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Review Article

Targeted Drug Delivery Using Niosomes: Progress, Obstacles, and Future Directions

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ABSTRACT

Niosomes are carriers that contain non-ionic surfactants in a vesicular form that have been presented as an innovative drug-delivery system of significant versatility due to their structural stability, biocompatibility, and drug loading capacity with various therapeutics. When comparing niosomes to standard liposomes, niosomes exhibit an enhanced physical and chemical stability, cost-effectiveness, and facility for a large-scale manufacture to be both clinically and industrially-relevant. Recent advances in formulation techniques focused on cholesterol, charge inducers, and newer surfactant combinations have initiated new methods of modulating vesicle-size, bilayer rigidity, and loading of attachment drugs, respectively. In addition, surface modifications of niosomes with ligands such as monoclonal antibodies, peptides, aptamers and folic acid, have greatly improved the ability to actively target cellular receptors, further providing site-specific delivery with improved therapeutic efficacy and a decreased potential for systemic toxicity. The inclusion of stimuli-responsive components such as pH-sensitive polymers, redox-reactive linkers, and thermoresponsive lipids have also afforded the development of smart niosome systems to trigger drug release according to pathological indicators. These characteristics have enabled niosomal applications across diverse disease models, such as solid tumors, fungal and bacterial infections, dermatological diseases, and neurological disorders. Apart from these encouraging characteristics, various translational challenges are still present, such as instability of the vesicles during storage, quick clearance in vivo, batch-to-batch reproducibility, and regulatory ambiguities. Novel strategies like PEGylation, freeze-drying, hybridization with biodegradable polymers, and utilization of scalable processes are being explored to resolve these issues. This review provides an integrative overview of recent research directions, challenges, and prospects of niosome-based targeted delivery, highlighting technological advancement as well as translational relevance. The observations made in this review will be useful for researchers, formulation scientists, and drug developers

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aiming to develop next-generation, patient-specific nanocarrier systems with superior specificity, safety, and clinical relevance.

INTRODUCTION

Targeted drug delivery systems have changed how we treat diseases because they enable localized concentrations of pharmacological agents to be given at the site of pathology while minimizing systemic adverse effects[1]. These systems improve drug bioavailability, provide controlled drug release, and reduce drug degradation before reaching the target localization[2]. Of the many nanocarrier systems synthesized over the last few decades, niosomes have been of increased interest, given their versatility, chemical stability, and incorporation of both lipophilic and hydrophilic drugs[3]. Niosomes are non-ionic surfactant-based vesicles that possess a similar structure to liposomes, but niosomes have advantages in shelf-life and costs associated with manufacturing that make them more marketable for large scale manufacturing[4]. Niosome formulations can undergo surface modification and are stimuli-responsive, which is vital for targeted delivery and controlled release systems[5]. As well, niosomes are biocompatible, biodegradable, and have relatively low immunogenicity which is desirable for systemic administration[6]. In this review, the scientific and technological advancements in niosome-based TDDSs are discussed systematically. Focus is given to their physicochemical attributes, formulation methods, active targeting functionalization approaches, and response to internal and external stimuli. Thereafter, therapeutic uses in various clinical fields like oncology, infectious diseases, and dermatology are addressed. Finally, the paper critically assesses the current limitations and translational issues and provides insights into future trends in the clinical development and marketing of niosomal systems. This review is designed as a core resource for formulators and research scientists aiming for the creation of next-generation, patient-specific nanocarriers.

1. METHODOLOGY

This narrative review was done with the aim of presenting an in-depth overview of recent research progress in niosome-based drug delivery systems. Pertinent literature in the form of articles published between 2000 and 2024 was accessed from databases like Scopus, Google Scholar, Web of Science, and PubMed using keywords like niosomal carriers, vesicles composed of non-ionic surfactants, site-specific drug delivery platforms, stimulus-sensitive systems, and nanocarriers. Peer-reviewed original articles, reviews, and clinical reports published in English were included according to the relevance to niosome architecture, formulation methods, targeting strategies, therapeutic uses, and translational issues. Selection was based on scientific relevance and thematic significance.

2. Comparative Overview of Targeted Nanocarriers

Various nanocarrier-based targeted drug delivery systems have been developed in recent decades, including liposomes, polymeric nanoparticles, solid lipid nanoparticles (SLNs), dendrimers, and micelles, each possessing certain advantages regarding stability of the drug, bioavailability, and site-specific targeting (Fig.1). Liposomes, while much researched, remain handicapped by high production costs and poor long-term stability. SLNs offer improved stability but have compromised drug loading capacity, whereas polymeric nanoparticles and dendrimers allow for accurate functionalization but issue in the case of biocompatibility and regulatory approval. Niosomes, which are vesicles composed of non-ionic surfactants, have recently gained significant

attention due to their enhanced chemical stability, affordability, and ability to encapsulate both hydrophilic and lipophilic agents. Moreover, their ease of surface functionalization for ligand attachment and the integration of stimulus-responsive elements further enhance their targeted delivery capabilities. These characteristics establish niosomes as a potential next-generation drug delivery platform with enhanced prospects for clinical translation[7].

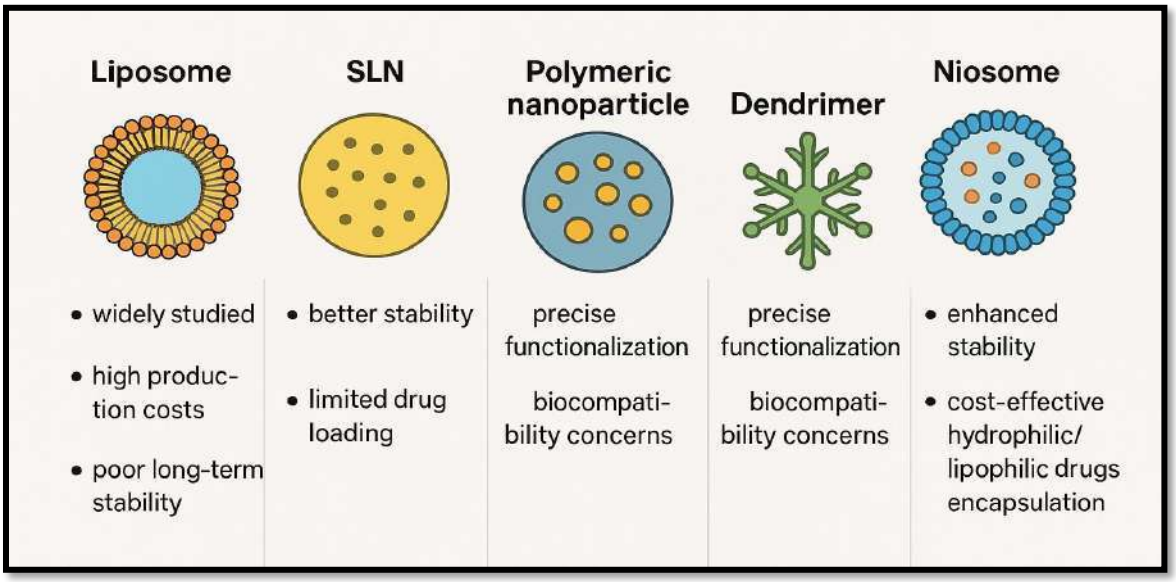

Fig. 1. Emerging role of niosomes among advanced nanocarrier systems for targeted therapeutics

3. Noisome Architecture and Composition

Niosomes are microscopic lamellar structures (Fig. 2) formed by non-ionic surfactants and cholesterol, which assemble into bilayer vesicles within aqueous medium[8]. The common surfactants employed are alkyl or dialkyl polyglycerol ethers, e.g., Span (sorbitan esters), Tween (polyoxyethylene sorbitan esters), and Brij (polyoxyethylene ethers) families[9]. The amphiphilic structures in these molecules lead to the creation of vesicles having their hydrophobic tails inward and hydrophilic heads toward the aqueous environment, thus facilitating the entrapment of both lipid- and water-soluble drugs. Cholesterol is often added to niosomal formulations to increase membrane rigidity, decrease permeability, and stabilize the vesicle structure at physiological conditions[10]. Niosomes are classified by size and number of lamellae: small unilamellar vesicle (SUV) (10-100 nm), large unilamellar vesicle (LUV) (greater than 100 nm), and the multilamellar vesicle (MLV) with multiple bilayers that can be in a size range to micron diameter[11]. Drug loading capacity, release profiles, and in vivo distribution is affected based upon these structures. In addition to the surface charge and overall stability of colloids, charge inducers (for example, dicetyl phosphate for negative charge or stearylamine for positive charge) can be added to other ingredients to influence circulation time and biodistribution[12]. Beyond the overall values, the physicochemical characteristics of niosomes aid in their biological behavior and include size, surface charge, lamellar structure, and bilayer elasticity. For example, small vesicles that are neutral or have a slight negative surface charge are not quickly cleared from circulation by the MPS (mononuclear phagocyte system) providing better systemic bioavailability. Size, lamellar structure, surface

charge, or drug to bilayer could be adjusted to modulate release profiles and enable targeting specific for tissue[13].

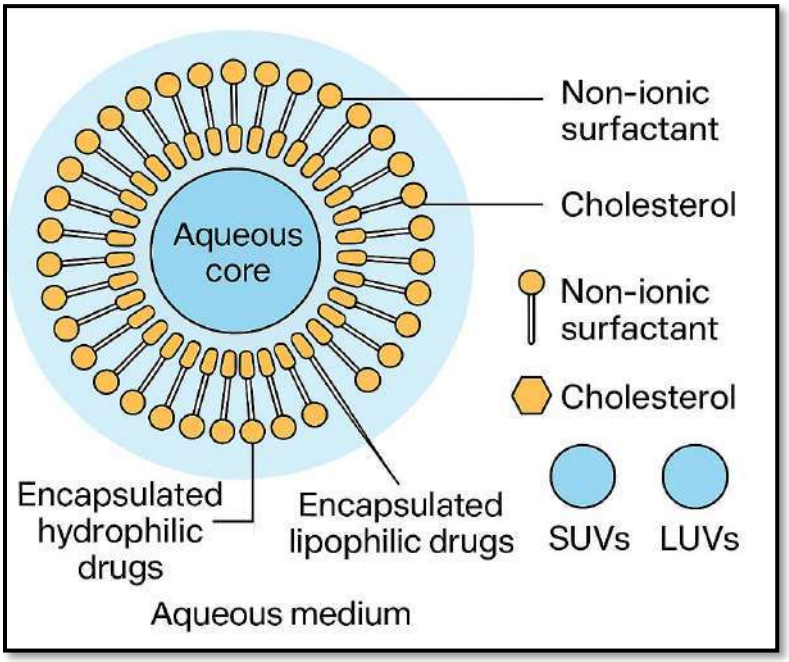

Fig.2. Structural design and functional architecture of niosomal vesicles for targeted drug delivery

4. Fabrication Technologies

5.1. Thin-film hydration (Rotary flask evaporation) method

Among the methods for preparing niosomes, the thin-film hydration approach is the most widely used due to simplicity and functionality. Thin film hydration, shown in Figure 3, involves dissolving cholesterol and non-ionic surfactants in a volatile organic solvent, typically a chloroform-methanol mixture, and then evaporating the solvent under reduced pressure with a rotary evaporator. This results in a thin film of lipids coating the inner wall of a round bottom flask. Hydration with an aqueous phase containing the drug then occurs, resulting in the dehydration and separation of the lipid film to produce multilamellar vesicles (MLVs)[14]. The size of the vesicles and the resulting lamellarity can then be manipulated post hydration by reducing the size by techniques such as sonication or by extrusion through polycarbonate membranes to generate small unilamellar vesicles (SUVs) or larger liposomes (LUVs) which can be used depending on the application[15]. The hydration parameters, including hydration temperature, surfactant to cholesterol (Chol) ratio, and the surfactant type are important to formulations particle size, encapsulation efficiency (EE), and stability[16]. This process is suitable to encapsulate both hydrophilic and lipophilic drugs. Thermolabile compounds are typically not suitable for this method because of heat produced during the film formation and hydration process. Nevertheless, its scalability, reproducibility, and high entrapment efficiency make it a staple in niosome drug delivery research and industry[17]. The thin film hydration techniques is a very common method for preparing niosomes due to its ease of preparation and its efficiency.

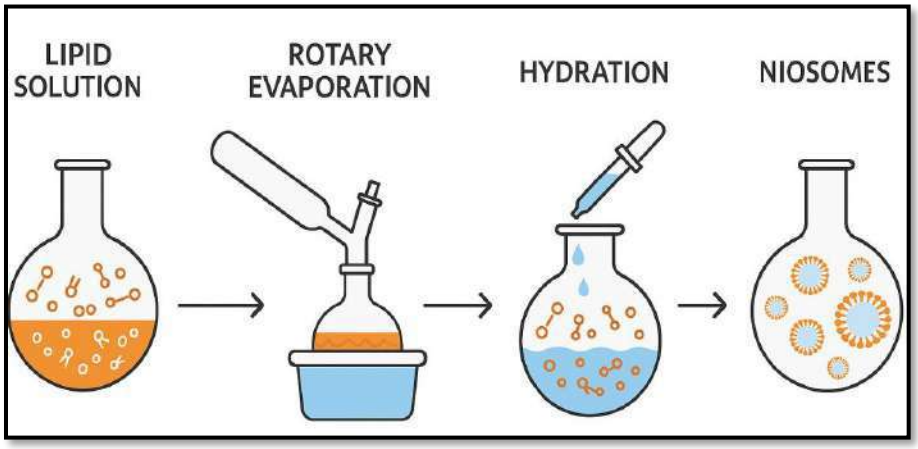

Fig. 3. Step-by-step visualization of niosome formulation through the thin film hydration method

5.2.Reverse Phase Evaporation Method (REV)

The REV approach is often employed for obtaining high encapsulation efficiency, particularly for hydrophilic materials (Fig.4). In REV, the aqueous phase solution is first sonicated along with the drug and a mixture of cholesterol and surfactants in organic solvents such as diethyl ether or isopropyl ether, which generates a water-in-oil (w/o) emulsion. On slow evaporation of the organic phase under diminished pressure, vesicles spontaneously form as the surfactant molecules rearrange themselves around the aqueous droplets[18].The vesicles thus obtained are usually unilamellar of high encapsulation efficiency because the aqueous and lipid phases are intimately mixed during emulsification. Niosomes derived from REV tend to disperse more stably and reproducibly. But solvent residue concerns and organic solvent removal requirements by vacuum methods create scalability issues[19].

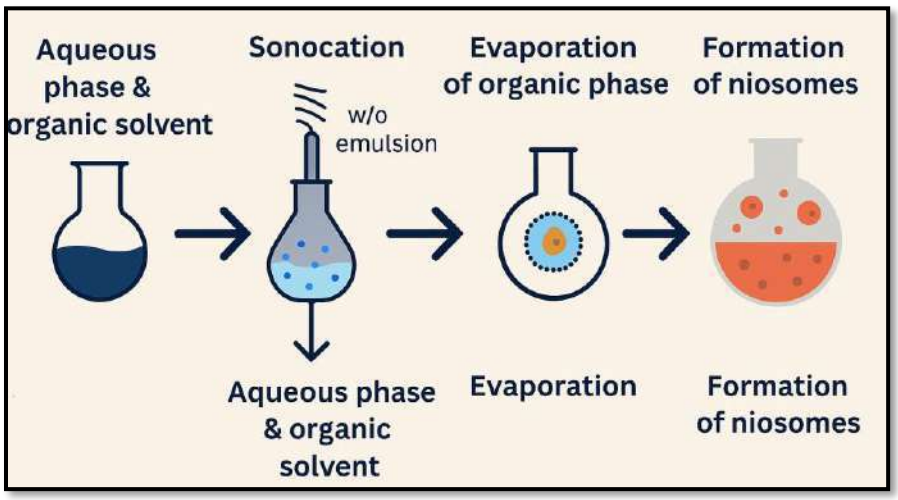

Fig. 4. Schematic illustration of niosome synthesis by REV method

5.3.Ether injection method

The ether injection technique (Fig.5) consists of slow injection of a lipid solution containing surfactants and cholesterol dissolved in diethyl ether or ethanol is added into preheated aqueous drug solution under continuous stirring. The organic solvent evaporates very quickly when it comes in contact with the hot aqueous phase, and

niosomal vesicles form[20]. This approach is appropriate for the generation of small unilamellar vesicles and provides vesicle size control by managing injection rate and temperature. Nevertheless, the application of volatile organic solvents and elevated temperatures could be limiting factors for heat-sensitive drugs. The requirement for strict temperature control and stirring conditions could also limit bulk production[21].

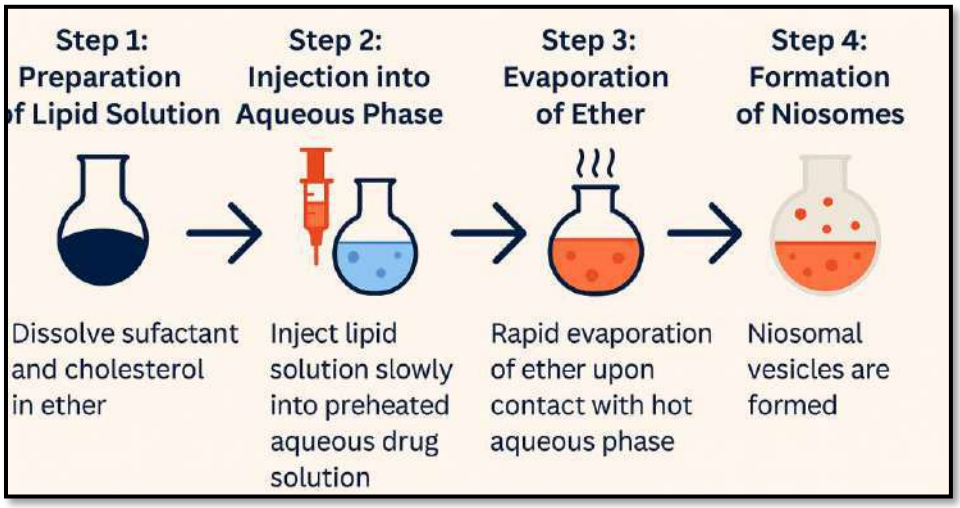

Fig. 5. Illustration of the ether injection method for niosome formation

5.4.Microfluidization and microfluidics

Microfluidization and microfluidic processing (Fig.6) have become sophisticated means of continuous and scalable manufacture of niosomes with controlled size and lamellarity. These processes involve the high-pressure impingement of liquid streams or controlled microchannel mixing to induce vesicle self-assembly[22]. These processes impart uniform size distribution and are scalable, and thus, they are of interest for industrial manufacture. Microfluidic platforms, specifically, enable automation and real-time control of process parameters. Despite this, high equipment cost and optimization of flow rates and channel sizes are still major hindrances[23].

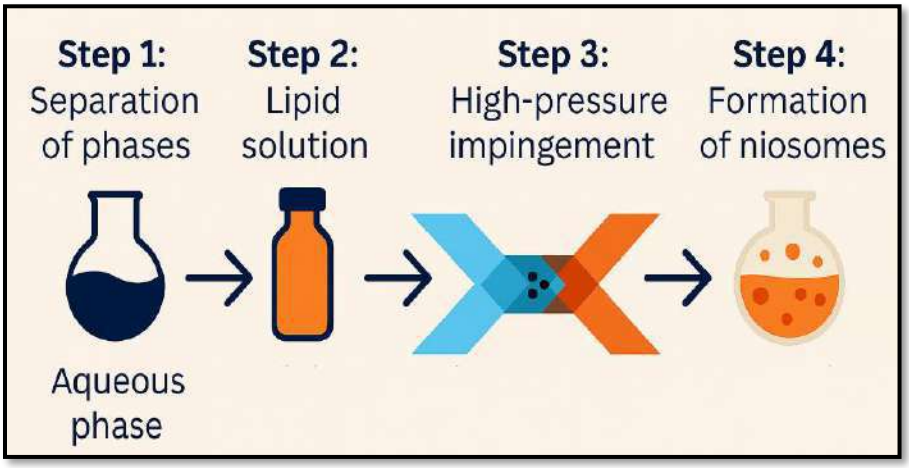

Fig. 6. Schematic representation of niosome synthesis using microfluidization and microfluidics

5.5.Proniosome-based reconstitution

Proniosomes are dehydrated free-flowing powders or gels that develop niosomal vesicles upon rehydration. The systems are composed of surfactants and cholesterol coated on carriers like maltodextrin or sorbitol by a solvent evaporation process (Fig. 7). When proniosomes come into contact with water or body fluids, they spontaneously rehydrate to produce niosomes[24]. Proniosomes resolve instability issues around aqueous niosomal suspensions, providing an extended shelf-life, ease of formulation and enhanced reproducibility. This approach is especially suited for the oral and transdermal delivery of drugs, because hydration may occur on-site after administration. While this approach does provide high encapsulation efficiency and scalability, complete hydration and vesicle formation are dependent on and variable on physiological conditions (which can vary from person to person)[25].

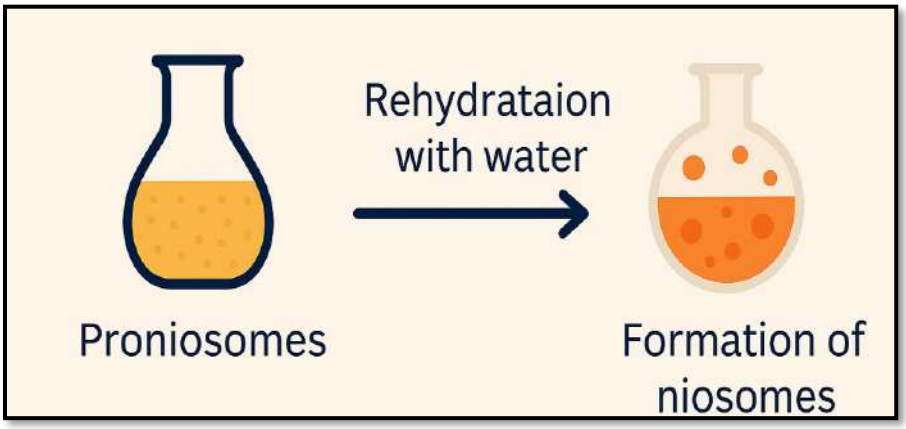

Fig. 7. Conversion of proniosomes to niosomes by rehydration.

5.6.Sonication and extrusion

Sonication and extrusion are supplemental methods typically used to reduce vesicle size and achieve uniformity after the initial formation of niosomes (Fig. 8). Sonication uses ultrasonic waves to break down larger vesicles into small unilamellars. The probe and bath-type sonicators are typically used, with the probe-type sonicator being more efficient, as it generates heat, which can be detrimental to sensitive drugs[26]. Extrusion involves passing the niosomal suspension through polycarbonate membranes with defined pore sizes under controlled pressure. This method yields vesicles with a narrow size distribution, increases batch-to-batch reproducibility. Both processes are illustrated in combination with other methods of fabrication to create slight changes in the properties of the vesicles[27].

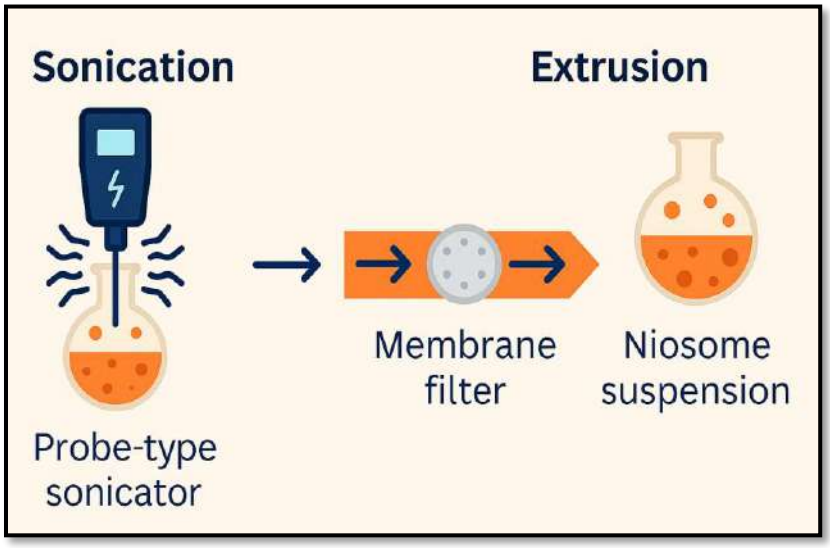

Fig. 8. Graphical representation of sonication and extrusion methods for niosome size reduction

5. Targeting Approaches Using Niosomes

Targeted drug delivery is aimed at improving the therapeutic effect by specifically targeting drug-loaded carriers to the diseased tissue or cell, thus reducing systemic toxicity. Niosomes are promising vehicles for drug delivery systems due to their structural versatility and modifiable surface chemistry for passive or active targeting methods.

6.1.Passive targeting

Passive targeting leverages the enhanced permeability and retention (EPR) effect, a feature of tumor vasculature marked by leaky endothelial junctions and impaired lymphatic drainage.Optimally sized niosomes (usually 100–200 nm) preferentially localize within tumor tissues via the EPR effect after systemic delivery[28]. Surface charge and hydrophilicity further affect circulation time; niosomes bearing hydrophilic polymer modifications like polyethylene glycol (PEG) acquire "stealth" properties by avoiding opsonization and subsequent clearance by the MPS, with extended systemic circulation and improved passive buildup at the target sites[29].

6.2.Active targeting

Active targeting involves modifying the niosome surface with ligands that bind specifically to receptors or antigens abundantly expressed on the target cells. This enhances the cellular uptake by receptor-mediated endocytosis and enhances drug
delivery intracellularly. Monoclonal antibodies, aptamers, peptides, and small molecules such as folic acid or transferrin are common targeting moieties[30]. In other cases, niosomes have shown to induce greater cytotoxic effects against cancer cell lines that overexpress folate receptors compared with niosomes without this targeting[31]. In addition to using an appropriating targeting moiety, ligand conjugation can be designed with either covalent linkers or non-covalent adsorption to create functional stability and bioactivity in a living system.

6.3.Stimuli-responsive targeting

Niosomes can be constructed to respond to internal stimuli like pH change, redox condition, and enzyme action, or external stimuli like light, temperature, and magnetic fields. pH-responsive niosomes have the potential to leverage the acidic

tumor microenvironment or endosomal environment to achieve targeted drug delivery with minimized off-target effects[32]. Redox-responsive niosomes possess breakable disulfide linkages that can be cleaved in the glutathione-abundant tumor cell environment, and enable on-demand drug release[33]. Thermosensitive formulations phase-separate under mild hyperthermia and enable controlled drug release in response to external thermal activation[34].

6.4.Multifunctional targeting

Emerging trends involve the convergence of various targeting strategies into one niosomal system such as passive targeting, active targeting and stimulus-responsiveness to attain maximal therapeutic response. Such multi-functional niosomes offer enhanced selectivity, reduced systemic toxicity and better pharmacokinetic properties[35].

6. Therapeutics Of Niosomes

Niosomes are a versatile nanocarrier employed in different therapeutic fields and can be easily employed for the delivery of hydrophilic and hydrophobic drugs in a controlled release form with targeted action against specific tissues. They possess inherent advantages like stability compared to liposomes and low toxicity characteristics that make them a promising addition to various clinical applications. This section describes some of the prime therapeutic applications of niosomes (Fig. 9) based on some recent advances and clinical importance.

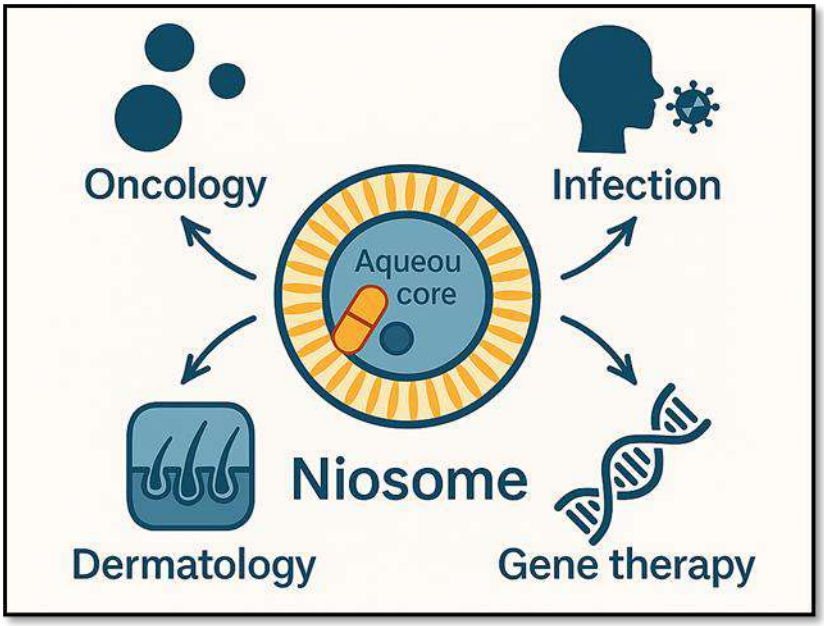

Fig.9. Application-Specific Roles of Niosomes in Targeted Drug Delivery

7.1.Oncology

Cancer remains a major cause of mortality globally, and chemotherapy is limited by toxicity, low tumor targeting, and drug-resistant tumors. Niosomes are capable of overcoming these limitations by optimizing anticancer agent pharmacokinetics and biodistribution. Due to their vesicular nature, niosomes are able to encapsulate hydrophobic drugs like paclitaxel and cisplatin or hydrophilic drugs like doxorubicin. Encapsulation in niosomes protects drugs from degradation and clearance, increasing circulation half-life[36]. Importantly, modifying the niosome surface with

ligands that target overexpressed cancer cell receptors - such as transferrin, folate, and epidermal growth factor receptors - can enhance selective uptake by drugs using receptor-mediated endocytosis and boost intracellular drug concentrations[37]. Stimuli-responsive niosomes can release their drug cargo in response to acidic pH or redox conditions within the tumor microenvironment, enabling precise and controlled delivery to the target site[38]. These representative designs provide additional multifunctionality for reducing off-target toxicity and moving forward against multidrug resistance due to enhancing intracellular drug retention.

7.2.Infectious diseases

Delivering antimicrobial drugs to the site of action is still a challenge due to the localization of the pathogen in intracellular spaces and biofilms. Niosomes offer a solution to this challenge through the enhanced intracellular delivery of antibiotics and antifungal agents, and therefore increased therapeutic efficacy, for example, for difficult-to-treat infections such as tuberculosis and systemic mycoses. For example, rifampicin niosomal encapsulation allows macrophage preferential uptake the main host cell for *Mycobacterium tuberculosis* enhancing local drug concentration and lowering systemic exposure[39]. In addition, niosomes improve the stability and solubility of drugs like amphotericin B, thereby lowering nephrotoxicity and minimizing infusion-related adverse effect[40]. Disruption of biofilm architecture further enhances antimicrobial effect. Recent developments include niosomes that are targeting ligand-functionalized or stimulus-responsive structures releasing antimicrobials in a targeted manner within infected tissues to achieve maximum efficacy with minimal toxicity[41].

7.3.Dermatology and transdermal delivery

Transdermal drug delivery is limited by the stratum corneum, which acts as a barrier and hinders the penetration of numerous therapeutic agents. Niosomes enhance drug permeation and retention within the skin, serving as an effective carrier for both local and systemic treatments via the dermal route. The encapsulation of anti-inflammatory drugs such as ketoprofen within niosomes has revealed increased drug deposition in dermis and epidermis, resulting in improved therapeutic effectiveness with decreased systemic absorption and side effects[42]. Niosomal delivery methods may be developed into gels or creams, for example proniosomal gels, which afford more stability and ease of use. They allow for extended delivery of drug-release and increased patient adherence in chronic diseases like psoriasis and eczema. They are less irritating and more biocompatible, which qualifies their appropriate use in treating dermatological conditions[43].

7.4.Gene therapy

Non-viral gene delivery systems are front and center in a new focus of attention that is attributed to the safety risks of viral vectors also known as viral delivery. Niosomes are multi-functional gene delivery carriers that can transmit nucleic acids to exceed the enzymatic upper limit and achieve successful cellular internalization. Niosomes can be surface modified with cationic lipids or polymers that facilitate compaction of plasmid DNA or siRNA into nanoscale nanoparticles achieving high transfection efficiency[44]. Niosomal gene delivery has been considered promising in the delivery of therapeutic genes for cancer immunotherapy, genetic illnesses, and regenerative medicine. The niosomal formulation has controllable release characteristics that allow for temporal control of gene expression. Localization of niosome delivery can be improved through surface modification with targeting

ligands[45]. Research is still ongoing with the aim to augment the formulation of niosomes in efforts to achieve safe, effective, and clinically translatable gene therapies.

7. Challenges And Limitations Of Niosomal Drug Delivery

Although niosomes exhibit beneficial qualities as drug carriers, they are still surrounded by numerous hindrances and limitations that do not allow them to easily transfer to clinical practice and into the marketplace. Being aware of these limitations is crucial for the optimization of niosomal formulations and the development of robust and reproducible manufacturing processes. Key factors affecting clinical transfer are outlined in Table 1.

Table 1. Niosome-Based Drug Delivery Strategies

Parameters	Composition	Advantages	Limitations
Niosome Constituents	Non-ionic surfactants & cholesterol forming bilayer vesicles	Biocompatibility, stability, encapsulation of diverse drugs	Potential vesicle instability & leakage
Fabrication Methods	Thin-film hydration, reverse phase evaporation, microfluidics	Scalability, control over size & drug loading	Solvent residues, batch variability
Targeting Approaches	Passive (EPR effect), active (ligand-mediated), stimuli-responsive	Enhanced specificity, reduced systemic toxicity	Rapid clearance, regulatory hurdles
Therapeutic Applications	Oncology, infectious diseases, dermatology, gene therapy	Improved drug delivery, lower toxicity	Biological barriers, formulation challenges
Translational Barriers	Storage stability, manufacturing scalability, biodistribution	PEGylation, hybridization with polymers	High production costs, regulatory complexities

8.1.Stability issues

While niosomes are generally more stable chemically than liposomes, physicochemical instability can arise during storage in the form of fusion, aggregation, and leakage of the encapsulated drugs [46]. The stability of the vesicle is influenced by the selection of cholesterol content, surfactant, and the preparation method. The surfactants in niosomes are vulnerable to hydrolysis and oxidation, leading to damage to the bilayer and subsequent occurrence of drug release before intended. Stabilizers and lyophilization have also been explored, but further optimization must be accomplished to guarantee that drug encapsulation efficiency and vesicle size distribution are preserved over time[47].

8.2.Challenges in scale-up and manufacturing

The development of niosomes with reproducible physicochemical characteristics for large-scale production is still a critical bottleneck. Conventional preparation procedures, including thin-film hydration and sonication, are extremely time-consuming, labor-intensive, and hard to scale up to generate quantities that are commercially relevant. It is difficult to obtain homogeneous control from batch to batch with respect to vesicle size, lamellarity, and drug loading, and both the product outcome and resulting regulatory approval are affected. While microfluidics and high-

pressure homogenization technologies have introduced scalable options, they need more testing and development before they are economically viable for use in commercial operations in the life sciences and pharmaceutical production arena[48].

8.3.Drug loading and release kinetics

The synchronized effective encapsulation of both hydrophilic and lipophilic drugs into niosomes is a complicated task. The bilayer structure heterogeneity might restrict drug capacity for loading, particularly for bulky or charged molecules. In addition, drug release kinetics regulation to meet therapeutic needs is challenging because of passive diffusion and destabilization of the vesicles in physiological conditions. This can result in early leakage or burst release of the drug, decreasing targeting efficiency and enhancing systemic toxicity[49].

8.4.Biological barriers and *in vivo* fate

After systemic administration, niosomes are quickly eliminated by the MPS, which shortens their circulation period and limits accretion at the target site[50]. Though surface modification with polyethylene glycol (PEGylation) can decrease opsonization and increase half-life, repeated dose administration can cause accelerated blood clearance (ABC phenomenon), rendering chronic dosing regimens challenging[51]. Additionally, interaction with serum proteins and the heterogeneous tumor microenvironment can hinder penetration and cellular uptake. Immunogenicity and possible toxicity with regard to surfactants and residual solvents employed in the process also require extensive scrutiny[52].

8.5.Regulatory and translational hurdles

The regulatory route for niosomal drug products is still less established than traditional dosage forms. Establishing stringent quality control measures, in particle size distribution, surface charge, and drug release characteristics, is indispensable for obtaining clinical approval. Additionally, thorough preclinical and clinical safety information on long-term toxicity, immunogenicity, and biodistribution needs to be presented. The lack of standardized characterization techniques and unified regulatory frameworks hinders the progression of niosomal formulations from laboratory research to clinical application[53].

8. Future Perspectives

The technology behind niosomal drug delivery is now changing at a fast pace, fuelled by ongoing developments in nanotechnology, materials science, and molecular targeting approaches. Perhaps the brightest horizon lies in the design of multifunctional niosomes that have both therapeutic and diagnostic capabilities (theranostics). By incorporating imaging probes into the niosomal framework, scientists can track drug biodistribution and therapeutic effect in real time, facilitating personalized treatment regimens with enhanced clinical outcomes. Target specificity will be significantly boosted by surface modification of niosomes with an assortment of ligands like monoclonal antibodies, aptamers, peptides, and small molecules for targeting overexpressed receptors on disease cells. Such active targeting will enhance cellular uptake and minimize off-target effects, especially important for cancer treatment and infectious diseases. Stimuli-sensitive niosomes are another frontier that is engineered to deliver their payload upon receiving internal signals like the acidic conditions characteristic of the tumor microenvironment, variations in redox potential, enzymatic activity,

and external triggers such as temperatureultrasound, or magnetism. These intelligent delivery systems allow drug delivery spatiotemporally, reducing systemic toxicity and improving therapeutic efficacy. In terms of manufacturing, scalability and reproducibility in the production of niosomes pose great challenges. Microfluidic platforms and continuous flow synthesis provide high control over vesicle size, lamellarity, and encapsulation efficiency, improving upon the limitations of the conventional batch processes. The product-independent variability assures regulatory compliance based on uniform quality of products that is conducive to clinical translation. Likewise, niosomal delivery for convergence of emerging modalities like RNA interference, CRISPR-Cas9 gene editing, and immunotherapy holds promise to treat critical conditions with an unmet medical need. In addition, the crossover with nanomedicine and artificial intelligence may reduce dosing regimens and potentially counteract patient-specific effects as a viable approach towards precision nanomedicine.

9. CONCLUSION

Niosomes are emerging as an effective and versatile vehicle for target-specific drug delivery because they are biocompatible, can encapsulate a wide variety of therapeutic agents, and have physicochemical parameters that can be easily modulated. They can improve upon traditional drug delivery systems by both enhancing drug stability and bioavailability, while also minimizing side effects due to targeted and controlled release. Even with these advancements towards clinical use and commercialization, there are barriers to long-term physical stability, cost-effective large-scale manufacture, and other biological barriers such as rapid clearance by the mononuclear phagocyte system (MPS) that continue to limit their use. Addressing these challenges vide rational design and innovative production technologies will unlock the clinical potential of niosomal formulations. The current review summarized recent advancements in niosome formulation research and highlighted their drug delivery applications in disease-specific therapies, while also offering a critical review of possible translational bottlenecks. The ongoing research to develop multifunctional, stimulus-responsive, and actively targeted niosomes, along with stable production methods, will accelerate the translation of these formulations to the clinic. Taken together, this research spectrum will improve approaches to safer, improved, and targeted therapeutic applications to stimulate exploration of the full niosome capability of drug delivery. Addressing these obstacles, through new formulation concepts, large-scale production economics, and wide-range safety evaluations, will be necessary for identifying optimal clinical value using niosomes. Future studies must focus on merging multifunctional targeting and stimulation sensitive release in advanced formulations to ultimately address existing delivery challenges.

Conflicts of interest

The authors declare that they have no conflicts of interest relevant to this article.

REFERENCE

1. Manzari MT, Shamay Y, Kiguchi H, Rosen N, Scaltriti M, Heller DA. Targeted drug delivery strategies for precision medicines. Nature Reviews Materials. 2021 Apr;6(4):351-70.
2. Ashique S, Sandhu NK, Chawla V, Chawla PA. Targeted drug delivery: Trends and perspectives. Current drug delivery. 2021 Dec 1;18(10):1435-55.
3. Ag Seleci D, Seleci M, Walter JG, Stahl F, Scheper T. Niosomes as nanoparticular drug

carriers: fundamentals and recent applications. Journal of nanomaterials. 2016;2016(1):7372306.
4. Patel P, Parashar AK, Kaurav M, Yadav K, Singh D, Gupta GD, Kurmi BD. Niosome: a vesicular drug delivery tool. InNanoparticles and Nanocarriers Based Pharmaceutical Preparations 2022 Dec 8 (pp. 333-364). Bentham Science Publishers.
5. Yasamineh S, Yasamineh P, Kalajahi HG, Gholizadeh O, Yekanipour Z, Afkhami H, Eslami M, Kheirkhah AH, Taghizadeh M, Yazdani Y, Dadashpour M. A state-of-the-art review on the recent advances of niosomes as a targeted drug delivery system. International journal of pharmaceutics. 2022 Aug 25;624:121878.
6. Neupane YR, Mahtab A, Siddiqui L, Singh A, Gautam N, Rabbani SA, Goel H, Talegaonkar S. Biocompatible nanovesicular drug delivery systems with targeting potential for autoimmune diseases. Current Pharmaceutical Design. 2020 Nov 1;26(42):5488-502.
7. Batool S, Sohail S, ud Din F, Alamri AH, Alqahtani AS, Alshahrani MA, Alshehri MA, Choi HG. A detailed insight of the tumor targeting using nanocarrier drug delivery system. Drug Delivery. 2023 Dec 31;30(1):2183815.
8. Izhar MP, Hafeez A, Kushwaha P, Simrah. Drug delivery through niosomes: a comprehensive review with therapeutic applications. Journal of Cluster Science. 2023 Sep;34(5):2257-73.
9. Pardakhty A. Non-ionic surfactant vesicles (Niosomes) as new drug delivery systems. Pharmaceutical Sciences: Breakthroughs in Research and Practice. 2017:154-84.
10. Camilo CJ, Leite DO, Silva AR, Menezes IR, Coutinho HD, Da Costa JG. Lipid vesicles: Applications, principal components and methods used in their formulations. A review. Acta Biológica Colombiana. 2020 Aug;25(2):339-52.
11. Wen J, Al Gailani M, Yin N, Rashidinejad A. Liposomes and niosomes. Emulsion‐based Systems for Delivery of Food Active Compounds: Formation, Application, Health and Safety. 2018 May 23:263-92.
12. Liga S, Paul C, Moacă EA, Péter F. Niosomes: Composition, formulation techniques, and recent progress as delivery systems in cancer therapy. Pharmaceutics. 2024 Feb 4;16(2):223.
13. Thabet Y, Elsabahy M, Eissa NG. Methods for preparation of niosomes: A focus on thin-film hydration method. Methods. 2022 Mar 1;199:9-15.
14. Ricci A, Stefanuto L, Gasperi T, Bruni F, Tofani D. Lipid nanovesicles for antioxidant delivery in skin: Liposomes, Ufasomes, Ethosomes, and Niosomes. Antioxidants. 2024 Dec 12;13(12):1516.
15. Khan MI, Madni A, Ahmad S, Mahmood MA, Rehman M, Ashfaq M. Formulation design and characterization of a non-ionic surfactant based vesicular system for the sustained delivery of a new chondroprotective agent. Brazilian Journal of Pharmaceutical Sciences. 2015;51(3):607-15.
16. Aljabali AA, Tambuwala MM, Obeid MA. Microfluidic manufacturing of niosomes. InMicrofluidics in Pharmaceutical Sciences: Formulation, Drug Delivery, Screening, and Diagnostics 2024 Jun 22 (pp. 77-108). Cham: Springer Nature Switzerland.
17. Rajni S, Singh DJ, Prasad DN, Sahil K, Anchal P. Formulation and evaluation of clindamycin phosphate niosomes by using reverse phase evaporation method. J Drug Deliv Ther. 2019 May 2;9(3-s):515-23.
18. Pirojiya H, Dudhat K. Niosomes: a revolution in sustainable and targeted drug delivery-green synthesis, precision medicine, and beyond.

Regenerative Engineering and Translational Medicine. 2024 Nov 25:1-37.

19. Ravalika V, Sailaja AK. Formulation and evaluation of etoricoxib niosomes by thin film hydration technique and ether injection method. Nano Biomed Eng. 2017 Sep 1;9(3):242-8.
20. Mawazi SM, Ge Y, Widodo RT. Niosome Preparation Techniques and Structure—An Illustrated Review. Pharmaceutics. 2025 Jan 6;17(1):67.
21. Ojeda E, Agirre M, Villate-Beitia I, Mashal M, Puras G, Zarate J, Pedraz JL. Elaboration and physicochemical characterization of niosome-based nioplexes for gene delivery purposes. Non-Viral Gene Delivery Vectors: Methods and Protocols. 2016:63-75.
22. Alavi SE, Alharthi S, Alavi SF, Alavi SZ, Zahra GE, Raza A, Shahmabadi HE. Microfluidics for personalized drug delivery. Drug Discovery Today. 2024 Apr 1;29(4):103936.
23. Ajrin M, Anjum F. Proniosome: A promising approach for vesicular drug delivery. Turkish Journal of Pharmaceutical Sciences. 2022 Aug 31;19(4):462.
24. Durak S, Esmaeili Rad M, Alp Yetisgin A, Eda Sutova H, Kutlu O, Cetinel S, Zarrabi A. Niosomal drug delivery systems for ocular disease—Recent advances and future prospects. Nanomaterials. 2020 Jun 18;10(6):1191.
25. Khan MS, Gupta G, Alsayari A, Wahab S, Sahebkar A, Kesharwani P. Advancements in liposomal formulations: A comprehensive exploration of industrial production techniques. International Journal of Pharmaceutics. 2024 May 8:124212.
26. Azarnezhad A, Samadian H, Jaymand M, Sobhani M, Ahmadi A. Toxicological profile of lipid-based nanostructures: are they considered as completely safe nanocarriers?. Critical reviews in toxicology. 2020 Feb 7;50(2):148-76.
27. Karpuz M, İlhan M, Gültekin HE, Ozgenc E, Şenyiğit Z, Atlihan-Gundogdu E. Nanovesicles for tumor-targeted drug delivery. InApplications of Nanovesicular Drug Delivery 2022 Jan 1 (pp. 219-244). Academic Press.
28. Krishnan J, Poomalai P, Ravichandran A, Reddy A, Sureshkumar R. A concise review on effect of PEGylation on the properties of lipid-based nanoparticles. ASSAY and Drug Development Technologies. 2024 Jul 1;22(5):246-64.
29. Yavari M, Foroushani ES, Nasri N, Zarepour A, Zarrabi A, Mostafavi E. Functionalized liposomes and niosomes for cancer therapy. InFunctionalized Nanomaterials for Cancer Research 2024 Jan 1 (pp. 345-363). Academic Press.
30. Bourbour M, Khayam N, Noorbazargan H, Yaraki MT, Lalami ZA, Akbarzadeh I, Yeganeh FE, Dolatabadi A, Rad FM, Tan YN. Evaluation of anti-cancer and anti-metastatic effects of folate-PEGylated niosomes for co-delivery of letrozole and ascorbic acid on breast cancer cells. Molecular Systems Design & Engineering. 2022;7(9):1102-18.
31. Salem HF, Kharshoum RM, Abo El-Ela FI, Abdellatif KR. Evaluation and optimization of pH-responsive niosomes as a carrier for efficient treatment of breast cancer. Drug delivery and translational research. 2018 Jun;8:633-44.
32. Zhang H, Wang K, Zhang P, He W, Song A, Luan Y. Redox-sensitive micelles assembled from amphiphilic mPEG-PCL-SS-DTX conjugates for the delivery of docetaxel. Colloids and Surfaces B: Biointerfaces. 2016 Jun 1;142:89-97.

33. Jhaveri A, Shvets V, Torchilin V. Stimuli-sensitive nanopreparations: Overview. Smart Pharm. Nanocarr. 2015 Dec 31;1:1-31.
34. Momekova DB, Gugleva VE, Petrov PD. Nanoarchitectonics of multifunctional niosomes for advanced drug delivery. ACS omega. 2021 Dec 6;6(49):33265-73.
35. Parsa MB, Tafvizi F, Chaleshi V, Ebadi M. Preparation, characterization, and Co-delivery of cisplatin and doxorubicin-loaded liposomes to enhance anticancer Activities. Heliyon. 2023 Oct 1;9(10).
36. Kunjiappan S, Pavadai P, Vellaichamy S, Ram Kumar Pandian S, Ravishankar V, Palanisamy P, Govindaraj S, Srinivasan G, Premanand A, Sankaranarayanan M, Theivendren P. Surface receptor‐mediated targeted drug delivery systems for enhanced cancer treatment: A state‐of‐the‐art review. Drug Development Research. 2021 May;82(3):309-40.
37. Mazidi Z, Javanmardi S, Naghib SM, Mohammadpour Z. Smart stimuli-responsive implantable drug delivery systems for programmed and on-demand cancer treatment: An overview on the emerging materials. Chemical Engineering Journal. 2022 Apr 1;433:134569.
38. Bach H, Lorenzo‐Leal AC. Use of niosomes for the treatment of intracellular pathogens infecting the lungs. Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2023 Jul;15(4):e1891.
39. Anjum A, Shabbir K, Din FU, Shafique S, Zaidi SS, Almari AH, Alqahtani T, Maryiam A, Moneeb Khan M, Al Fatease A, Bashir S. Co-delivery of amphotericin B and pentamidine loaded niosomal gel for the treatment of Cutaneous leishmaniasis. Drug Delivery. 2023 Dec 31;30(1):2173335.
40. Shahrivar RY, Fakhr ZA, Abbasgholinejad E, Doroudian M. Smart Lipid‐Based Nanoparticles in Lung Cancer Treatment: Current Status and Future Directions. Advanced Therapeutics. 2023 Dec;6(12):2300275.
41. Maestrelli F, Bragagni M, Mura P. Advanced formulations for improving therapies with anti-inflammatory or anaesthetic drugs: A review. Journal of Drug Delivery Science and Technology. 2016 Apr 1;32:192-205.
42. Muzzalupo R. Niosomes and proniosomes for enhanced skin delivery. Percutaneous Penetration Enhancers Chemical Methods in Penetration Enhancement: Nanocarriers. 2016:147-60.
43. Grijalvo S, Puras G, Zárate J, Sainz-Ramos M, Qtaish NA, López T, Mashal M, Attia N, Diaz Diaz D, Pons R, Fernández E. Cationic niosomes as non-viral vehicles for nucleic acids: Challenges and opportunities in gene delivery. Pharmaceutics. 2019 Jan 22;11(2):50.
44. Abtahi NA, Naghib SM, Ghalekohneh SJ, Mohammadpour Z, Nazari H, Mosavi SM, Gheibihayat SM, Haghiralsadat F, Reza JZ, Doulabi BZ. Multifunctional stimuli-responsive niosomal nanoparticles for co-delivery and co-administration of gene and bioactive compound: In vitro and in vivo studies. Chemical Engineering Journal. 2022 Feb 1;429:132090.
45. Liga S, Paul C, Moacă EA, Péter F. Niosomes: Composition, formulation techniques, and recent progress as delivery systems in cancer therapy. Pharmaceutics. 2024 Feb 4;16(2):223.
46. Vaiswade R, Chandrakar S, Roy A, Prasad P, Yadav C. Stability aspects of niosome. Int J Creat Res Thoughts. 2020;8(12):813-23.
47. Thakkar M. Opportunities and challenges for niosomes as drug delivery systems. Current Drug Delivery. 2016 Dec 1;13(8):1275-89.

48. Kamboj S, Saini V, Bala S. Formulation and characterization of drug loaded nonionic surfactant vesicles (niosomes) for oral bioavailability enhancement. The scientific world journal. 2014;2014(1):959741.
49. Awais M, Batool S, Khan M, Asim L, Riaz R, Zafar R. Strategies for crossing biological barriers in drug delivery. Proceedings of the national academy of sciences, India section B: biological sciences. 2024 Apr;94(2):235-43.
50. Shi B, Fang C, Pei Y. Stealth PEG-PHDCA niosomes: effects of chain length of PEG and particle size on niosomes surface properties, in vitro drug release, phagocytic uptake, in vivo pharmacokinetics and antitumor activity. Journal of pharmaceutical sciences. 2006 Sep 1;95(9):1873-87.
51. Riccardi D, Baldino L, Reverchon E. Liposomes, transfersomes and niosomes: Production methods and their applications in the vaccinal field. Journal of Translational Medicine. 2024 Apr 9;22(1):339.
52. Imperlini E, Celia C, Cevenini A, Mandola A, Raia M, Fresta M, Orrù S, Di Marzio L, Salvatore F. Nano-bio interface between human plasma and niosomes with different formulations indicates protein corona patterns for nanoparticle cell targeting and uptake. Nanoscale. 2021;13(10):5251-69.
53. Đorđević S, Gonzalez MM, Conejos-Sánchez I, Carreira B, Pozzi S, Acúrcio RC, Satchi-Fainaro R, Florindo HF, Vicent MJ. Current hurdles to the translation of nanomedicines from bench to the clinic. Drug delivery and translational research. 2022 Mar:1-26.

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