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Intranasal Niosomal Gel for Brain Drug Delivery: A Promising Strategy for Quetiapine Fumarate Targeting

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ABSTRACT
Intranasal drug delivery has gained attention as a non-invasive approach to enhance brain targeting by bypassing the blood-brain barrier. Niosomal in situ nasal gels provide a promising platform for improving drug retention, mucoadhesion, and controlled release. Quetiapine fumarate, an atypical antipsychotic, suffers from poor oral bioavailability due to extensive first-pass metabolism. Chitosan-coated niosomal in situ nasal gels offer enhanced permeability, bio adhesion, and sustained drug release, ensuring efficient brain delivery. This review explores the formulation, characterization, and therapeutic potential of intranasal niosomal gels for brain drug delivery, with a focus on their pharmacokinetic advantages, challenges, and future prospects. The integration of nanotechnology with intranasal administration could revolutionize neuropsychiatric drug therapy, offering improved patient compliance and therapeutic efficacy.

Keywords: *Intranasal drug delivery, Schizophrenia, Quetiapine Fumarate , CNS drug delivery, nasal gels*

1. INTRODUCTION

Schizophrenia is a chronic psychotic disorder that affects approximately 1% of the global population. The onset of symptoms typically occurs in adulthood and persists throughout the individual's lifetime. Antipsychotic medications, particularly atypical antipsychotics, have demonstrated efficacy in mitigating both the positive symptoms (e.g., delusions, auditory hallucinations) and negative symptoms (e.g., social withdrawal, disorganized behavior, impaired attention) associated with schizophrenia [1]. Quetiapine (QTF) is an atypical antipsychotic medication with a broader efficacy profile compared to conventional and other atypical antipsychotics [2]. Chemically, QTF is a dibenzothiazepine derivative, formally named 2-[2-(4-dibenzo[b,f][1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol. The precise mechanism of action of QTF remains uncertain; however, it is believed to function through the antagonism of dopamine type 2 (D2) and serotonin type 2 (5-HT2) receptors, thereby modulating neurotransmission [3]. Additionally, QTF exhibits antidepressant properties, potentially mediated by its metabolite, N-desalkyl quetiapine fumarate, which inhibits selective norepinephrine reuptake and activates 5-HT1A and 5-HT7 receptors [3]. Multiple clinical trials have demonstrated the favorable safety profile of QTF [4]. Patients with schizophrenia have reported cognitive improvements with QTF, and it is particularly well tolerated among elderly populations [5]. Due to its demonstrated efficacy, QTF has been approved as a first-line treatment for schizophrenia and is also effective in managing bipolar mania [6–9]. Despite its therapeutic benefits, QTF presents pharmacokinetic limitations that hinder its conventional administration. As a highly lipophilic compound, QTF exhibits poor water solubility and low oral bioavailability (5–15%) due to extensive hepatic metabolism [10]. Its metabolism primarily occurs in the liver, resulting in significant first-pass effects that reduce systemic drug availability [11–13]. To enhance QTF bioavailability and bypass hepatic metabolism, an alternative drug delivery strategy is required. Given that the primary site of QTF action is the brain, a targeted delivery system that facilitates direct transport to the central nervous system (CNS) would be highly advantageous. Achieving effective brain targeting is a significant challenge in drug delivery. The blood-brain barrier (BBB) imposes a

major limitation on conventional oral and parenteral administration routes, reducing drug penetration into the CNS and necessitating higher systemic doses, which may lead to adverse effects. Intranasal drug delivery has emerged as a promising non-invasive strategy for bypassing the BBB, facilitating direct nose-to-brain transport [14]. Niosomal in situ nasal gels present an innovative approach to improving drug retention, mucoadhesion, and controlled release, thereby enhancing therapeutic efficacy. Although intracerebroventricular or intraparenchymal drug administration can achieve direct brain delivery, these methods are invasive, expensive, and necessitate surgical intervention, making them impractical for routine use [14]. In contrast, intranasal administration provides a safer, more convenient, and efficient alternative for CNS drug delivery, as supported by previous studies demonstrating rapid and enhanced brain drug concentrations following intranasal administration [15–19]. The olfactory epithelium serves as a conduit for drug transport into both the CNS and peripheral circulation. Two primary pathways facilitate drug movement from the nasal cavity to the brain: the intra-neuronal and extra-neuronal routes [20,21]. The intra-neuronal pathway, which relies on axonal transport, is a slower process requiring hours to days for drug distribution across brain regions. Conversely, the extra-neuronal pathway facilitates rapid drug transport via bulk flow through perineural channels, delivering therapeutics directly to the brain parenchyma and cerebrospinal fluid (CSF) within minutes [22]. Drug absorption across the nasal mucosa requires passage through the mucus layer, where molecular properties influence permeability. Small, uncharged molecules traverse the mucosa with relative ease, whereas large or charged molecules face greater diffusion challenges. Following mucosal passage, drugs may be absorbed via simple diffusion, paracellular transport, or transcytosis [23]. Despite the advantages of intranasal administration for topical, systemic, and CNS drug delivery, several limitations impede nasal bioavailability. Factors such as low drug solubility, enzymatic degradation within the nasal cavity, poor membrane permeability, and rapid mucociliary clearance hinder effective drug absorption [24]. To address these challenges, this review explores the potential of chitosan-coated niosomal in situ nasal gel as a targeted delivery system for quetiapine fumarate, a widely utilized atypical antipsychotic. This novel formulation strategy aims to enhance nasal drug retention, improve CNS targeting, and optimize therapeutic outcomes in the treatment of schizophrenia.

2. NIOSOMES AS NANOCARRIERS FOR BRAIN DRUG DELIVERY

The treatment of neurological disorders remains a significant challenge due to the presence of the blood-brain barrier (BBB), which restricts the passage of most therapeutic agents. Nanotechnology-based drug delivery systems, such as niosomes, have emerged as a promising strategy to enhance drug transport across the BBB. Niosomes are non-ionic surfactant vesicles that can encapsulate both hydrophilic and lipophilic drugs, improving their bioavailability and targeted delivery to the brain. Niosomes are nanoscale vesicles, having a stable bilayer structure, and are mainly composed of non-ionic surfactants and cholesterol. Niosomes are highly biocompatible and biodegradable [25]. They exhibit high chemical stability, long shelf life, low toxicity, and inexpensive manufacturing cost. Niosomes have the ability to entrap lipophilic or hydrophilic drugs and are able to deliver the drug molecules at target site in a sustained and/or controlled manner [26]. Niosomes have been reported to modify drugs organ distribution and metabolic stability [27]. Niosomes can be tailored in terms of size, charge, and surface modifications to enhance their stability and brain-targeting efficiency.

Mechanisms of Niosomal Brain Targeting

Niosomes can facilitate drug delivery to the brain through multiple mechanisms [28-32]:

1. **Endocytosis and Transcytosis** – Niosomes can be taken up by endothelial cells of the BBB via receptor-mediated or adsorptive-mediated endocytosis, leading to drug release into the brain parenchyma.
2. **Surface Modification with Ligands** – Functionalizing niosomes with targeting ligands (e.g., transferrin, lactoferrin, or glucose) enhances receptor-mediated transport across the BBB.
3. **Enhanced Permeability via Surfactants** – Certain surfactants in niosomes can modulate tight junctions, transiently increasing BBB permeability.
4. **Intranasal Delivery Route** – Niosomes can bypass the BBB by utilizing the olfactory and trigeminal nerve pathways for direct nose-to-brain drug delivery.

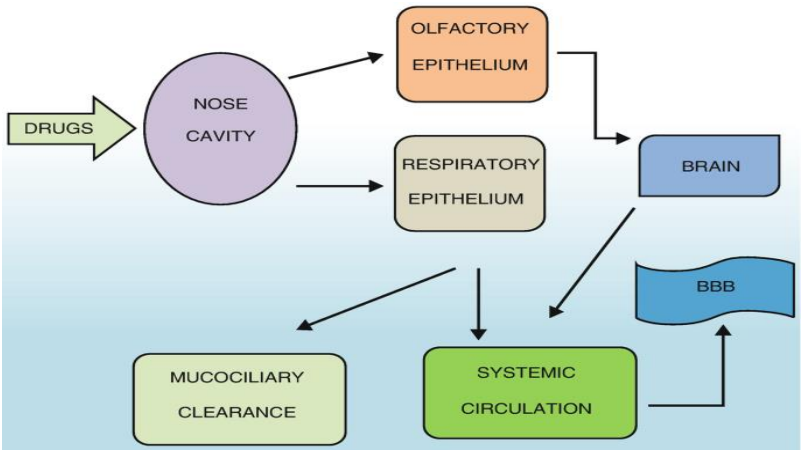

Figure 1: Mechanism of action of Niosomal drug delivery from brain to nose

Advantages of Niosomal Drug Delivery for the Brain

- **Enhanced Drug Stability and Bioavailability** – Protects drugs from enzymatic degradation and improves systemic circulation time.
- **Controlled and Sustained Release** – Provides prolonged drug release, reducing dosing frequency and minimizing side effects.
- **Targeted Delivery** – Reduces systemic toxicity by increasing drug accumulation in brain tissues.
- **Non-immunogenic and Biodegradable** – Composed of biocompatible surfactants, reducing the risk of adverse immune responses [33-37].

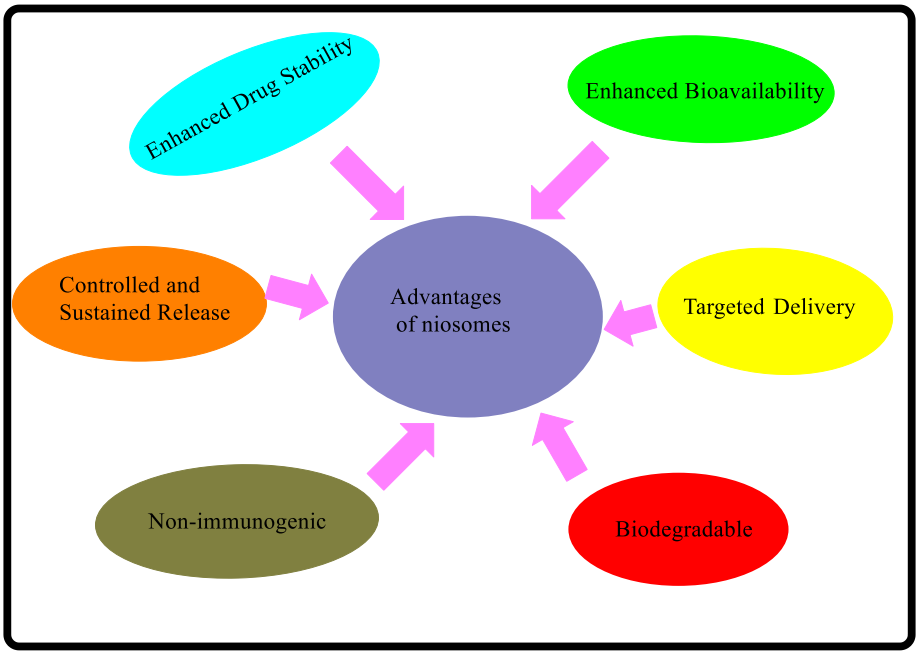

Figure 2: Advantages of Niosomal drug delivery from brain to nose

3. APPLICATIONS OF NIOSOMES IN NEUROLOGICAL DISORDERS

Niosomes have shown significant promise in treating neurological disorders due to their ability to enhance drug delivery across the blood-brain barrier (BBB). Their biocompatibility, stability, and ability to encapsulate both hydrophilic and lipophilic drugs make them ideal for targeted brain therapy. Niosomes improve drug bioavailability, reduce systemic toxicity, and enable sustained drug release, which is crucial for chronic neurological conditions like Alzheimer's disease, Parkinson's disease, epilepsy, and brain tumors. Additionally, they can be functionalized with ligands or surface modifications to enhance brain targeting via receptor-mediated transport. These advantages position niosomes as a versatile and efficient nanocarrier

system for neurotherapeutics, offering new possibilities for improved treatment outcomes [38-41].

Table 1: Application of different type of niosomal formulation

Type of Niosomal Formulation	Application in Brain Targeting	Example Drugs/Compounds	Key Benefits	References
Conventional Niosomes	General brain drug delivery	Doxorubicin, Curcumin	Improved bioavailability, reduced toxicity	42
PEGylated Niosomes	Extended circulation time for brain targeting	Rivastigmine, Tacrine	Enhanced BBB penetration, prolonged drug release	43
Ligand-Conjugated Niosomes	Targeted drug delivery via receptor-mediated transport	Galantamine (transferrin-conjugated niosomes)	Increased brain specificity, reduced peripheral side effects	44
Magnetic Niosomes	Magnetic field-guided brain targeting	Doxorubicin (iron oxide-loaded niosomes)	Site-specific delivery, enhanced therapeutic efficiency	45
pH-Sensitive Niosomes	Controlled drug release in brain tumor therapy	Paclitaxel, Methotrexate	Selective drug release in acidic tumor microenvironments	46
Thermosensitive Niosomes	Temperature-responsive drug delivery	Temozolomide	Controlled release in hyperthermic conditions for brain tumors	47
Ultrasound-Responsive Niosomes	Focused ultrasound-mediated brain targeting	Carbamazepine	BBB disruption for efficient drug delivery	48

4. CHITOSAN-COATED NIOSOMES: ENHANCING NASAL DRUG DELIVERY

Nasal drug delivery has gained significant attention due to its potential for rapid systemic absorption, avoidance of first-pass metabolism, and non-invasiveness. However, limitations such as mucociliary clearance and enzymatic degradation pose challenges to efficient drug transport. Chitosan-coated niosomes offer a novel approach to overcoming these barriers, enhancing drug retention, permeability, and bioavailability [49]. This review explores the structural properties, mechanisms of action, advantages, and recent advancements in chitosan-coated niosomal formulations for nasal drug delivery. The nasal route is increasingly explored for drug administration, particularly for systemic and central nervous system (CNS) targeting. Despite its advantages, effective nasal drug delivery faces challenges, including limited residence time, enzymatic degradation, and restricted permeability of macromolecules [50]. Niosomes, as non-ionic surfactant-based vesicles, have demonstrated potential in enhancing drug stability and controlled release. When coated with chitosan, a biodegradable, mucoadhesive, and permeation-enhancing polymer, niosomes exhibit superior properties for intranasal applications. Chitosan, a cationic polymer derived from chitin, enhances the physicochemical properties of niosomes through electrostatic interactions, improving vesicular stability and mucoadhesion. The preparation methods include thin-film hydration, reverse-phase evaporation, and microfluidization, ensuring optimized particle size, polydispersity index, and encapsulation efficiency for nasal administration. Chitosan-coated niosomes improve drug delivery through multiple mechanisms [51]. The cationic charge of chitosan facilitates adhesion to the negatively charged nasal mucosa, prolonging retention time and reducing drug clearance. Additionally, chitosan transiently opens tight junctions, allowing enhanced paracellular transport. The vesicular

structure of niosomes ensures sustained drug release, reducing the dosing frequency and improving therapeutic outcomes. Chitosan-coated niosomes offer multiple benefits compared to conventional nasal formulations such as solutions, suspensions, and gels. These advantages include enhanced mucoadhesion, which prolongs nasal residence time and improves absorption; controlled and sustained release, which maintains therapeutic drug concentrations for an extended period; protection against enzymatic degradation, preventing premature drug breakdown in the nasal cavity; and improved drug stability and encapsulation efficiency, providing a versatile platform for both hydrophilic and lipophilic drugs [52]. Chitosan-coated niosomes have been investigated for various therapeutic applications, including central nervous system disorders, facilitating nose-to-brain delivery of drugs for Alzheimer's, Parkinson's, and epilepsy; vaccines and biologics, enhancing the mucosal immune response for intranasal vaccine administration; anti-inflammatory and analgesic drugs, providing sustained relief for conditions like allergic rhinitis and sinusitis; and antiviral and antimicrobial agents, improving targeted delivery of drugs for respiratory infections. Recent studies have explored advanced formulation techniques, including hybrid polymeric-niosomal systems, surface-modified nanoparticles, and stimuli-responsive chitosan derivatives [53]. Despite promising results, challenges such as large-scale manufacturing, regulatory approval, and patient acceptability remain to be addressed. Chitosan-coated niosomes represent a cutting-edge approach to overcoming the limitations of nasal drug delivery. Their mucoadhesive, permeation-enhancing, and sustained-release properties make them an excellent platform for diverse therapeutic applications. With continued advancements in formulation science and nanotechnology, chitosan-coated niosomes hold great promise for revolutionizing intranasal drug administration and improving patient outcomes.

Table 2: Chitosan-Coated Niosomes for Nasal Drug Delivery

Aspect	**Details**	
Description	Chitosan-coated niosomes are vesicular nanocarriers modified with chitosan, a natural biopolymer, to enhance drug retention, mucoadhesion, and permeability in nasal drug delivery.	54
Advantages	- **Enhanced mucoadhesion:** Chitosan interacts with nasal mucosa, prolonging drug residence time.	55
	- **Improved permeability:** Enhances drug absorption by opening tight junctions.	
	- **Biocompatibility:** Chitosan is biodegradable and non-toxic.	
	- **Sustained release:** Reduces dosing frequency, improving patient compliance.	
	- **Protection from enzymatic degradation:** Shields drugs from nasal enzymes.	
Disadvantages	- **Potential nasal irritation:** Chitosan at high concentrations may cause discomfort.	56
	- **Limited drug loading capacity:** May restrict the type and dose of drugs that can be encapsulated.	
	- **Stability concerns:** Niosomes can aggregate over time, affecting drug release.	
Applications with Examples	1. **Peptide and Protein Drugs** (e.g., Insulin) – Improves nasal absorption of insulin for non-invasive diabetes treatment.	57
	2. **Neurological Drugs** (e.g., Rivastigmine) – Enhances brain targeting for Alzheimer's disease.	
	3. **Vaccines** (e.g., Influenza vaccine) – Acts as an adjuvant system for intranasal immunization.	58
	4. **Pain Management** (e.g., Sumatriptan) – Provides rapid migraine relief via nasal absorption.	
	5. **Antiviral Therapy** (e.g., Acyclovir) – Enhances nasal delivery for systemic viral infections.	

5. FORMULATION STRATEGIES FOR INTRANASAL NIOSOMAL GEL FOR BRAIN DRUG DELIVERY

Intranasal drug delivery offers a promising non-invasive route for brain-targeted therapy by bypassing the blood-brain barrier (BBB) through the olfactory and trigeminal nerve pathways. Niosomal gels, which combine the advantages of niosomes (nano-vesicular carriers) and mucoadhesive gel formulations, enhance drug residence time in the nasal cavity, improve bioavailability, and facilitate brain targeting. Various formulation strategies are employed to optimize niosomal gel formulations for efficient intranasal drug delivery [59].

A. Niosome Preparation Strategies

The formulation of an intranasal niosomal gel begins with the preparation of niosomes using various techniques, each offering distinct advantages and limitations.

a) Thin-Film Hydration Method

The thin-film hydration method is a widely used technique for preparing niosomes due to its ability to produce highly stable and uniform vesicles. In this process, non-ionic surfactants and cholesterol are first dissolved in an organic solvent, which is then evaporated under vacuum to form a thin lipid film on the walls of a round-bottom flask [60]. The film is subsequently hydrated with an aqueous phase containing the drug, leading to vesicle formation. This method is particularly advantageous as it allows for better control over particle size and results in niosomes with high stability. However, optimization of hydration conditions, such as temperature, pH, and agitation speed, is necessary to ensure the formation of homogeneous vesicles. Additionally, post-processing steps like sonication or extrusion are often required to achieve the desired vesicle size [61].

b) Reverse Phase Evaporation Method (RPEM)

The reverse phase evaporation method (RPEM) is an alternative approach that enables the formation of niosomes with high drug encapsulation efficiency, particularly for hydrophilic drugs. In this technique, surfactants and cholesterol are first dissolved in an organic solvent, and the drug is incorporated into an aqueous phase. These two phases are emulsified to form a water-in-oil emulsion, which is then subjected to solvent removal under reduced pressure, leading to the formation of niosomal vesicles. This method allows for greater drug entrapment compared to the thin-film hydration method, making it suitable for water-soluble drugs. However, it is relatively time-consuming and requires specialized equipment, making large-scale production challenging [62].

c) Microfluidization and Sonication Methods

Microfluidization and sonication techniques are commonly used to reduce niosome size and achieve a uniform vesicle distribution, which is crucial for enhancing nasal drug absorption. Microfluidization involves high-pressure fluid flow through a narrow channel, leading to uniform vesicle formation, while sonication applies ultrasonic waves to break down larger vesicles into nanosized structures. These methods improve the bioavailability of intranasal formulations by enhancing mucoadhesion and penetration across the nasal epithelium. Additionally, nanosized vesicles facilitate controlled drug release and prolonged retention at the site of absorption. However, these methods require sophisticated equipment, and process parameters such as pressure, sonication time, and temperature must be carefully optimized to avoid vesicle degradation [63].

d) Ether Injection Method

The ether injection method is a simple and rapid approach for niosome formation, involving the injection of an organic solvent containing surfactants and cholesterol into an aqueous phase under constant stirring. As the organic solvent diffuses into the aqueous medium, spontaneous vesicle formation occurs. This method is advantageous due to its ease of execution and the ability to control vesicle size through injection speed and stirring conditions. However, residual organic solvent in the final formulation may pose toxicity concerns, necessitating additional purification steps. Furthermore, this method may not be ideal for large-scale production due to limitations in achieving consistent batch-to-batch reproducibility [64].

B. Selection of Surfactants and Cholesterol Ratio

The selection of surfactants and the cholesterol ratio plays a crucial role in determining the stability, drug encapsulation efficiency, and permeability of niosomal formulations. Non-ionic surfactants such as Span (Span 20, Span 40, Span 60, and Span 80) and Tween (Tween 20, Tween 40, Tween 60, and Tween 80) are commonly used due to their ability to form stable vesicles with low toxicity. The choice of surfactant is influenced by its hydrophilic-lipophilic balance (HLB), which affects vesicle size and membrane rigidity. Surfactants with a low HLB value, such as Span 60, tend to form more rigid and stable vesicles, whereas higher HLB surfactants like Tween 80 produce more flexible and permeable vesicles, which may enhance drug release [65].

Cholesterol is incorporated into the niosomal bilayer to modulate membrane rigidity and permeability. A higher cholesterol concentration increases vesicle stability by reducing leakage and preventing premature drug release. However, excessive cholesterol may lead to a reduction in drug entrapment efficiency by disrupting the packing of surfactant molecules. The optimal surfactant-to-cholesterol ratio typically ranges from 2:1 to 4:1, depending on the physicochemical properties of the drug and the desired release profile. A lower ratio may result in vesicles that are too flexible and prone to aggregation, while

a higher ratio may lead to excessive rigidity, compromising drug release. Therefore, an optimized balance between surfactant type and cholesterol content is essential to achieve an effective intranasal niosomal formulation with enhanced drug delivery and stability [65].

C. Mucoadhesive Gel Formulation for Intranasal Delivery

Once the niosomes are prepared, they are incorporated into a mucoadhesive gel to enhance their residence time in the nasal cavity and improve drug absorption. The nasal mucosa presents a favorable route for drug delivery to the brain due to its rich vascularization and the presence of the olfactory and trigeminal pathways, which facilitate direct nose-to-brain transport. However, rapid mucociliary clearance can limit drug retention, making the use of mucoadhesive polymers essential for prolonging drug contact with the nasal mucosa and enhancing bioavailability [66].

a) Selection of Gelling Agents

Mucoadhesive polymers are incorporated into the formulation to ensure prolonged contact of the drug-loaded niosomes with the nasal epithelium, improving drug absorption and therapeutic efficacy. Carbopol 934/940 is widely used due to its excellent mucoadhesive properties and ability to control gel viscosity. It swells in water, forming a stable gel that adheres to the mucosal surface, preventing premature clearance. Hydroxypropyl methylcellulose (HPMC) is another commonly used gelling agent that enhances gel consistency and bioadhesion, ensuring uniform drug distribution. Chitosan, a biocompatible and biodegradable polymer, not only enhances mucoadhesion but also facilitates drug transport by transiently opening tight junctions in the nasal epithelium, allowing for improved absorption. Additionally, Pluronic F127, a thermosensitive polymer, remains in a liquid state at lower temperatures but transitions into a gel upon reaching nasal temperature, ensuring prolonged drug retention and controlled release. The selection of the appropriate gelling agent depends on factors such as the required viscosity, bioadhesion strength, and the physicochemical properties of the encapsulated drug [66].

b) Incorporation of Permeation Enhancers

To facilitate drug transport across the nasal mucosa and improve drug absorption, permeation enhancers are incorporated into the gel formulation. Lecithin and bile salts promote paracellular absorption by modifying the structure of tight junctions, thereby increasing drug permeation through the epithelial layer. Cyclodextrins function as solubilizing agents, improving the stability and solubility of poorly water-soluble drugs, thus enhancing their bioavailability. Additionally, surfactants such as Tween 80 act as absorption enhancers by transiently disrupting the mucosal barrier, increasing drug diffusion across the nasal membrane. However, the concentration of permeation enhancers must be carefully optimized, as excessive use can lead to nasal irritation or toxicity [67].

c) pH and Osmolarity Adjustment

Maintaining the appropriate pH and osmolarity is crucial for ensuring the stability of the formulation and compatibility with the nasal mucosa. The physiological pH of the nasal cavity ranges from 4.5 to 6.5, and formulations should be within this range to prevent irritation and maintain mucosal integrity. Deviations from this pH range may lead to discomfort and reduced drug absorption due to mucosal irritation or enzymatic degradation. Furthermore, osmolarity plays a vital role in maintaining the isotonicity of the formulation. Hypertonic or hypotonic solutions can cause nasal irritation, excessive fluid secretion, or mucosal dehydration, which may reduce drug absorption. Isotonicity agents such as mannitol and sodium chloride are commonly added to ensure the osmolarity remains within physiological limits, promoting patient comfort and formulation stability.

By carefully selecting gelling agents, incorporating suitable permeation enhancers, and adjusting the pH and osmolarity, an optimized intranasal mucoadhesive niosomal gel can be formulated to enhance drug delivery, prolong retention in the nasal cavity, and improve therapeutic efficacy [68].

6. CHARACTERIZATION AND OPTIMIZATION OF NIOSOMAL GEL

The development of an effective intranasal niosomal gel requires systematic characterization and optimization to ensure stability, drug loading efficiency, mucoadhesion, and drug release kinetics. Several critical parameters are evaluated to fine-tune the formulation and achieve optimal therapeutic efficacy [69].

a. Vesicle Size, Morphology, and Zeta Potential

The size and morphology of niosomal vesicles play a crucial role in their stability, penetration, and drug release properties. Dynamic Light Scattering (DLS) is commonly used to determine the average vesicle size, which ideally falls within the 100–500 nm range for effective nasal absorption. Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM) provide insights into vesicle morphology, ensuring the formation of uniform, spherical, and intact vesicles. Additionally, zeta potential measurements assess the surface charge, which is essential for determining colloidal stability. A zeta potential value above ±30 mV indicates good electrostatic repulsion between vesicles, preventing aggregation and ensuring prolonged shelf stability [70].

b. Drug Entrapment Efficiency (EE%) and Drug Loading Capacity

The efficiency of drug encapsulation within niosomes directly influences therapeutic performance. Entrapment efficiency (EE%) is quantified using ultracentrifugation or dialysis methods, followed by UV-Vis spectrophotometry or High-Performance Liquid Chromatography (HPLC) to determine drug content. High EE% (typically above 70%) is desired to ensure adequate drug loading within the niosomal vesicles. Drug loading capacity is optimized by adjusting the surfactant-to-cholesterol ratio, hydrophilic-lipophilic balance (HLB) of surfactants, and processing conditions to maximize drug retention and minimize leakage [71].

c. Rheological Properties and Mucoadhesion Studies

The viscosity and mucoadhesive strength of the gel formulation significantly impact its nasal retention and drug absorption. Rheological analysis using a rotational viscometer evaluates the gel's consistency, ensuring it has an optimal viscosity that facilitates easy administration while preventing rapid nasal drainage. Mucoadhesion studies, typically performed using a texture analyzer or ex vivo goat/bovine nasal mucosa, assess the gel's adhesive strength. A high mucoadhesion force ensures prolonged residence time in the nasal cavity, allowing for sustained drug release and enhanced bioavailability [71].

d. In Vitro Drug Release and Release Kinetics

To ensure controlled and sustained drug delivery, in vitro drug release studies are conducted using Franz diffusion cells or dialysis membranes in simulated nasal fluid (pH 5.5–6.5). The release profile is analyzed over time to determine the drug diffusion rate and release kinetics, which are fitted to mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. An optimized formulation should exhibit sustained release, preventing burst drug release while maintaining effective drug levels for an extended period.

e. Ex Vivo Permeation and Histopathological Studies

Ex vivo permeation studies using goat or porcine nasal mucosa in Franz diffusion cells evaluate the rate of drug permeation across the nasal membrane. Permeability coefficients (Papp) and flux values are determined to ensure efficient drug transport to the systemic circulation and brain. Histopathological analysis of nasal mucosa after exposure to the niosomal gel ensures that the formulation does not cause irritation or damage to the epithelial layer, confirming its safety for nasal administration [72].

f. Stability Studies

The physical and chemical stability of the niosomal gel is assessed under accelerated stability conditions (40°C ± 2°C, 75% RH) and long-term storage conditions. Parameters such **as** vesicle size, zeta potential, drug content, and pH are monitored over time. An ideal formulation should retain its physicochemical properties and drug integrity for at least 3–6 months without significant degradation or aggregation [73].

7. CONCLUSION

Intranasal niosomal gel-based drug delivery has emerged as a promising strategy for enhancing the brain targeting of therapeutics, particularly for drugs like Quetiapine Fumarate. This approach leverages the advantages of niosomes, such as biocompatibility, stability, and the ability to improve drug permeability across biological barriers. Additionally, the gel formulation enhances mucoadhesion and prolongs nasal residence time, potentially improving drug absorption and therapeutic outcomes. Current literature supports the potential of this delivery system in overcoming the limitations of conventional oral and parenteral routes, particularly in addressing challenges associated with poor bioavailability and systemic side effects. However, gaps remain in understanding the long-term stability, scalability, and clinical applicability of intranasal niosomal gels. Future research should focus on refining formulation techniques, conducting rigorous preclinical and clinical evaluations, and addressing regulatory considerations to facilitate translation into clinical practice.

In conclusion, intranasal niosomal gel delivery represents a novel and promising frontier in brain-targeted therapy, offering a non-invasive and efficient alternative for managing neuropsychiatric disorders. Continued advancements in formulation science and drug delivery technologies will be crucial in realizing its full therapeutic potential.

8. CHALLENGES AND FUTURE PERSPECTIVES

Despite the promising potential of intranasal niosomal gel for brain-targeted delivery of Quetiapine Fumarate, several challenges must be addressed before clinical translation. One of the primary concerns is formulation stability, as factors such as vesicle aggregation, drug leakage, and degradation can impact the efficacy of the delivery system over time. Additionally, large-scale manufacturing of niosomal gels with consistent physicochemical properties remains a challenge, requiring optimization of fabrication techniques to ensure reproducibility and cost-effectiveness. Another critical issue is the variability in nasal physiology among individuals, which can affect mucoadhesion, nasal residence time, and ultimately, drug absorption and bioavailability. While intranasal delivery provides a direct pathway to bypass the blood-brain barrier (BBB), achieving efficient and reproducible drug transport into the brain remains a significant hurdle. Furthermore, concerns regarding the long-term safety and biocompatibility of niosomes, as well as the potential for nasal irritation or toxicity due to repeated administration, necessitate comprehensive safety assessments. In addition to these technical challenges, regulatory hurdles

pose another major barrier to clinical translation, as novel drug delivery systems must meet stringent regulatory requirements and undergo extensive clinical evaluation to establish efficacy and safety.

To address these challenges, future research should focus on advanced formulation strategies, such as incorporating penetration enhancers, bioadhesive polymers, or stimuli-responsive materials to improve drug delivery efficiency. The integration of nanotechnology-based innovations, including hybrid carriers like lipid nanoparticles or exosomes, may enhance drug stability and brain targeting. Moreover, extensive in vivo and clinical studies are essential to establish the pharmacokinetics, therapeutic efficacy, and long-term safety of intranasal niosomal gel formulations. The exploration of personalized medicine approaches, where formulations are tailored to optimize individual nasal drug absorption and therapeutic response, could further enhance the effectiveness of this delivery system. Additionally, streamlining the regulatory approval process by collaborating with regulatory agencies to develop standardized guidelines for intranasal nanocarrier-based drug delivery systems will be crucial for clinical implementation.

In conclusion, while intranasal niosomal gel delivery offers a promising non-invasive strategy for enhancing brain drug targeting, addressing formulation, safety, and regulatory challenges is essential for its clinical success. Future advancements in nanotechnology, formulation science, and regulatory compliance will be pivotal in translating this innovative approach into a viable therapeutic option for neuropsychiatric disorders.

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