World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

ADVANCING NIOSOMAL DRUG DELIVERY: MANUFACTURING, CHARACTERIZATION, AND THERAPEUTIC APPLICATIONS - A COMPREHENSIVE REVIEW

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Article Received on 11/01/2024 **Article Revised on 01/02/2024** **Article Accepted on 21/02/2024**

ABSTRACT
Niosomes, self-assembled vesicular nanocarriers composed of non-ionic surfactants, have emerged as a promising alternative to liposomes in drug delivery systems. This review highlights the recent advancements in niosomal drug delivery, focusing on manufacturing methods, characterization techniques, and therapeutic applications. Niosomes are lipid-based nanoparticles that mimic the structure of the cell membrane. These biocompatible and biodegradable carriers can be loaded with various drugs, including small molecules, peptides, and proteins. The manufacturing of niosomes involves a series of steps, starting with the preparation of the lipid bilayer, followed by drug encapsulation and sterilization. Various techniques, such as film hydration, reverse phase evaporation, and microfluidic-based methods, have been developed to produce high-quality niosomes with desired characteristics. Niosomes offer several advantages over liposomes, including simple manufacturing, biodegradable, biocompatible, and non-immunogenic surfactants, and osmotic stability. They can encapsulate both hydrophilic and hydrophobic drugs, and their surfaces can be functionalized for targeted delivery, enhancing therapeutic performance. The review discusses the preparation of niosomes, their lamellarity, and specialised niosomes, such as pH-responsive niosomes, which are designed to improve drug delivery for specific diseases and conditions. The characterization of niosomes includes physical properties like size, polydispersity index, and drug entrapment efficiency, which are crucial for optimizing drug delivery systems. Niosomes have demonstrated potential in various therapeutic applications, including cancer treatment, gene delivery, and natural product delivery. They have shown promise in reducing toxicity, enhancing drug solubility and bioavailability, and improving pharmacokinetics. The review concludes by discussing the limitations and prospects for this technology, highlighting the need for further research to optimize niosomal drug delivery systems and obtain necessary licenses for their application as drug carriers.

KEYWORDS: Niosomes, Drug delivery, Manufacturing, Characterization, Therapeutic applications.

INTRODUCTION
Niosomal drug delivery system is a novel technology that has been gaining significant attention in the field of pharmaceutical sciences. Niosomes are nanovesicles that consist of a lipid bilayer surrounding an aqueous core.[1] They are formed by self-assembly of phospholipid and cholesterol molecules, resulting in a structure that resembles small vesicles. The advantage of niosomes is

their ability to encapsulate various drugs or therapeutic agents, protecting them from degradation and enhancing their stability and bioavailability.[2] Niosomes can be tailored to have specific properties such as size, composition, and surface charge, which can influence their targeting efficacy and drug delivery characteristics. One of the key advantages of niosomal drug delivery is their ability to enhance drug solubility and stability. Many drugs have poor aqueous solubility, which limits their bioavailability and therapeutic efficacy. Niosomes can overcome this challenge by encapsulating the drug in an aqueous core, leading to improved dissolution and absorption.[3] Moreover, niosomes offer potential for achieving targeted drug delivery. By modifying the surface properties of niosomes, such as adding targeting ligands, they can selectively bind to specific receptors or cells in the body. This targeting ability can enhance the therapeutic efficacy and reduce off-target effects. Niosomes can also be designed to release the encapsulated drug in a controlled manner. By incorporating release-controlling agents, such as pH-sensitive polymers or enzymes, in niosomes, the encapsulated drug can be released at a specific time or site of action.[4] This allows for better control over drug delivery and enhances patient compliance. In addition to their drug delivery advantages, niosomes have shown potential in reducing side effects associated with conventional drug delivery systems.[5] The encapsulation of drugs in niosomes can minimize drug toxicity, enhance patient tolerability, and improve the overall therapeutic outcomes.[6] This comprehensive review aims to provide an in-depth analysis of the advancements in niosomal drug delivery, focusing on manufacturing techniques, characterization methods, and therapeutic applications.[7] By examining the latest research findings and developments in the field, this review seeks to elucidate the potential of niosomes as drug delivery systems and address the challenges and opportunities for further exploration. The scope encompasses a wide range of therapeutic areas, including cancer therapy, infectious diseases, and central nervous system disorders, highlighting the versatility and efficacy of niosomal drug delivery[5] Through this review, we aim to contribute to the understanding of niosomal technology and its implications for the future of drug delivery.[2] This review article provides a comprehensive overview of niosomal drug delivery, exploring its manufacturing processes, characterization techniques, and therapeutic applications. By synthesizing current research and discussing future prospects, this review aims to shed light on the potential of niosomes as versatile and effective drug delivery vehicles.[8]

Manufacturing of niosomes

Formulation ingredients

Niosomal drug delivery formulations depend on a carefully balanced combination of ingredients to achieve optimal stability, efficacy, and functionality. Among these essential components, surfactants play a pivotal role in facilitating the formation of stable vesicles, crucial for encapsulating drug molecules.[9] These surfactants, characterized by their amphiphilic nature, possess both hydrophilic and hydrophobic regions, allowing them to self-assemble into bilayer structures that efficiently trap and deliver drugs.[5] The selection of surfactant type, whether non-ionic, cationic, or anionic, is guided by the desired characteristics of the final niosomal product, including biocompatibility, release kinetics, and targeting specificity. Additionally, cholesterol is commonly integrated into niosomal formulations to bolster the rigidity and stability of the membrane.[3] By modulating the fluidity of the lipid bilayer, cholesterol not only influences drug encapsulation efficiency and release kinetics but also serves to prevent drug leakage and enhance the physical integrity of niosomes. Moreover, the inclusion of other excipients further fine-tunes the properties of niosomes to meet specific formulation requirements and therapeutic goals.[10] These additional components, which may include stabilizers, antioxidants, buffering agents, and targeting ligands, among others, play critical roles in optimizing vesicle stability, drug loading capacity, and site-specific delivery.[6] The careful selection and incorporation of these excipients are guided by considerations such as desired release kinetics, stability under physiological conditions, and compatibility with targeted biological systems.[2] Thus, by harnessing the synergistic effects of surfactants, cholesterol, and other excipients, niosomal drug delivery systems offer a versatile and effective platform for the targeted delivery of therapeutic agents, with potential applications spanning a wide range of medical conditions.[11]

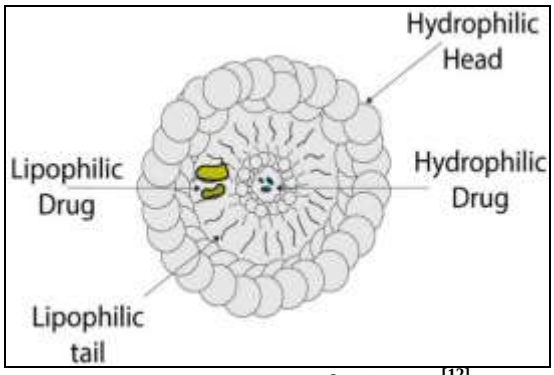

Figure 1: Structure of noisome.[12]

Methods of preparation

Thin film hydration

Thin film hydration is a widely used method for the preparation of niosomes, involving the formation of a lipid film by evaporating a mixture of lipids dissolved in an organic solvent. Initially, the lipid components, including surfactants and cholesterol, are dissolved in an appropriate organic solvent to form a homogeneous solution.[13] This solution is then spread thinly over the surface of a glass vessel or rotary evaporator and subjected to gentle heating or vacuum evaporation to remove the solvent. As the solvent evaporates, a thin

lipid film forms on the inner surface of the vessel.[3] Subsequently, the lipid film is hydrated with an aqueous phase containing the drug of interest. The hydration process causes the lipid bilayers to swell and form multilamellar vesicles (MLVs) or unilamellar vesicles (ULVs), depending on the degree of agitation and hydration conditions. The resulting niosomes encapsulate the drug molecules within their aqueous compartments, ready for further characterization and application in drug delivery.[14] Thin film hydration offers several advantages, including simplicity, scalability, and the ability to produce niosomes with controlled size and composition. However, optimization of parameters such as lipid concentration, hydration temperature, and hydration time is crucial to ensure uniform vesicle formation and optimal drug encapsulation efficiency.[5]

Ether injection method

The ether injection method is a popular technique used in the preparation of niosomes. In this method, lipid components such as surfactants and cholesterol are dissolved in an organic solvent, typically ether or chloroform.[4] The organic solution containing the lipid components is then injected into an aqueous phase containing the drug of interest under vigorous stirring or sonication. As the lipid solution comes into contact with the aqueous phase, rapid mixing occurs, leading to the spontaneous formation of niosomes.[15] The organic solvent evaporates quickly in the aqueous environment, leaving behind lipid bilayers that encapsulate the drug molecules. The resulting niosomes can vary in size and structure, depending on factors such as the composition of the lipid mixture, the ratio of organic solvent to aqueous phase, and the intensity of mixing. The ether injection method offers several advantages, including simplicity, rapidity, and the ability to produce niosomes with high encapsulation efficiency.[16] However, careful optimization of parameters is necessary to ensure reproducibility and uniformity in niosome characteristics. Additionally, the use of volatile organic solvents like ether requires appropriate safety precautions to prevent exposure and ensure worker safety during the manufacturing process.[17]

Reverse phase evaporation method

The reverse phase evaporation method is a commonly employed technique for the preparation of niosomes. In this method, lipid components, including surfactants and cholesterol, are dissolved in an organic solvent along with a water-miscible organic solvent, such as ethanol or methanol.[7] The organic phase containing the lipid mixture is then emulsified with an aqueous phase containing the drug of interest, typically by high-speed homogenization or sonication.[18] As the two phases are mixed, an emulsion is formed, with the organic solvent acting as a bridge between the lipid and aqueous phases. Subsequently, the organic solvent is removed under reduced pressure using techniques such as rotary evaporation or nitrogen gas blowing. This results in the formation of niosomes, where the lipid bilayers encapsulate the drug molecules within their aqueous compartments. The reverse phase evaporation method offers several advantages, including the ability to produce niosomes with high encapsulation efficiency and uniform size distribution.[19] Moreover, this method allows for the encapsulation of both hydrophilic and hydrophobic drugs, making it versatile for various therapeutic applications.[12] However, optimization of parameters such as lipid concentration, emulsification time, and solvent removal conditions is essential to ensure reproducibility and control over niosome characteristics. Additionally, the use of organic solvents necessitates proper safety measures to minimize exposure and ensure worker safety during the manufacturing process.[20]

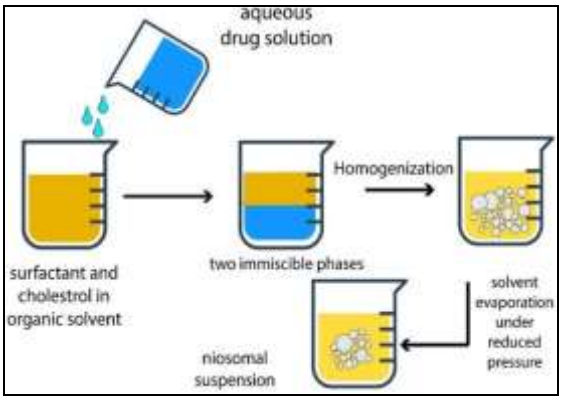

Figure 2: Preparation of niosomes with the reverse-phase evaporation method.[12]

Microfluidic techniques

Microfluidic techniques represent an innovative approach to the fabrication of niosomes with precise control over size, morphology, and composition. In microfluidic devices, fluids are manipulated within microscale channels, allowing for the precise mixing of lipid and aqueous phases under controlled flow conditions.[21] One common microfluidic method for niosome production involves the use of laminar flow focusing, where streams of lipid solution and aqueous phase containing the drug are introduced into a microfluidic channel. As the two streams flow side by side within the channel, they interact and merge, leading to the formation of niosomes through the process of self-assembly. The dimensions of the microfluidic channels can be precisely engineered to control the size and shape of the resulting niosomes.[5] Additionally, microfluidic techniques offer advantages such as rapid mixing, reduced sample volumes, and the potential for high-throughput production.[22] Furthermore, microfluidic devices can be easily scaled up for industrial manufacturing, providing a promising platform for the mass production of niosomes with uniform properties. However, optimization of microfluidic parameters, including flow rates, channel geometry, and surface chemistry, is crucial to ensure reproducibility and optimize niosome characteristics.[23] Moreover, the integration of microfluidic techniques with online

monitoring and control systems enables real-time monitoring of the niosome fabrication process, facilitating process optimization and quality assurance.[7] Overall, microfluidic techniques hold great promise for advancing niosome-based drug delivery systems, offering opportunities for precise control over formulation parameters and enhanced therapeutic efficacy.[24]

Other advanced manufacturing techniques

In addition to traditional methods such as thin film hydration, ether injection, reverse phase evaporation, and microfluidic techniques, several other advanced manufacturing techniques have been explored for the preparation of niosomes.[11] These techniques offer unique advantages in terms of scalability, reproducibility, and control over niosome characteristics. One such method is sonication, where lipid components are dispersed in an aqueous solution containing the drug and subjected to ultrasonic waves.[25] The energy generated by the sonication process leads to the formation of niosomes through disruption and reassembly of lipid bilayers. Sonication is known for its simplicity and versatility, making it suitable for both laboratory-scale and large-scale production of niosomes. Another advanced technique is extrusion, where lipid suspensions are forced through small pores under controlled pressure to produce uniform-sized niosomes.[26] Extrusion enables precise control over vesicle size and size distribution, making it suitable for applications requiring narrow size ranges.[5] Additionally, freeze-drying or lyophilization has been explored as a method for niosome preparation, where aqueous niosome suspensions are frozen and then subjected to vacuum drying to remove water content, resulting in lyophilized niosomes with enhanced stability and shelf-life. These advanced manufacturing techniques offer opportunities for tailoring niosome properties to meet specific formulation requirements and therapeutic applications.[27] However, optimization of process parameters and validation of scale-up capabilities are essential to ensure consistent and reproducible production of niosomes using these methods.[13] Overall, the exploration of advanced manufacturing techniques underscores the ongoing efforts to enhance the versatility and efficacy of niosomal drug delivery systems for various biomedical applications. Table 1 provides a diverse range of methods of preparation for niosomal drug delivery systems, along with examples of drugs, composition, solvents used, and their applications in various therapeutic areas.[28]

Table 1: Overview of Niosomal Drug Delivery Systems: Methods of Preparation, Drugs, Composition, Solvents, and Applications.

Method of Preparation	Drug	Composition	Solvent	Application	Reference
Thin Film Hydration	Paclitaxel	Nonionic surfactants, cholesterol, drug	Organic solvent	Cancer therapy, targeted drug delivery	[29]
Ether Injection Method	Ciprofloxacin	Nonionic surfactants, cholesterol, drug	Ether	Treatment of bacterial infections	[5]
Reverse Phase Evaporation	Curcumin	Nonionic surfactants, cholesterol, drug	Organic solvent	Anti-inflammatory, antioxidant therapy	[3]
Microfluidic Techniques	Acyclovir	Nonionic surfactants, cholesterol, drug	Aqueous solvent	Antiviral therapy, herpes treatment	[30]
Lipid Film Hydration	Insulin	Nonionic surfactants, cholesterol, drug	Aqueous solvent	Diabetes management, insulin delivery	[2]
Double Emulsion Method	Doxorubicin	Nonionic surfactants, cholesterol, drug	Organic solvent	Cancer therapy, treatment of solid tumors	[19]
Reverse-Phase Evaporation	Methotrexate	Nonionic surfactants, cholesterol, drug	Organic solvent	Rheumatoid arthritis, autoimmune therapy	[3]
Solvent Injection Method	Amphotericin B	Nonionic surfactants, cholesterol, drug	Organic solvent	Treatment of fungal infections	[5]
Emulsification-Condensation	Tacrolimus	Nonionic surfactants, cholesterol, drug	Organic solvent	Immunosuppressive therapy, organ transplantation	[11]
Modified Solvent Injection	Dexamethasone	Nonionic surfactants, cholesterol, drug	Organic solvent	Treatment of ocular inflammation, uveitis	[16]

Characterization techniques

Particle Size and Size distribution

Particle size and size distribution refer to the dimensions and spread of sizes among particles within a sample. In the context of niosomal drug delivery, particle size analysis provides critical information about the physical characteristics of niosome formulations. Techniques such as dynamic light scattering (DLS) or laser diffraction are commonly employed to measure particle size and size distribution.[31] These methods involve illuminating the

sample with a light source and analyzing the intensity of scattered light to determine the size distribution profile.[17] Particle size analysis allows researchers to assess the uniformity and homogeneity of niosome populations, which is crucial for ensuring consistent drug delivery performance and therapeutic efficacy. Additionally, knowledge of particle size and distribution aids in optimizing formulation parameters and predicting the behavior of niosomes in biological systems.[32]

Surface charge

Surface charge, also known as zeta potential, refers to the electric potential difference between the surface of particles and the surrounding medium. In the context of niosomal drug delivery, surface charge plays a crucial role in the stability and interaction of niosome formulations with biological systems.[33] Zeta potential measurements are commonly used to quantify surface charge, with techniques such as electrophoretic light scattering employed for analysis.[20] Zeta potential reflects the extent of electrostatic repulsion or attraction between particles, influencing their dispersion, aggregation, and interaction with cells and tissues. Niosomes with higher zeta potential values exhibit greater stability and resistance to aggregation due to increased repulsive forces between particles.[19] Moreover, surface charge characteristics influence the cellular uptake, biodistribution, and pharmacokinetics of niosome formulations, making it a critical parameter to consider in the design and optimization of drug delivery systems.[34]

Morphology

Morphology refers to the physical structure, shape, and appearance of particles within a sample. In the context of niosomal drug delivery, morphology analysis provides valuable insights into the size, shape, and surface characteristics of niosome formulations. Techniques such as transmission electron microscopy (TEM) or scanning electron microscopy (SEM) are commonly used to visualize and characterize the morphology of niosomes at the micro- and nanoscale levels.[35] These imaging techniques allow researchers to observe the integrity, shape, and surface morphology of individual niosome vesicles, providing information about their structural properties. Morphological analysis helps assess the uniformity, dispersion, and aggregation tendencies of niosomes, which are crucial factors affecting their stability, drug loading capacity, and drug release behavior.[21] Additionally, knowledge of niosome morphology aids in understanding the interactions of niosomes with biological systems, including cellular uptake mechanisms and biodistribution profiles, contributing to the rational design and optimization of niosomal drug delivery systems.[36]

Encapsulation efficiency

Encapsulation efficiency refers to the proportion of drug molecules successfully entrapped or encapsulated within the niosome vesicles relative to the total amount of drug added during the formulation process.[2] It is a critical parameter that directly influences the efficacy and performance of niosomal drug delivery systems.[37] Encapsulation efficiency is typically determined by comparing the amount of drug encapsulated within the niosomes to the total amount of drug added, often measured using analytical techniques such as high-performance liquid chromatography (HPLC) or spectrophotometry. High encapsulation efficiency indicates that a significant portion of the drug payload has been successfully incorporated into the niosome vesicles, minimizing drug loss and maximizing the therapeutic potential of the formulation.[17] Optimization of formulation parameters, such as lipid composition, hydration conditions, and drug-to-lipid ratio, is essential for achieving high encapsulation efficiency and ensuring consistent drug loading across batches.[38] Encapsulation efficiency is a key consideration in the development and characterization of niosomal drug delivery systems, as it directly impacts drug release kinetics, pharmacokinetics, and therapeutic efficacy.

Drug loading capacity

Drug loading capacity refers to the maximum amount of drug that can be encapsulated or loaded into the niosome vesicles per unit mass or volume of the formulation.[18] It is a critical parameter that influences the drug delivery efficiency and efficacy of niosomal drug delivery systems. Drug loading capacity is determined by measuring the amount of drug encapsulated within the niosomes and expressing it relative to the total mass or volume of the niosome formulation.[39] Optimization of drug loading capacity involves balancing factors such as lipid composition, drug-to-lipid ratio, and formulation conditions to achieve maximal drug encapsulation while maintaining niosome stability and integrity.[28] High drug loading capacity allows for the delivery of therapeutically effective doses of drugs within a smaller volume of niosome formulation, minimizing potential side effects and improving patient compliance. However, achieving high drug loading capacity without compromising niosome stability and drug release kinetics requires careful optimization and characterization of the formulation parameters.[29] Drug loading capacity is a crucial consideration in the design, development, and characterization of niosomal drug delivery systems, as it directly impacts their therapeutic potential and clinical utility.[40]

Structural characterization

X-ray diffraction

X-ray diffraction is a technique used to analyze the crystal structure and molecular arrangement of materials, including niosome components such as surfactants and cholesterol.[18] In this method, a sample is exposed to X-ray radiation, and the resulting diffraction pattern is recorded and analyzed. The diffraction pattern provides information about the spacing and orientation of atoms or molecules within the sample, allowing researchers to determine the crystalline structure and phase behavior of

niosome components.[41] X-ray diffraction is commonly employed to investigate the lipid bilayer structure of niosomes, providing insights into the packing arrangement of lipid molecules and the formation of ordered or disordered phases.[30] By studying X-ray diffraction patterns, researchers can assess the stability, polymorphism, and phase transitions occurring within niosome formulations, which are important considerations for optimizing their drug delivery performance and shelf-life stability. X-ray diffraction is a valuable tool for characterizing the structural properties of niosomes and gaining insights into their behavior under different environmental conditions.[42]

Differential scanning calorimetry

Differential scanning calorimetry (DSC) is a thermal analysis technique used to study the heat flow associated with physical and chemical changes in materials.[2] In the context of niosomal drug delivery, DSC is utilized to investigate the thermal behavior of niosome formulations and their components. During a DSC experiment, the sample is heated or cooled at a controlled rate, while the heat flow into or out of the sample is measured relative to a reference material.[43] Changes in heat flow correspond to phase transitions, such as melting, crystallization, or phase separation, occurring within the niosome lipid bilayers or drug molecules. By analyzing the resulting DSC thermogram, researchers can determine the temperature at which these phase transitions occur, as well as the associated enthalpy changes.[16] This information provides insights into the thermal stability, phase behavior, and lipid composition of niosome formulations, which are crucial for understanding their physical properties and optimizing their drug delivery performance. Differential scanning calorimetry is a powerful tool for characterizing the thermal properties of niosomes and assessing their suitability for pharmaceutical applications.[44]

Fourier transform infrared spectroscopy

Fourier Transform Infrared Spectroscopy (FTIR) is a technique used to analyze the chemical composition and molecular structure of materials by measuring their interactions with infrared radiation. In the context of niosomal drug delivery, FTIR is employed to characterize the functional groups and chemical bonds present in niosome formulations and their components.[32] During an FTIR experiment, infrared radiation is passed through a sample, and the resulting absorption spectrum is recorded.[45] The absorption spectrum provides information about the vibrational modes of chemical bonds within the sample, allowing researchers to identify specific functional groups and molecular species. By comparing the FTIR spectra of niosome formulations with reference spectra of individual components, researchers can assess the compatibility, interactions, and structural changes occurring within the niosomes.[46] FTIR analysis is particularly useful for studying lipid bilayer formation, hydrogen bonding interactions, and changes in molecular conformation that may affect the stability and performance of niosomal drug delivery systems.[35] Fourier Transform Infrared Spectroscopy is a valuable analytical tool for investigating the chemical composition and structural properties of niosomes, providing insights into their formulation characteristics and behavior in biological environments.[47]

Stability studies

Stability studies for niosomal drug delivery systems are essential for assessing their long-term viability and performance. These studies encompass two primary aspects: shelf-life assessment and stability in biological milieu. Shelf-life assessment involves monitoring the stability of niosomal formulations over time under controlled storage conditions, evaluating changes in physicochemical properties such as particle size, surface charge, and drug encapsulation efficiency to determine their shelf-life and storage recommendations.[48] On the other hand, stability in biological milieu evaluates the behavior of niosome formulations when exposed to physiological conditions, assessing parameters like particle size, drug release kinetics, and stability of encapsulated drugs to predict their behavior in vivo.[19] Together, stability studies provide critical insights into the durability, efficacy, and safety of niosomal drug delivery systems, guiding their development and ensuring their suitability for clinical applications.[49]

Therapeutic applications

A. Cancer therapy

1. Targeted drug delivery

Cancer remains one of the leading causes of death worldwide, with millions of lives affected by its devastating impact each year. Traditional cancer treatments, such as chemotherapy and radiation therapy, often exhibit limited efficacy and significant systemic toxicity, resulting in adverse side effects and diminished quality of life for patients.[28] In recent years, targeted drug delivery has emerged as a promising strategy for improving the effectiveness of cancer therapy while minimizing off-target effects and enhancing patient outcomes.[50] Targeted drug delivery involves the selective delivery of therapeutic agents to cancer cells or tumor tissues, thereby maximizing drug concentration at the site of action while sparing healthy tissues from cytotoxic effects. Among the various drug delivery systems investigated for targeted cancer therapy, niosomal drug delivery systems have garnered significant interest due to their versatility, biocompatibility, and tunable properties.[30] Niosomal drug delivery systems are lipid-based vesicles composed of nonionic surfactants and cholesterol, which can encapsulate a wide range of therapeutic agents, including chemotherapeutic drugs, targeted agents, and nucleic acid-based therapies.[51] These vesicular carriers offer several advantages for cancer therapy, including high drug-loading capacity, controlled release kinetics, and enhanced stability. Furthermore, niosomes can be engineered to modify their surface properties, such as size, charge, and targeting ligands, to achieve specific

drug delivery objectives. This inherent flexibility makes niosomal drug delivery systems well-suited for targeted cancer therapy, where treatment strategies are tailored to the unique molecular characteristics of cancer cells and tumor microenvironments.[38] One of the key strategies in targeted drug delivery for cancer therapy is the functionalization of niosomes with targeting ligands that can specifically recognize and bind to overexpressed receptors or antigens on cancer cells. By conjugating targeting ligands, such as antibodies, peptides, or aptamers, to the surface of niosomes, it is possible to enhance their selective uptake by cancer cells while minimizing uptake by normal cells.[52] This targeted approach allows for the preferential accumulation of therapeutic agents within the tumor tissue, thereby maximizing drug efficacy and minimizing systemic toxicity.[41] Moreover, targeted drug delivery using niosomal carriers can overcome several challenges associated with conventional chemotherapy, such as drug resistance, limited drug penetration, and dose-limiting side effects. Niosomal formulations can encapsulate hydrophobic drugs within their lipid bilayer membranes, protecting them from degradation and facilitating their intracellular delivery to cancer cells.[42] Additionally, niosomes can be engineered to release drugs in a controlled manner, prolonging their circulation time and enhancing their accumulation within the tumor tissue through the enhanced permeability and retention (EPR) effect.[53] By optimizing formulation parameters and targeting strategies, niosomal drug delivery systems offer opportunities to overcome multidrug resistance mechanisms and improve therapeutic outcomes for cancer patients. Furthermore, targeted drug delivery using niosomes enables combination therapy approaches, wherein multiple therapeutic agents with complementary mechanisms of action are co-delivered to cancer cells to enhance treatment efficacy and overcome resistance.[49] By encapsulating different drugs within the same niosomal carrier, it is possible to achieve synergistic effects, reduce the likelihood of drug resistance, and target multiple signaling pathways involved in cancer progression.[54] For example, niosomal formulations can combine chemotherapy agents with targeted therapies, immunotherapies, or gene therapies to create multifunctional drug delivery systems with enhanced anticancer activity. In addition to targeted drug delivery, niosomal drug delivery systems offer opportunities for personalized medicine approaches in cancer therapy, where treatment strategies are tailored to individual patient characteristics, such as genetic mutations, tumor heterogeneity, and treatment response.[13] By leveraging advancements in genomics, proteomics, and biomarker-based diagnostics, healthcare providers can identify molecular signatures and predictive biomarkers that inform treatment decisions and guide the selection of optimal therapeutic regimens for cancer patients. Niosomal formulations can be customized to encapsulate specific drug combinations, dosage forms, or targeting ligands based on patient-specific factors, resulting in personalized treatment approaches that maximize therapeutic efficacy and minimize adverse effects.[55]

2. Combination therapy

Combination therapy, also known as multimodal therapy or polytherapy, involves the simultaneous administration of two or more therapeutic agents to achieve synergistic effects and enhance treatment outcomes.[49] In the context of cancer therapy, combination therapy is a widely utilized strategy aimed at targeting multiple pathways involved in tumor growth, metastasis, and drug resistance. By combining drugs with different mechanisms of action, combination therapy can enhance anticancer efficacy, overcome drug resistance, and reduce the likelihood of tumor recurrence.[56] Niosomal drug delivery systems offer unique advantages for combination therapy in cancer treatment due to their versatility, biocompatibility, and tunable properties.[30] These lipid-based vesicles can encapsulate a wide range of therapeutic agents, including chemotherapeutic drugs, targeted agents, and nucleic acid-based therapies, within their aqueous core or lipid bilayer membranes.[42] By encapsulating multiple drugs within the same niosomal carrier, it is possible to achieve synergistic effects, enhance drug stability, and optimize drug release kinetics for combination therapy applications. One key advantage of combination therapy using niosomal drug delivery systems is the ability to co-deliver drugs with different physicochemical properties and pharmacokinetic profiles.[57] For example, hydrophobic drugs can be encapsulated within the lipid bilayer membranes of niosomes, while hydrophilic drugs can be loaded into the aqueous core or conjugated to the surface of niosomes. This allows for the simultaneous delivery of drugs with diverse solubility characteristics, enabling more efficient drug delivery and enhanced therapeutic efficacy.[20] Moreover, combination therapy using niosomal carriers can overcome several challenges associated with conventional chemotherapy, such as drug resistance, limited drug penetration, and dose-limiting side effects. Niosomes can enhance the intracellular delivery of therapeutic agents to cancer cells, thereby overcoming multidrug resistance mechanisms and increasing drug accumulation within the tumor tissue.[56] Additionally, niosomal formulations can be engineered to release drugs in a controlled manner, prolonging their circulation time and enhancing their accumulation within the tumor tissue through the enhanced permeability and retention (EPR) effect.[58] Furthermore, combination therapy using niosomal drug delivery systems enables the co-delivery of drugs with complementary mechanisms of action to target multiple signaling pathways involved in cancer progression.[27] For example, chemotherapeutic drugs can be combined with targeted therapies, immunotherapies, or gene therapies to create multifunctional drug delivery systems with enhanced anticancer activity. By targeting different aspects of tumor biology, combination therapy approaches can achieve additive or synergistic effects, resulting in improved treatment outcomes and prolonged survival for cancer patients.[59]

B. Infectious diseases

1. Antimicrobial delivery

Infectious diseases pose significant global health challenges, with a wide range of pathogens causing illnesses such as bacterial infections, viral infections, fungal infections, and parasitic infections. The emergence of antimicrobial resistance has further exacerbated the problem, highlighting the need for innovative approaches to combat infectious diseases effectively,[16] Antimicrobial delivery, particularly through advanced drug delivery systems like niosomes, offers a promising strategy to enhance the efficacy of antimicrobial agents while minimizing adverse effects and overcoming drug resistance.[60] Antimicrobial delivery using niosomal drug delivery systems involves encapsulating antimicrobial agents within lipid-based vesicles composed of nonionic surfactants and cholesterol. These vesicular carriers offer several advantages for antimicrobial therapy, including enhanced drug stability, controlled release kinetics, and improved bioavailability. By encapsulating antimicrobial agents within niosomes, it is possible to achieve targeted delivery to the site of infection, thereby maximizing therapeutic efficacy while minimizing systemic toxicity.[61] One key advantage of antimicrobial delivery using niosomal carriers is the ability to overcome the limitations associated with conventional antimicrobial therapy, such as poor solubility, low bioavailability, and rapid clearance from the body.[17] Niosomal formulations can encapsulate hydrophobic antimicrobial agents within their lipid bilayer membranes, protecting them from degradation and facilitating their uptake into microbial cells. Additionally, niosomes can be engineered to release antimicrobial agents in a controlled manner, prolonging their retention time at the site of infection and enhancing their antimicrobial activity.[62] Moreover, antimicrobial delivery using niosomal drug delivery systems offers opportunities to address antimicrobial resistance, a growing threat to global public health. By encapsulating multiple antimicrobial agents within the same niosomal carrier, it is possible to achieve synergistic effects and overcome resistance mechanisms employed by microbial pathogens. Furthermore, niosomes can be engineered to deliver antimicrobial agents via novel mechanisms of action, such as disrupting microbial biofilms, inhibiting virulence factors, or modulating host immune responses, thereby reducing the likelihood of resistance development.[63] In addition to enhancing therapeutic efficacy, antimicrobial delivery using niosomal carriers can also minimize off-target effects and reduce systemic toxicity compared to conventional antimicrobial therapy.[29] By selectively delivering antimicrobial agents to the site of infection while sparing healthy tissues from cytotoxic effects, niosomal formulations can improve patient tolerability and treatment outcomes. This targeted approach is particularly advantageous for treating localized infections, such as skin infections, respiratory tract infections, and urinary tract infections, where precise drug delivery is essential for effective treatment.[64] Furthermore, antimicrobial delivery using niosomal drug delivery systems enables the development of novel treatment strategies for challenging infectious diseases, such as multidrug-resistant bacterial infections, viral infections, and fungal infections. By optimizing formulation parameters and incorporating targeting ligands or penetration enhancers, niosomal formulations can achieve enhanced antimicrobial activity and improved tissue penetration, thereby overcoming barriers to effective antimicrobial therapy.[5,65]

2. Antiviral delivery

Antiviral delivery using niosomal drug delivery systems presents a promising approach for combating viral infections by enhancing the efficacy of antiviral agents while minimizing adverse effects and overcoming viral resistance mechanisms. Viral infections, including those caused by viruses such as influenza, HIV, hepatitis, and herpesviruses, pose significant public health challenges worldwide, necessitating the development of innovative strategies for antiviral therapy.[66] Niosomal drug delivery systems offer several advantages for antiviral delivery, including enhanced drug stability, controlled release kinetics, and improved bioavailability, making them well-suited for delivering antiviral agents to target sites of viral replication.[41] One key advantage of niosomal antiviral delivery is the ability to encapsulate antiviral agents within lipid-based vesicles composed of nonionic surfactants and cholesterol. These vesicular carriers protect antiviral agents from degradation and facilitate their uptake into infected cells, thereby enhancing their antiviral activity.[67] Additionally, niosomes can be engineered to release antiviral agents in a controlled manner, prolonging their retention time at the site of infection and maximizing their therapeutic efficacy while minimizing systemic toxicity.[51] Moreover, niosomal antiviral delivery offers opportunities to address challenges associated with conventional antiviral therapy, such as poor drug solubility, low bioavailability, and rapid clearance from the body. By encapsulating antiviral agents within niosomes, it is possible to overcome these limitations and achieve targeted delivery to the site of viral replication, thereby maximizing therapeutic efficacy while minimizing adverse effects on healthy tissues.[17] Furthermore, niosomal antiviral delivery enables the co-delivery of multiple antiviral agents within the same carrier, thereby enhancing treatment efficacy and reducing the likelihood of viral resistance development. By encapsulating different antiviral agents with complementary mechanisms of action, such as viral entry inhibitors, nucleoside analogs, and protease inhibitors, it is possible to achieve synergistic effects and overcome resistance mechanisms employed by viral pathogens.[23] In addition to enhancing therapeutic efficacy, niosomal antiviral delivery can also minimize off-target effects and reduce systemic toxicity compared to conventional antiviral therapy.[68] By selectively delivering antiviral agents to infected cells while sparing healthy tissues from cytotoxic effects, niosomal formulations can

improve patient tolerability and treatment outcomes. This targeted approach is particularly advantageous for treating viral infections with high morbidity and mortality rates, such as HIV/AIDS, influenza, and viral hepatitis.[31] Furthermore, niosomal antiviral delivery enables the development of novel treatment strategies for emerging and re-emerging viral diseases, such as COVID-19, by optimizing formulation parameters and incorporating targeting ligands or penetration enhancers.[50] By leveraging the unique properties of niosomes, researchers and healthcare providers can develop innovative antiviral formulations that enhance drug efficacy, minimize adverse effects, and overcome resistance mechanisms employed by viral pathogens.[69]

C. Central nervous system disorders

1. Blood-Brain barrier penetration

Blood-brain barrier penetration refers to the ability of drugs to cross the blood-brain barrier (BBB) and reach the central nervous system (CNS) for the treatment of neurological disorders. In the context of niosomal drug delivery systems, achieving blood-brain barrier penetration involves designing formulations that can overcome the selective permeability of the BBB.[70] Niosomes offer promising strategies for enhancing drug delivery to the brain by encapsulating therapeutic agents within carrier systems capable of crossing the BBB.[28] This can be achieved through various approaches, including surface modification with targeting ligands, such as peptides or antibodies, that can interact with receptors expressed on the BBB endothelial cells.[49] Additionally, optimizing the physicochemical properties of niosomes, such as size, surface charge, and lipid composition, can facilitate BBB penetration and enhance drug delivery to the brain. Blood-brain barrier penetration using niosomal drug delivery systems holds potential for the treatment of neurological disorders, including Alzheimer's disease, Parkinson's disease, brain tumors, and neuroinfections.[71]

2. Neurodegenerative disease treatment

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), represent a significant and growing public health concern worldwide. These debilitating conditions are characterized by progressive degeneration of neurons in the central nervous system, leading to cognitive decline, motor dysfunction, and loss of functional independence.[72] Current treatment options for neurodegenerative diseases are limited and often focus on symptomatic management rather than disease modification.[58] However, emerging evidence suggests that niosomal drug delivery systems hold promise for improving the treatment of neurodegenerative diseases by enhancing the delivery of therapeutic agents to the brain, mitigating disease progression, and improving patient outcomes.[57] Niosomes, lipid-based vesicles composed of nonionic surfactants and cholesterol, offer several advantages for drug delivery to the central nervous system (CNS). These vesicular carriers can encapsulate a wide range of therapeutic agents, including small molecules, peptides, proteins, and nucleic acids, within their aqueous core or lipid bilayer membranes.[73] By encapsulating neuroprotective agents or disease-modifying drugs within niosomes, it is possible to enhance their stability, prolong their circulation time, and improve their bioavailability for targeted delivery to the brain.[60] One key advantage of niosomal drug delivery systems in neurodegenerative disease treatment is their ability to overcome the blood-brain barrier (BBB), a highly selective membrane that limits the passage of drugs from the bloodstream into the brain parenchyma. Niosomes can be engineered to cross the BBB via various mechanisms, including receptor-mediated transcytosis, adsorptive-mediated transcytosis, and passive diffusion, thereby facilitating the delivery of therapeutic agents to the site of action within the CNS.[32] This targeted approach enables the selective delivery of neuroprotective agents or disease-modifying drugs to affected brain regions, minimizing off-target effects and maximizing therapeutic efficacy.[74] Moreover, niosomal drug delivery systems offer opportunities to address challenges associated with conventional drug administration routes for neurodegenerative diseases, such as oral administration, intravenous injection, or intrathecal infusion. By encapsulating therapeutic agents within niosomes, it is possible to overcome limitations such as poor drug solubility, rapid metabolism, and systemic toxicity, thereby improving drug pharmacokinetics and enhancing CNS drug delivery. Additionally, niosomal formulations can be tailored to release drugs in a controlled manner, prolonging their retention time within the brain and optimizing their therapeutic effects.[21] Furthermore, niosomal drug delivery systems enable the co-delivery of multiple therapeutic agents within the same carrier, thereby enhancing treatment efficacy and addressing the multifactorial nature of neurodegenerative diseases. By encapsulating different neuroprotective agents or disease-modifying drugs with complementary mechanisms of action, it is possible to achieve synergistic effects and target multiple pathogenic pathways involved in disease progression.[75] This multifunctional approach holds promise for slowing disease progression, preserving neuronal function, and improving clinical outcomes for patients with neurodegenerative diseases.[29] In addition to enhancing therapeutic efficacy, niosomal drug delivery systems can also minimize off-target effects and reduce systemic toxicity compared to conventional drug administration routes.[39] By selectively delivering therapeutic agents to the brain while sparing peripheral tissues from cytotoxic effects, niosomal formulations can improve patient tolerability and treatment compliance. This targeted approach is particularly advantageous for neurodegenerative diseases, where precise drug delivery to affected brain regions is essential for optimal therapeutic outcomes.[76]

D. Other therapeutic applications

1. Cardiovascular diseases

Neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), represent a significant and growing public health concern worldwide.[45] These debilitating conditions are characterized by progressive degeneration of neurons in the central nervous system, leading to cognitive decline, motor dysfunction, and loss of functional independence.[77] Current treatment options for neurodegenerative diseases are limited and often focus on symptomatic management rather than disease modification. However, emerging evidence suggests that niosomal drug delivery systems hold promise for improving the treatment of neurodegenerative diseases by enhancing the delivery of therapeutic agents to the brain, mitigating disease progression, and improving patient outcomes.[51] Niosomes, lipid-based vesicles composed of nonionic surfactants and cholesterol, offer several advantages for drug delivery to the central nervous system (CNS). These vesicular carriers can encapsulate a wide range of therapeutic agents, including small molecules, peptides, proteins, and nucleic acids, within their aqueous core or lipid bilayer membranes.[78] By encapsulating neuroprotective agents or disease-modifying drugs within niosomes, it is possible to enhance their stability, prolong their circulation time, and improve their bioavailability for targeted delivery to the brain.[65] One key advantage of niosomal drug delivery systems in neurodegenerative disease treatment is their ability to overcome the blood-brain barrier (BBB), a highly selective membrane that limits the passage of drugs from the bloodstream into the brain parenchyma. Niosomes can be engineered to cross the BBB via various mechanisms, including receptor-mediated transcytosis, adsorptive-mediated transcytosis, and passive diffusion, thereby facilitating the delivery of therapeutic agents to the site of action within the CNS.[79] This targeted approach enables the selective delivery of neuroprotective agents or disease-modifying drugs to affected brain regions, minimizing off-target effects and maximizing therapeutic efficacy. Moreover, niosomal drug delivery systems offer opportunities to address challenges associated with conventional drug administration routes for neurodegenerative diseases, such as oral administration, intravenous injection, or intrathecal infusion.[58] By encapsulating therapeutic agents within niosomes, it is possible to overcome limitations such as poor drug solubility, rapid metabolism, and systemic toxicity, thereby improving drug pharmacokinetics and enhancing CNS drug delivery.[80] Additionally, niosomal formulations can be tailored to release drugs in a controlled manner, prolonging their retention time within the brain and optimizing their therapeutic effects.[41] Furthermore, niosomal drug delivery systems enable the co-delivery of multiple therapeutic agents within the same carrier, thereby enhancing treatment efficacy and addressing the multifactorial nature of neurodegenerative diseases. By encapsulating different neuroprotective agents or disease-modifying drugs with complementary mechanisms of action, it is possible to achieve synergistic effects and target multiple pathogenic pathways involved in disease progression.[81] This multifunctional approach holds promise for slowing disease progression, preserving neuronal function, and improving clinical outcomes for patients with neurodegenerative diseases. In addition to enhancing therapeutic efficacy, niosomal drug delivery systems can also minimize off-target effects and reduce systemic toxicity compared to conventional drug administration routes.[52] By selectively delivering therapeutic agents to the brain while sparing peripheral tissues from cytotoxic effects, niosomal formulations can improve patient tolerability and treatment compliance. This targeted approach is particularly advantageous for neurodegenerative diseases, where precise drug delivery to affected brain regions is essential for optimal therapeutic outcomes.[82]

2. Dermatological disorders

Dermatological disorders encompass a wide range of conditions affecting the skin, hair, and nails, including eczema, psoriasis, acne, fungal infections, and skin cancer. These disorders can significantly impact patients' quality of life and often require long-term treatment regimens to manage symptoms and prevent complications.[69] Niosomal drug delivery systems offer a promising approach to improve the treatment of dermatological disorders by enhancing the delivery of therapeutic agents to the skin, improving drug penetration, and minimizing adverse effects.[83] Niosomes, lipid-based vesicles composed of nonionic surfactants and cholesterol, possess several characteristics that make them well-suited for drug delivery in dermatological disorders. These vesicular carriers can encapsulate a variety of therapeutic agents, including corticosteroids, antibiotics, antifungals, retinoids, and anti-inflammatory agents, within their aqueous core or lipid bilayer membranes.[69] By encapsulating dermatological drugs within niosomes, it is possible to improve drug stability, prolong drug retention on the skin, and enhance drug penetration into the deeper layers of the skin, thereby optimizing therapeutic efficacy.[84] One key advantage of niosomal drug delivery systems in dermatological disorders is their ability to enhance drug penetration and retention in the skin, thereby improving treatment outcomes. Niosomes can be engineered to modify their surface properties, such as size, charge, and composition, to achieve optimal drug delivery to the target site within the skin.[70] This targeted approach enables the selective delivery of therapeutic agents to affected skin regions while minimizing systemic exposure and adverse effects on other tissues or organs.[85] Moreover, niosomal drug delivery systems offer opportunities to address challenges associated with conventional topical drug administration routes for dermatological disorders, such as poor drug solubility, limited drug penetration, and

rapid drug clearance from the skin.[25] By encapsulating dermatological drugs within niosomes, it is possible to overcome these limitations and achieve controlled drug release, prolonged drug retention, and enhanced drug penetration into the skin layers.[29] Additionally, niosomal formulations can be tailored to release drugs in response to specific stimuli, such as pH or temperature changes, further enhancing drug delivery and efficacy. Furthermore, niosomal drug delivery systems enable the co-delivery of multiple therapeutic agents within the same carrier, thereby enhancing treatment efficacy and addressing the multifactorial nature of dermatological disorders.[86] By encapsulating different dermatological drugs with complementary mechanisms of action, such as anti-inflammatory agents with antimicrobial agents or antioxidants with moisturizers, it is possible to achieve synergistic effects and target multiple pathogenic pathways involved in disease progression.[15] This multifunctional approach holds promise for improving treatment outcomes and reducing the risk of complications in patients with dermatological disorders.[87] In addition to enhancing therapeutic efficacy, niosomal drug delivery systems can also minimize adverse effects and improve patient compliance compared to conventional topical drug formulations. By delivering therapeutic agents directly to the target site within the skin while minimizing systemic exposure, niosomal formulations can reduce the risk of systemic toxicity and adverse reactions. Additionally, niosomal formulations can enhance the stability of sensitive drugs, such as retinoids or vitamin C, thereby improving their efficacy and tolerability in dermatological treatments.[88]

3. Ocular delivery

Ocular delivery poses unique challenges due to the protective barriers of the eye, including the cornea, conjunctiva, and blood-aqueous barrier, which limit the penetration of drugs into intraocular tissues. However, niosomal drug delivery systems offer a promising approach to overcome these challenges and improve the treatment of various ocular conditions, including glaucoma, macular degeneration, diabetic retinopathy, and ocular infections.[89] Niosomes, lipid-based vesicles composed of nonionic surfactants and cholesterol, possess several characteristics that make them well-suited for ocular drug delivery, including enhanced drug solubilization, sustained drug release, and improved ocular bioavailability. One key advantage of niosomal drug delivery systems in ocular delivery is their ability to improve drug retention and penetration into intraocular tissues.[27] Niosomes can encapsulate a variety of therapeutic agents, including anti-glaucoma drugs, corticosteroids, antibiotics, and anti-inflammatory agents, within their aqueous core or lipid bilayer membranes. By encapsulating ocular drugs within niosomes, it is possible to prolong drug residence time on the ocular surface, enhance drug penetration into the cornea and anterior chamber, and achieve targeted drug delivery to the posterior segment of the eye.[90] Moreover, niosomal drug delivery systems offer opportunities to address challenges associated with conventional ocular drug administration routes, such as eye drops, ointments, and injections. By encapsulating ocular drugs within niosomes, it is possible to improve drug stability, prolong drug retention, and enhance drug bioavailability, thereby optimizing therapeutic efficacy while minimizing the frequency of dosing and the risk of adverse effects.[61] Additionally, niosomal formulations can be engineered to release drugs in a controlled manner, prolonging drug residence time in the eye and minimizing systemic exposure, thereby reducing the risk of systemic side effects. Furthermore, niosomal drug delivery systems enable the co-delivery of multiple therapeutic agents within the same carrier, thereby enhancing treatment efficacy and addressing the multifactorial nature of ocular diseases.[91] By encapsulating different ocular drugs with complementary mechanisms of action, such as anti-glaucoma agents with anti-inflammatory agents or anti-VEGF agents with corticosteroids, it is possible to achieve synergistic effects and target multiple pathogenic pathways involved in disease progression.[72] This multifunctional approach holds promise for improving treatment outcomes and reducing the need for multiple medications in patients with ocular diseases. In addition to enhancing therapeutic efficacy, niosomal drug delivery systems can also improve patient compliance and comfort compared to conventional ocular drug formulations.[80] By delivering therapeutic agents directly to the target site within the eye while minimizing systemic exposure and adverse effects, niosomal formulations can reduce the frequency of dosing and the burden of treatment for patients with ocular diseases. Additionally, niosomal formulations can enhance the stability of sensitive drugs, such as proteins or peptides, thereby improving their efficacy and tolerability in ocular treatments.[92]

Challenges and Future perspectives

A. Biocompatibility and Toxicity concerns

One of the significant challenges in niosomal drug delivery is ensuring biocompatibility and minimizing toxicity risks associated with niosome formulations.[76] While niosomes are generally considered safe, concerns regarding potential cytotoxicity, immunogenicity, and long-term effects on biological systems must be addressed. Future research efforts should focus on optimizing niosome composition, surface modification strategies, and formulation parameters to enhance biocompatibility and reduce toxicity, ensuring the safety of niosomal drug delivery systems for clinical applications.[93]

B. Regulatory Hurdles and Approval pathways

Navigating regulatory hurdles and approval pathways presents a significant challenge for the translation of niosomal drug delivery systems from research to clinical practice.[60] Regulatory agencies require comprehensive preclinical and clinical data to demonstrate the safety, efficacy, and quality of niosome-based drug products.[58]

Future efforts should focus on streamlining regulatory processes, establishing standardized evaluation criteria, and fostering collaboration between researchers, pharmaceutical companies, and regulatory authorities to accelerate the approval and commercialization of niosomal drug delivery systems.[94]

C. Future directions in niosomal drug delivery

Multifunctional Niosomes: Niosomes, lipid-based vesicular carriers, have emerged as promising drug delivery systems due to their ability to encapsulate a wide range of therapeutic agents and deliver them to target sites within the body. Multifunctional niosomes, a novel advancement in drug delivery technology, offer unique opportunities to enhance drug delivery efficiency and therapeutic efficacy through the incorporation of multiple functionalities into a single carrier system.[92] In this comprehensive exploration, we delve into the multifaceted aspects of multifunctional niosomes, including their design principles, applications, challenges, and future prospects. Multifunctional niosomes are characterized by their ability to perform multiple tasks simultaneously, such as targeted drug delivery, imaging, diagnostics, and therapeutic monitoring.[95] This versatility is achieved through the integration of various functional components, including targeting ligands, imaging agents, stimuli-responsive materials, and therapeutic payloads, within the niosome structure.[65] By combining these functionalities, multifunctional niosomes offer synergistic effects that can significantly enhance drug delivery efficiency and therapeutic outcomes. The design of multifunctional niosomes involves careful consideration of several key factors, including the selection of appropriate lipid components, incorporation of functional moieties, and optimization of formulation parameters.[42] Lipid composition plays a crucial role in determining the stability, biocompatibility, and drug-loading capacity of multifunctional niosomes. Additionally, surface modification strategies, such as conjugation with targeting ligands or surface engineering with stimuli-responsive polymers, enable selective targeting of diseased tissues and controlled release of therapeutic agents.[96] Multifunctional niosomes have diverse applications across various therapeutic areas, including cancer therapy, infectious diseases, central nervous system disorders, and cardiovascular diseases. In cancer therapy, multifunctional niosomes can deliver chemotherapeutic drugs to tumor sites while simultaneously imaging the tumor microenvironment using contrast agents or monitoring treatment response through theranostic approaches.[45] Similarly, in infectious diseases, multifunctional niosomes can target specific pathogens using antimicrobial peptides or antibodies while enabling real-time monitoring of microbial load or drug resistance.[32] Despite their promising potential, multifunctional niosomes face several challenges that must be addressed for their widespread adoption in clinical practice. These challenges include the complexity of formulation design, potential toxicity concerns associated with multifunctional components, and regulatory hurdles related to approval pathways for combination products.[90] Overcoming these challenges requires interdisciplinary collaboration, innovative research approaches, and robust preclinical and clinical evaluations to ensure the safety, efficacy, and quality of multifunctional niosome-based drug products.[97] Personalized Medicine Approaches: Personalized medicine, also known as precision medicine, is an innovative approach to healthcare that tailors medical treatments and interventions to individual patients based on their unique genetic makeup, physiological characteristics, and environmental factors.[31] In recent years, personalized medicine has gained significant attention as a promising strategy for improving patient outcomes, optimizing therapeutic efficacy, and minimizing adverse effects. In the context of drug delivery, personalized medicine approaches offer opportunities to develop tailored treatment regimens that address the specific needs and characteristics of individual patients. Niosomal drug delivery systems, with their versatility, biocompatibility, and tunable properties, are well-positioned to support personalized medicine initiatives and drive innovation in drug delivery technologies.[69] Looking ahead, the future of personalized medicine in niosomal drug delivery holds immense potential for transforming healthcare delivery and improving patient outcomes. Advances in genomics, proteomics, and data analytics are expected to further enhance our understanding of disease mechanisms, drug responses, and patient variability, driving the development of increasingly sophisticated personalized medicine approaches.[98] By harnessing the versatility and tunability of niosomal drug delivery systems, researchers and healthcare providers can continue to innovate and optimize drug delivery strategies that are tailored to the specific needs and characteristics of individual patients, ushering in a new era of precision medicine. Nanotechnology integration involves incorporating nanoscale materials and structures into niosomal drug delivery systems to enhance their performance, functionality, and therapeutic efficacy. Nanotechnology offers opportunities to manipulate matter at the molecular and nanometer scale, enabling precise control over drug delivery parameters and interactions with biological systems.[43] In the context of niosomal drug delivery, nanotechnology integration encompasses various approaches, including the incorporation of nanomaterials such as nanoparticles, liposomes, polymeric micelles, and quantum dots, as well as the utilization of nanoscale fabrication techniques and surface modification strategies.[99] One key aspect of nanotechnology integration in niosomal drug delivery is the use of nanomaterials as functional components or additives to enhance the properties of niosome formulations. For example, nanoparticles can be encapsulated within niosomes to serve as drug carriers, imaging agents, or stimuli-responsive triggers for controlled drug release. Similarly, liposomes or polymeric micelles can be incorporated into niosomes to modify their membrane properties, stability, or targeting

capabilities.[88] These hybrid nanosystems offer synergistic advantages, combining the unique properties of different nanomaterials to achieve superior drug delivery performance. Another approach to nanotechnology integration in niosomal drug delivery involves the utilization of nanoscale fabrication techniques to engineer niosomes with precise control over size, shape, and structure.[99] Techniques such as nanoprecipitation, microfluidics, and electrospraying enable the fabrication of uniform niosomes with tailored physicochemical properties and enhanced drug encapsulation efficiency. Additionally, surface modification strategies, such as PEGylation, coating with targeting ligands, or functionalization with stimuli-responsive polymers, can further optimize niosome interactions with biological systems and improve drug delivery specificity.[100] Furthermore, nanotechnology integration in niosomal drug delivery extends to the development of advanced characterization techniques and analytical methods for evaluating niosome properties and behavior at the nanoscale.[101] Techniques such as atomic force microscopy (AFM), dynamic light scattering (DLS), transmission electron microscopy (TEM), and nanoparticle tracking analysis (NTA) enable researchers to visualize and characterize niosomes with high resolution and sensitivity. These tools provide insights into niosome morphology, size distribution, surface charge, and drug encapsulation efficiency, facilitating the design, optimization, and quality control of niosomal drug delivery systems.[102]

D. Opportunities for Collaboration and Research funding

Collaboration between academia, industry, and government agencies is essential for advancing niosomal drug delivery research and overcoming existing challenges.[103] Opportunities for collaboration include interdisciplinary research initiatives, technology transfer partnerships, and joint funding programs aimed at fostering innovation and translation of niosome-based drug delivery technologies.[4] Additionally, securing research funding from government grants, private foundations, and venture capital investors is crucial for supporting continued research and development efforts in niosomal drug delivery and realizing its full potential for clinical applications.[104]

CONCLUSION

This comprehensive review highlights the potential of niosomal drug delivery systems as versatile and efficient platforms for delivering therapeutic agents across various medical applications. Through an examination of manufacturing techniques, characterization methods, therapeutic applications, challenges, and future perspectives, several key findings and insights have emerged. Niosomes offer distinct advantages such as improved drug stability, controlled release kinetics, enhanced bioavailability, and targeted delivery, making them valuable tools for addressing complex medical needs. The implications for the drug delivery field are profound, suggesting a shift towards more personalized and targeted therapeutic interventions that can minimize adverse effects and maximize therapeutic efficacy. However, challenges such as biocompatibility concerns, regulatory hurdles, and scale-up issues must be addressed to fully realize the potential of niosomal drug delivery systems. In light of these findings, recommendations for future research and development efforts include continued optimization of niosomal formulations, exploration of novel manufacturing techniques, and collaboration between academia, industry, and regulatory agencies to accelerate the translation of niosomal-based therapies from bench to bedside. Ultimately, the integration of niosomal drug delivery systems into clinical practice has the potential to revolutionize patient care by offering safer, more effective, and personalized treatment options across a wide range of medical conditions.

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