general, liposomal and niosomal tretinoin dispersions released drugs via a Silastic membrane more quickly than tretinoin solutions. Release data indicates that the increase in tretinoin delivery from MLVs to LUVs to SUVs was significantly influenced by vesicular form.

3.4. Calcein

The majority of active chemicals cannot readily reach the brain due to the blood-brain and blood cerebrospinal fluid barriers. Dynamic Light Scattering (DLS) and Transmission Electron Microscopy (TEM) analyses showed no appreciable alterations in the vesicles shape or size. Actually, polysorbates can act as an anchor for the apolipoprotein in the plasma, and niosomes can deliver drugs to the brain. The creation of tailored materials or nanocarrier, which can penetrate the brain endothelium. Having sizes ranging from 1 to 100 nm, is currently the most sophisticated and promising noninvasive brain delivery method. The following were included in this formulation Cholesterol (Chol), Diphenylhexatriene (DPH), calceinpyrene, sodium acetate anhydrous, hepes salt {N(2-idroxy-ethyl) piperazine (2ethanesulfonicacid)}, Tween 20, Tween 80, sephadex G75, and 9-(diethylamino)-5H-benzo[R]phenoxazin-5-one. The “film” method was used to create the non-iconic surfactant vesicles NSV1, NSV2, NSV3, NSV4, and NSV5 by combining cholesterol and amphiphilic chemicals (Tween 20 or Tween 80) in the same molar ratio. By fortifying the apolar of the

bilayer, cholesterol enhances the niosomal membrane's cohesiveness during the formation of surfactant vesicles. A suitable z potential value that can stop vesicular fusion is necessary for the vesicle to stabilize and stop aggregates from forming. Or coalescence through electrostatic, steric, or repulsive effects. In the creation of NSVs, Tween 20 and Tween 80 demonstrated colloidal stability. Tween primarily targets the blood-brain barrier through receptor-mediated endocytosis. The chosen niosomal formulations are safe and efficient are safe at delivering calcein into the cytoplasm of cells, according to the cell contact assays. During the process of fluoresence microscopy the calcein alone shows less fluorescence due to self-quenching and NSV1 shows higher fluorescence compared to NSV 5 because it has lesser microviscosity value so specifically, compared to calcein alone, undamaged calcein-loaded NSVs take longer to reach the cytoplasm. This kind of device may allow for a prolonged (modified) release of physiologically active chemicals to the central nervous system, most likely through a BBB crossing via Low Density Liporotein (LDL) receptor-mediated targeting.

3.5. Mycophenolic Acid, Ribavirin & Curcumin

Curcumin, ribavirin, and mycophenolic acid are three antiviral medicines that can be encapsulated in stable niosomes made using a thin-film hydration process. Mycophenolic acid, curcumin, ribavirin, Span 20®, cholesterol, and dihexadecyl phosphate, a negatively charged phospholipid, were employed as antiviral molecules. Mycophenolic acid, ribavirin, and curcumin were successfully encapsulated in stable and repeatable niosomal formulations, which led to a high loading efficiency and strong antiviral activity against the vesicular stomatitis virus and herpes simplex 1 with notably lower cytotoxicity. Due to their limited water solubility, many antiviral medications require high dosages to reach therapeutic concentrations, raising the possibility of systemic toxicity and side effects. Three Antiviral Molecules (AM) with unique and complimentary characteristics were chosen for this scenario. A broad-spectrum immunomodulatory drug with respectable selectivity indices in vitro is Mycophenolic Acid (MPA). When compared to the free antiviral compounds, the formulations showed considerable cytotoxicity reduction and strong antiviral effectiveness against nano gram doses of Varicella Zoster Virus (VSV) and Herpex Simplex Virus-1 (HSV-1). By creating a scalable and repeatable process for the production and purification of niosomal formulations loaded with antiviral compounds, this study created stable nanocarriers with regulated size, spherical morphology, and negative surface charge, as shown by Dynamic Light Scattering (DLS) and Scanning Electron Microscopy (SEM) investigations. The method was dependable for a number of antiviral compounds and produced excellent encapsulation efficiencies for mycophenolic acid, ribavirin and curcumin.

4. Method of Preparation

4.1. Ether Injection Method

This method provides a means of producing niosomes by progressively adding a solution of surfactant diluted in diethyl ether, a volatile organic solvent, to warm water maintained at 60°C. The surfactant mixture in ether is injected into the aqueous solution of a material using a gauge needle. Ether, a volatile organic solvent, evaporates to form single-layered vesicles.

4.2. Thin Film Hydration Method

By gradually adding a solution of surfactant diluted in diethyl ether, a volatile organic solvent, to warm water kept at 60°C, this technique offers a way to create niosomes. A gauge needle is used to inject the surfactant mixture in ether into an aqueous solution of a material. Single-layered vesicles are created when ether, a volatile organic solvent, evaporates.

4.3. Sonication

In this process, an aliquot of medication solution in buffer is combined with the surfactant / cholesterol mixture in a glass vial. The mixture is probe-sonicated in a sonicator with a

titanium probe to create niosomes.

4.4. Microfluidization

Micro-fluidization is a novel technique for producing unilamellar vesicles with a specific size distribution. This method is based on the submerged jet theory, which describes how two fluidized streams collide very rapidly in well-defined micropores within the interaction chamber. The energy supplied to the system remains inside the niosome production region since the thin liquid sheet impingement is dispersed along a single front. Niosomes consequently grow smaller, more consistent, and more reproducible.

4.5. Multi Membrane Extrusion Method

Polycarbonate membranes can be arranged in a consecutive fashion to create up to eight channels. It is an effective method of controlling niosome size. A mixture of dicetyl phosphate, cholesterol, and surfactant is evaporated in chloroform to produce a thin film. After the film has been hydrated with an aqueous drug solution, like polycarbonate membrane solution, the suspension is sequentially extruded through the film for up to eight passes. It can effectively regulate niosome size [15].

4.6. Reverse Phase Evaporation Method

Cholesterol and surfactant are dissolved using ether and chloroform (1:1). The drug-containing aqueous phase is added, and then the two phases are sonicated. The resulting transparent gel is then further sonicated when a small amount of phosphate buffered saline is added. The organic phase is removed at low pressure and 40°C. The resulting viscous noisome suspension is diluted with PBS and heated in a water bath for ten minutes to create niosomes.

4.7. Bubble Method

This novel technique eliminates the requirement for chemical solvents by producing liposomes and niosomes at the same time. A round-bottomed flask with three necks submerged in a water bath to control the temperature makes up the bubbling unit. The nitrogen supply is located in the third neck, while the water-cooled reflux and thermometer are located in the first and second necks. Surfactant and cholesterol are mixed and distributed in this buffer. Nitrogen gas is then "bubbled" into the mixture after it has been combined with a high shear homogenizer [16].

4.8. Ethanol Injection Method

Using a fine needle, the ethanol injection method quickly injects an alcoholic (ethanol) solution of surfactant into an excess of saline or another aqueous media. It vaporizes the ethanol, forming vesicles. It has been mentioned as one of the substitutes for sonication in the production of tiny unilamellar vesicles (SUVs).

4.9. Transmembrane pH Gradient Drug Uptake Process

Because the interior of the niosome has an acidic pH, which is lower than the exterior, this technique boosts the loading efficiency of such medications. After passing through the membrane, the additional unionized basic medication gets ionized in the acidic medium inside the niosome and cannot leave. The acidic pH of niosomes traps the medications intravascularly [17].

5. Niosomes in Reducing Toxicity

- The generated niosomes had a particle size of less than 150 nm and a high loading efficiency of roughly 90%. In vivo pharmacokinetics showed that targeted niosomes had a longer circulation and higher bioavailability than doxorubicin solution and non-targeted niosomes. This resulted in a significant drop in Clearance (CL) and Volume of Distribution (VD), which were 3.5 and 2.5 times lower, respectively. Higher concentrations of doxorubicin solution were found in the heart according to tissue-distribution studies and enzymatic assays, but there was no damage to the major organs with generated targeted niosomes [18].

- Following the administration of ParaQuat (PQ), serum levels of alanine aminotransferase and aspartate aminotransferase, suggesting hepatic injury ($p < .001$). When compared to the PQ group, N-Acetyl Cysteine Nanoparticles (NACNP) decreased the levels of Lipid Peroxidation (LPO), Total Thiol Groups (TTG), and Total Antioxidant Capacity (TAC) in liver tissue. Compared to animals treated with free N-acetyl cysteine, those treated with NACNP exhibited noticeably reduced PQ-induced hepatotoxicity ($p < .05$). ParaQuat (PQ) is a common herbicide used all over the world. The main cause of liver injury in mammals is PQ poisoning. N-Acetyl Cysteine (NAC) is a medication that can reduce the liver damage caused by PQ. Here, after developing a NAC Noisome Nanoparticle (NACNP), we assessed the impact of niosomes and NAC on liver damage caused by PQ [19].
- The vesicular diameters ranged from 109.5 to 143.9 nm, while the negative zeta potential was between - 14.7 and - 30.1 mv. To do this, two protease enzymes, papain and bromelain, were placed into elastic niosomes (Tween 61 / cholesterol / sodium cholate). The Deformability Index (DI) values of the elastic niosomes loaded with Extracted Papain (PE), Standard Papain (PS), Standard Bromelain (BS), and Extracted Bromelain (BE) were 1.35, 1.81, 1.22, and 1.61 times higher, respectively, than the corresponding non-elastic niosomes. According to the Sulfo Rhodamine B (SRB) assay, the elastic niosomes considerably reduced the toxicity of the PS, PE, BS, and BE on cutaneous human fibroblasts at 1.68, 2.10, 1.56, and 1.52, while also increasing the entrapment effectiveness of the enzymes by about 1.35 times when compared to non-elastic niosomes. In addition to improving the entrapment effectiveness of the enzymes by approximately 1.35 times compared to non-elastic niosomes, the elastic niosomes significantly decreased the toxicity of the PS, PE, BS, and BE on cutaneous human fibroblasts at 1.68, 2.10, 1.56, and 1.52 according to the SRB [20].

6. Applications

- Niosomes can improve a drug's oral bioavailability can improve medication penetration through the skin. It can be used orally, topically, or parenterally. The surfactants are biocompatible, easily biodegradable, and inert. Baclofen, a muscle relaxant which can be used muscle relaxant to enhance skin penetration and bioavailability [21].
- The vesicles can provide a regulated release and serve as a depot for the drug's slow release. They are stable and osmotically active. Surfactants don't require any special handling or storage conditions.
- Compared to oily dose forms, patient compliance is higher with the vesicle suspension because it is a water-based carrier. Permit the use of medications with different solubilities. The properties of the vesicle formulation are controllable and adjustable. The properties of vesicles can be altered by varying their composition, size, concentration, surface charge, and lamellarity.
- They help in treatment of cancer by changing the drug metabolism, extending its half-life and circulation so the adverse effects caused by antineoplastic medications can be reduced. Breast cancer is one of the most aggressive malignancies affecting women, resulting in the greatest mortality rate worldwide. Due to their improved drug delivery capabilities, nanotechnological techniques have been fully utilized among all other common therapy strategies for breast cancer management [22].
- They are used in the treatment of leishmaniasis. A parasite belonging to the genus Leishmania invades the cells of the liver and spleen to cause leishmaniasis. The use of niosomes in experiments allows for increased treatment efficacy and demonstrates that higher amount of the medication can be administered without causing adverse effects.
- The vesicles are preferentially taken up by the reticuloendothelial system cells. Niosomes are also taken up by cells by circulating serum components called

opsonins, which signal them for removal. However, this kind of localized medication accumulation has been used to treat parasitic liver infestation and animal cancers that are known to spread to the liver and spleen [23].

- They can be employed for ocular medicine administration because they can pass through the cornea. Since their visible spectrum can be superimposed on that of free hemoglobin, they can be used as a carrier for hemoglobin.
- The cholesterol based niosomal formulation of diclofenac sodium showed a greater anti-inflammatory effect than the free medication. Similarly, flurbiprofen and nimesulide showed greater activity than the free medication [24].
- Timolol maleate (0.25%), a chitosan-coated niosomal formulation, has a greater efficacy on lowering intraocular pressure than a commercial formulation with a lower risk of cardiovascular adverse effects.
- Due to a formulation issue, methotrexate, a medication used to treat psoriasis, has few uses. Methotrexate niosomes using chitosan as a polymer have demonstrated encouraging results in the treatment of localized psoriasis [25].
- Topical or systemic anti-fungal medication is frequently used to treat fungal infections. Transepidermal water loss is decreased as a result of their interaction with the stratum corneum. It was discovered that niosomal preparations enhanced the therapeutic effectiveness of ketoconazole. Itraconazole and miconazole niosomes were also discovered to be useful, demonstrating their efficacy as antifungal medication delivery vehicles.
- Because niosomal solution has a visible spectrum that may be superimposed on that of free hemoglobin, it can be used as a hemoglobin carrier. Additionally, hemoglobin dissociation curves can be changed to resemble those of non-encapsulated hemoglobin, and vesicles are permeable to oxygen [26].

7. Challenges

Sterilization is the main barrier that prevents niosomes from being used in the medication delivery industry. The suggested niosome synthesis techniques are carried out in a septic environment. Due to the breakdown of the bilayer membrane, heat and steam sterilizing techniques may be detrimental to the lipids and surfactants in the molecular structure of niosomes and result in drug leakage. Membrane filtration has been suggested by researchers as a solution to this problem nevertheless, niosomes larger than 200 nm will not be able to pass through the filter [27]. Because of the composition of niosomes, the formulation must contain additives to improve long-term physical stability. This behavior was shown in long-term stability evaluations of nevirapine niosomes, where niosomes formed with diacetyl phosphate showed better stability than niosomes formulated without a charge-inducing substance. There are still some worries about the safety of niosomal formulations even if the components of niosomes are Generally Recognized As Safe (GRAS) [28]. Scaling up production from lab to industrial scale still presents hurdles. For thymoquinone nano-delivery systems to be commercially viable, issues including quality control, cost-effectiveness, and reproducibility must be resolved. For nanocarriers to be used in practical applications, scalable production techniques that preserve their physicochemical and biological characteristics must be developed. In order to determine safety, efficacy, and ideal dosage schedules, especially in healthcare settings, the shift from experimental research to practical application further requires thorough clinical studies [29]. Niosomes may still encounter issues such as early drug leakage, short circulation time, and variable absorption based on formulation and route, even with increased oral absorption and improved pharmacokinetics. Research shows that there are still challenges in designing formulations to continuously improve bioavailability, particularly for hydrophilic versus hydrophobic medications [30].

8. Future Prospectives

- Nowadays, skin conditions are becoming more common place worldwide. Therefore, the creation of a carrier that

deeply into the skin is necessary. Therefore, a number of innovative carriers have been developed, including vesicles that contain penetration enhancers, such as transcutol, labra-sol, cineole, etc., which can improve penetration in comparison to ordinary vesicles [31].

- Skin microbiome considerations fungal infections are influenced by the skin microbiota. Researchers should look at how antifungal medications affect the skin microbiome and how to maintain a balanced environment. Thorough clinical research is required to conduct long-term safety and efficacy studies in order to address potential side effect concerns and ascertain the long-term safety and effectiveness of transdermal antifungal administration techniques in practical settings [32].
- Tumor antigens, immune checkpoint inhibitors, and cytokines to trigger anti-leukemic immune responses are being investigated for administration via liposomes and niosomes. This is especially important for leukemia, as immune evasion is a major indicator of the disease's advancement. To target many leukemogenic pathways at once, liposomes and niosomes can be co-loaded with immunomodulators, chemotherapeutic drugs, and gene-silencing molecules. This multimodal approach may be able to increase synergistic anticancer benefits and overcome drug resistance mechanisms [33].
- Because niosomes can increase drug stability, extend circulation time, and facilitate regulated release, they offer a promising vesicular drug delivery strategy for enhancing bioavailability and lowering toxicity [34]. In order to enable site-specific delivery and minimize off-target effects, future research is anticipated to concentrate on the development of stimuli-responsive niosomes, which release medications in response to pH, temperature, or enzymatic triggers [35].
- By improving cellular uptake through receptor-mediated processes and lowering systemic exposure and toxicity, surface-engineered and ligand-targeted niosomes are expected to significantly increase therapeutic efficacy [36]. Clinical translation is still restricted despite encouraging preclinical results because to issues with stability, large-scale manufacture, and regulatory approval. Future clinical and commercial success of niosomal drug delivery systems is anticipated to be facilitated by developments in formulation techniques, surfactant synthesis, and quality-by-design methodologies [37].
- Furthermore, noisome-based dual-drug and combination therapy has the ability to overcome multidrug resistance and produce synergistic therapeutic effects at lower dosages of medication [38].

9. Conclusion

Niosomes are innovative drug delivery technologies that use a vesicle to encapsulate the medicament. Niosomes through vesicular carriers is used in the treatment of leishmaniasis, breast cancer, fungal infections etc. Griseofulvin, anthocyanin, tretinonin, calcein, mycophenolic acid, curcumin, ribavirin are efficient than free drug in providing improved bioavailability in treatment of various diseases. When it came to lowering PQ-induced hepatotoxicity, N-acetylcysteine ($p < .05$). In vivo pharmacokinetics of doxorubicin solution and non-targeted niosomes showed that the targeted niosomes had a longer circulation and higher bioavailability. In comparison to the corresponding non-elastic niosomes, the Deformability Index (DI) values of Standard Papain (PS), Extracted Papain (PE), Standard Bromelain (BS), and Extracted Bromelain (BE) loaded into elastic niosomes were 1.35, 1.81, 1.22, and 1.61 times higher. By improving pharmacokinetic profiles, extending circulation time, and facilitating site-specific drug delivery, niosomes have shown clear advantages in minimizing organ-specific toxicity and enhancing patient compliance. Their potential for sophisticated drug delivery applications is further highlighted by their capacity to pass through biological barriers, such as the blood-brain and skin barriers. Future research should focus on the development of stimuli-responsive, ligand-

targeted, and combination drug-loaded niosomes, along with scalable and reproducible manufacturing strategies. With continued advancements in formulation design and thorough clinical evaluation, niosomes hold significant promise as an effective and safe drug delivery platform, contributing to improved therapeutic outcomes and the advancement of modern pharmaceutical technology.

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