

VESICULAR NANOCARRIERS FOR NOSE-TO-BRAIN DELIVERY: COMPARATIVE INSIGHTS INTO LIPOSOMES, NIOSOMES, TRANSFERSOMES AND SPANLASTICS**Anju G. A.^{*1}, Athira K.², Dr. Roma Mathew³**¹Department of Pharmaceutics, College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram, Kerala, India.²Department of Pharmaceutics, College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram, Kerala, India.³Department of Pharmaceutics, College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram, Kerala, India.***Corresponding Author: Anju G. A.**Department of Pharmaceutics, College of Pharmaceutical Sciences, Govt. Medical College, Thiruvananthapuram, Kerala, India. DOI: <https://doi.org/10.5281/zenodo.23828123>**How to cite this Article:** Anju G. A.^{*1}, Athira K.², Dr. Roma Mathew³ (2026). Vesicular Nanocarriers For Nose-To-Brain Delivery: Comparative Insights Into Liposomes, Niosomes, Transfersomes And Spanlastics. World Journal of Pharmaceutical and Medical Research, 12(11), 69–78.

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ABSTRACT

Nose-to-brain drug delivery is a promising non-invasive approach for treating central nervous system disorders by bypassing the blood-brain barrier through olfactory and trigeminal pathways. However, mucociliary clearance, enzymatic degradation, and limited nasal residence time restrict its effectiveness. Vesicular nanocarriers, including liposomes, niosomes, transfersomes, and spanlastics, can enhance drug permeation, protect drugs from degradation, improve brain targeting, and provide sustained release. This review discusses nasal anatomy and physiology, brain-targeting mechanisms, and the structural and functional characteristics of these vesicular systems. Particular emphasis is given to elastic nanovesicles such as transfersomes and spanlastics due to their enhanced deformability and permeation. Current challenges and future prospects, including stability, scale-up, toxicity, regulatory considerations, surface modification, in situ gels, Quality by Design, and precision nanomedicine, are also highlighted.

KEYWORDS: Nose-To-Brain Delivery, Vesicular Nanocarriers, Liposomes, Niosomes, Transfersomes, Spanlastics.**1. INTRODUCTION**

Treating disorders of the central nervous system (CNS) remains a formidable challenge in modern medicine due to the presence of the blood–brain barrier (BBB), a highly selective physiological barrier that severely limits the transport of therapeutic agents into the brain. Although conventional routes such as oral and parenteral administration are widely used for neurological therapies, they often result in poor brain targeting, extensive systemic distribution, enzymatic degradation, and undesirable side effects. These limitations have significantly restricted the effective management of neurological disorders including Alzheimer's disease, Parkinson's disease, epilepsy, brain tumors, depression, and multiple sclerosis. Consequently, the search for innovative, non-invasive, and targeted drug delivery approaches capable of bypassing the BBB has become a major focus in pharmaceutical and biomedical

research.^[1,2]

In recent years, nose-to-brain drug delivery has attracted tremendous scientific interest as a promising alternative approach for direct CNS targeting. The nasal cavity possesses unique anatomical connections with the brain through the olfactory and trigeminal neural pathways, enabling therapeutic agents to bypass the BBB and reach the brain directly. This route offers several remarkable advantages such as rapid onset of action, improved bioavailability, avoidance of hepatic first-pass metabolism, non-invasive administration, enhanced patient compliance, and reduced systemic toxicity. These advantages have positioned intranasal delivery as a highly attractive platform for the treatment of both acute and chronic neurological disorders.^[3,4]

Vesicular carriers such as liposomes, niosomes,

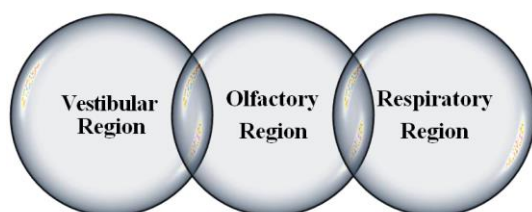
transfersomes, and spanlastics represent some of the most extensively explored nanoplateforms for intranasal brain targeting. Liposomes, composed primarily of phospholipid bilayers, are well known for their excellent biocompatibility and drug-carrying capacity. Niosomes, formed from non-ionic surfactants, offer improved stability and cost-effectiveness compared with conventional liposomes. Transfersomes are highly deformable vesicles containing edge activators that enable efficient penetration across biological membranes. More recently, spanlastics have emerged as advanced elastic nanovesicles exhibiting remarkable deformability, enhanced permeability, higher entrapment efficiency, and superior brain targeting potential, making them highly promising carriers for CNS therapeutics.^[1,5]

Furthermore, the integration of vesicular nanocarriers with advanced formulation strategies such as thermoreversible in situ gels, mucoadhesive polymers, and surface-functionalized systems has further revolutionized intranasal drug delivery. These hybrid approaches not only improve nasal residence time and formulation stability but also enhance drug permeation and sustained release within the brain. As a result, vesicular nanosystems are increasingly being recognized as next-generation platforms capable of transforming the therapeutic landscape of CNS disorders.^[2,6]

1.1 Anatomy and Physiology of the Nasal Cavity

The nasal cavity is an important anatomical structure that serves as the primary pathway for respiration and also acts as a promising route for drug delivery, particularly in nose-to-brain targeting. Its unique anatomical connection with the central nervous system through the olfactory and trigeminal pathways enables direct transport of therapeutic agents to the brain while bypassing the blood–brain barrier (BBB).^[1]

Anatomically, the nasal cavity is divided into two symmetrical chambers by the nasal septum and extends from the nostrils to the nasopharynx. Each chamber possesses a total surface area of approximately 150–200 cm² due to the presence of highly folded structures called nasal turbinates or conchae. These turbinates increase the surface area available for air conditioning and drug absorption.^[7] The nasal cavity is broadly divided into three functional regions.



1.1.1 Vestibular Region

The vestibular region is the anterior portion of the nasal cavity lined with stratified squamous epithelium and nasal hairs. It primarily acts as a protective filter that traps

dust particles and foreign contaminants. Due to its limited surface area and poor permeability, this region has minimal importance in drug absorption.^[8]

1.1.2 Respiratory Region

The respiratory region is the largest and most highly vascularized portion of the nasal cavity, comprising the superior, middle, and inferior turbinates. It is lined with pseudostratified ciliated columnar epithelium containing goblet cells that secrete mucus. This region plays a major role in systemic drug absorption because of its rich blood supply and relatively permeable epithelial membrane.^[9]

1.1.3 Olfactory Region

The olfactory region is located at the roof of the nasal cavity and is lined with specialized olfactory epithelium containing olfactory receptor neurons. This region provides a direct connection between the nasal cavity and the brain via the olfactory bulb, making it the most important site for nose-to-brain drug delivery. Drugs absorbed through this pathway can bypass the BBB and directly reach the CNS.^[3]

Physiologically, the nasal cavity performs several important functions including humidification, filtration, warming of inspired air, mucociliary clearance, and olfaction. The mucus layer covering the nasal epithelium acts as a protective barrier and traps inhaled particles. The coordinated movement of cilia continuously transports mucus toward the nasopharynx, a mechanism known as mucociliary clearance. Although this mechanism protects the respiratory tract, it can reduce nasal residence time and limit drug absorption.^[10]

2. MECHANISM OF BRAIN TARGETING

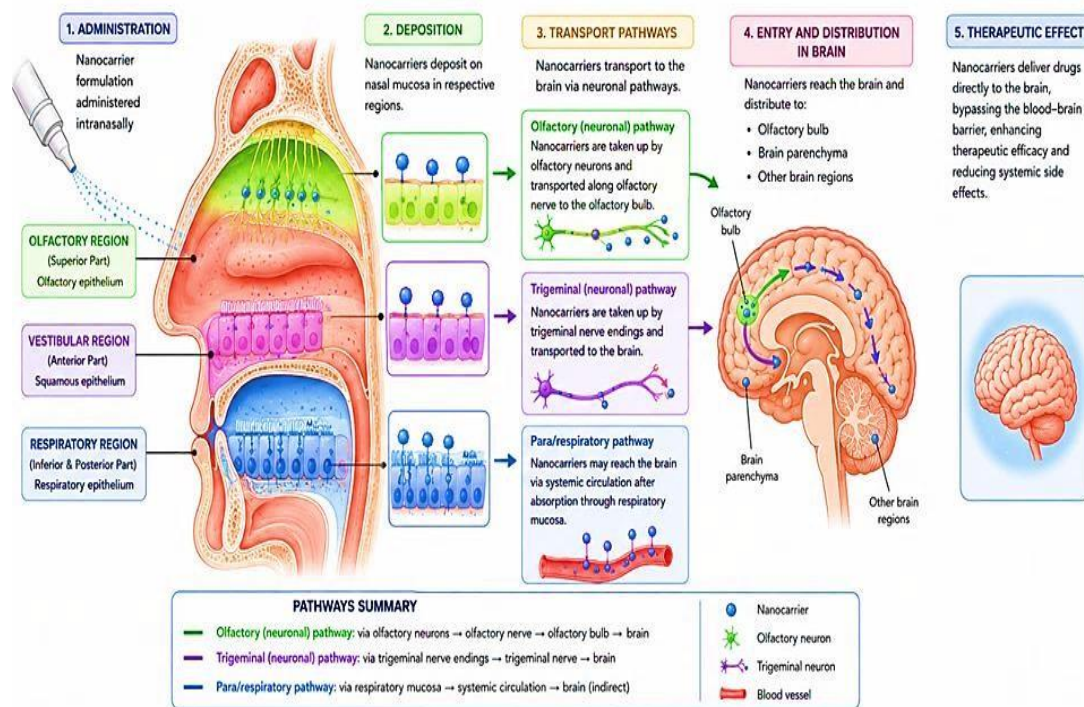


Fig. 1: Mechanism of brain targeting via intranasal delivery.

Nose-to-brain drug delivery enables therapeutic agents to reach the central nervous system (CNS) directly through neuronal pathways connecting the nasal cavity and the brain, thereby bypassing the blood-brain barrier (BBB). The two major pathways involved in brain targeting are the olfactory pathway and the trigeminal nerve pathway (3).

2.1 Olfactory Pathway

The olfactory region, located at the roof of the nasal cavity, contains olfactory receptor neurons that are directly connected to the olfactory bulb of the brain. Drugs deposited in this region can be transported intracellularly through olfactory neurons or extracellularly via perineural channels to reach various brain regions. This pathway is considered the primary route for direct nose-to-brain transport.^[9]

2.2 Trigeminal Nerve Pathway

The trigeminal nerve innervates both the respiratory and olfactory regions of the nasal cavity. Drugs absorbed through this pathway can reach the brainstem and spinal cord, contributing to CNS targeting. The trigeminal pathway plays an important supportive role in enhancing overall brain delivery efficiency.^[7]

2.3 Systemic Pathway

A fraction of the administered drug may also be absorbed into systemic circulation through the highly vascularized nasal mucosa and subsequently cross the BBB to enter the brain.

NOSE-TO-BRAIN DRUG DELIVERY

Nose-to-brain drug delivery has emerged as a promising non-invasive strategy for delivering therapeutic agents directly to the CNS. The nasal route provides rapid access to the brain through olfactory and trigeminal neural pathways while avoiding the limitations associated with conventional drug administration routes.^[3]

3.1 Advantages

- **Bypass of Blood-Brain Barrier:** Intranasal delivery bypasses the BBB and enables direct transport of drugs into the brain, thereby improving CNS bioavailability and therapeutic efficacy.^[9]
- **Rapid Onset of Action**
- The rich vascularization and high permeability of the nasal mucosa facilitate rapid drug absorption and fast therapeutic response, making this route suitable for acute neurological conditions.^[7]
- **Reduced Systemic Exposure**
- Direct brain targeting minimizes systemic drug distribution and reduces peripheral side effects and systemic toxicity.^[2]
- **Non-invasive and Patient Friendly**
- Intranasal administration is painless, convenient, and improves patient compliance compared to injectable therapies.^[8]
- **Avoidance of First-Pass Metabolism**
- Drugs administered intranasally bypass hepatic first-pass metabolism, leading to improved bioavailability.^[3]

3.2 Disadvantages

- **Mucociliary Clearance**
- The continuous movement of mucus by cilia rapidly removes administered formulations from the nasal cavity, resulting in reduced residence time and decreased drug absorption.
- **Limited Dose Volume**
- Only a small volume of formulation can be administered intranasally, which restricts the amount of drug delivered through this route.^[3]
- **Enzymatic Degradation**
- Various enzymes present in the nasal cavity can metabolize drugs before they reach the brain, thereby reducing therapeutic effectiveness.^[2]
- **Nasal Irritation and Toxicity**
- Repeated administration of certain formulations may cause irritation, epithelial damage, or toxicity to the nasal mucosa.^[8]

4. VESICULAR NANOCARRIERS

Vesicular nanocarriers are colloidal drug delivery systems composed of one or more concentric bilayers

capable of encapsulating both hydrophilic and lipophilic therapeutic agents. These nano-systems have attracted considerable attention in nose-to-brain drug delivery because of their biocompatibility, controlled drug release properties, enhanced permeation capability, and ability to improve drug targeting to the central nervous system (CNS). Vesicular carriers protect drugs from enzymatic degradation, increase nasal residence time, and facilitate transport across biological membranes, thereby enhancing brain bioavailability.^[6]

Among various vesicular systems, liposomes, niosomes, transfersomes, and spanlastics are widely investigated for intranasal brain targeting applications due to their unique structural and functional characteristics.

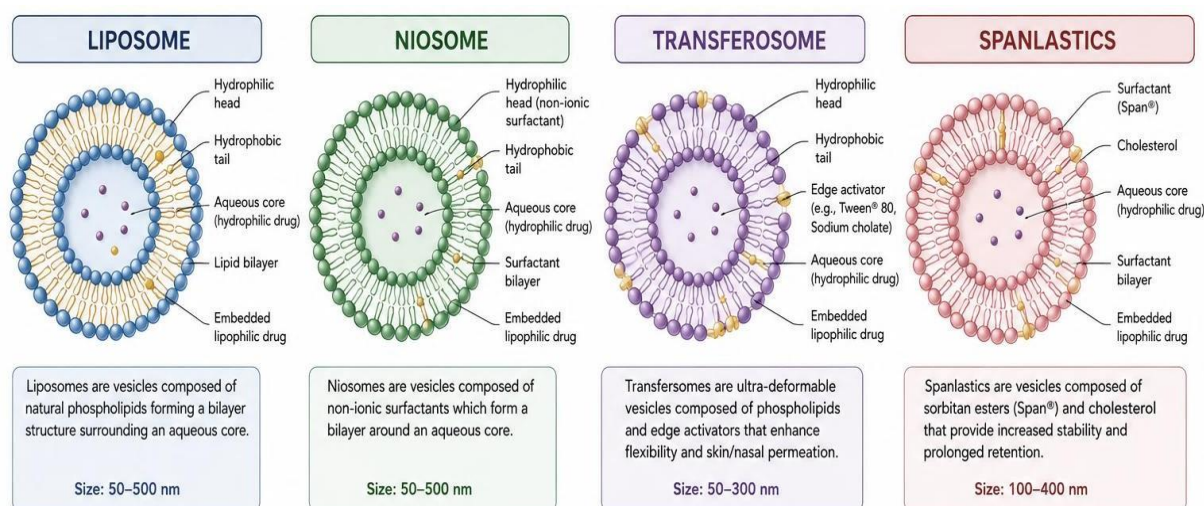


Fig. 2: Types of Vesicular Nanocarriers.

4.1 Liposomes

Liposomes are spherical vesicular systems composed of one or more phospholipid bilayers surrounding an aqueous core. Since their discovery by Bangham in the 1960s, liposomes have become one of the most extensively investigated nanocarriers for drug delivery applications owing to their biocompatibility, biodegradability, and structural similarity to biological membranes.^[11] Liposomes can encapsulate hydrophilic drugs within their aqueous core and lipophilic drugs within the phospholipid bilayer, making them highly versatile carriers for a wide range of therapeutic agents.

Structurally, liposomes are classified into unilamellar vesicles and multilamellar vesicles depending on the number of lipid bilayers present. Their size may range from nanometers to several micrometers based on the method of preparation. Common components used in

liposomal formulations include phosphatidylcholine, phosphatidylethanolamine, cholesterol, and charge-inducing agents. Cholesterol is frequently incorporated to improve membrane rigidity and stability.^[12]

Liposomes offer several advantages in nose-to-brain drug delivery. Their lipidic composition enhances interaction with biological membranes, thereby improving drug permeation across the nasal mucosa. Liposomes also protect encapsulated drugs from enzymatic degradation within the nasal cavity and facilitate sustained drug release. Furthermore, they can reduce systemic toxicity and improve drug localization in brain tissues.^[1]

Despite these advantages, liposomes possess certain limitations including poor physical stability, phospholipid oxidation, drug leakage during storage, and

high manufacturing cost. Their relatively short shelf life and susceptibility to hydrolysis remain major formulation challenges.^[13]

Numerous studies have demonstrated the potential of liposomes for CNS drug delivery. Intranasal liposomal formulations of rivastigmine, olanzapine, quetiapine, and donepezil have shown enhanced brain uptake and improved therapeutic efficacy in the treatment of neurodegenerative disorders and psychiatric conditions. Surface-modified liposomes and mucoadhesive liposomal systems have further improved nasal residence time and brain targeting efficiency.^[14]

4.2 Niosomes

Niosomes are non-ionic surfactant-based vesicular systems capable of encapsulating both hydrophilic and lipophilic drugs. They were developed as an alternative to liposomes to overcome issues related to phospholipid instability and high formulation cost. Niosomes are generally composed of non-ionic surfactants, cholesterol, and charge-inducing agents that self-assemble into bilayer vesicles upon hydration.^[15]

One of the major advantages of niosomes is their superior chemical stability compared to liposomes. Since non-ionic surfactants are less susceptible to oxidative degradation, niosomes exhibit longer shelf life and better formulation stability. Additionally, they are relatively inexpensive, easy to prepare, and capable of controlled drug release.^[16]

Niosomes enhance nose-to-brain drug delivery by improving drug permeation through the nasal epithelium and increasing nasal residence time. Their nanosized structure facilitates uptake through olfactory and trigeminal pathways, resulting in enhanced brain bioavailability. Niosomal systems have been investigated for intranasal delivery of bromocriptine, venlafaxine, sumatriptan, and other CNS-active agents.^[17]

However, niosomes may still face issues such as vesicle fusion, aggregation, leakage of entrapped drug, and limited deformability compared to newer elastic vesicular systems. These limitations have encouraged the development of advanced deformable carriers such as transfersomes and spanlastics.^[18]

4.3 Transfersomes

Transfersomes are highly deformable and elastic lipid vesicles specifically designed to enhance permeation across biological membranes. They are considered advanced vesicular carriers due to their ability to squeeze through pores significantly smaller than their own diameter without losing structural integrity.^[19]

Transfersomes are mainly composed of phospholipids and edge activators. Edge activators are single-chain surfactants that destabilize the phospholipid bilayer and impart flexibility to the vesicle membrane. Commonly

used edge activators include Tween 80, sodium cholate, and sodium deoxycholate. These surfactants reduce interfacial tension and increase membrane fluidity, thereby enhancing vesicle deformability.^[20]

Transfersomal formulations have shown promising applications in the intranasal delivery of drugs such as rasagiline, zolmitriptan, curcumin, and sumatriptan. These systems demonstrated enhanced brain targeting efficiency, increased bioavailability, and improved therapeutic outcomes in neurological disorders.^[21]

Despite their advantages, transfersomes may exhibit limitations such as phospholipid instability, oxidative degradation, and relatively complex formulation requirements. In addition, the use of phospholipids increases formulation cost compared to surfactant-based vesicular systems.^[22]

4.4 Spanlastics

Spanlastics are novel elastic nanovesicles composed primarily of Span surfactants and edge activators. They were developed as modified niosomal systems to overcome limitations associated with conventional vesicular carriers such as rigidity, low deformability, and limited permeation efficiency.^[23]

Structurally, spanlastics consist of non-ionic Span surfactants forming the vesicular bilayer, while edge activators such as Tween 80 or Tween 60 provide elasticity and membrane flexibility. Commonly used Span surfactants include Span 60 and Span 80. The incorporation of edge activators disrupts the vesicular membrane structure and increases deformability, enabling enhanced transport across biological membranes.^[24]

One of the major advantages of spanlastics is their superior elasticity and deformability compared to conventional niosomes and even transfersomes in certain formulations. Their flexible structure enables efficient penetration through the nasal mucosa and facilitates improved drug delivery to the brain. Spanlastics also exhibit high entrapment efficiency, improved physical stability, enhanced drug release characteristics, and lower formulation cost compared with phospholipid-based systems.^[25]

In nose-to-brain delivery, spanlastics have emerged as highly promising carriers for CNS therapeutics. Intranasal spanlastic formulations of risperidone, donepezil, zolmitriptan, and riluzole have demonstrated enhanced nasal permeation, prolonged residence time, improved brain uptake, and superior pharmacological activity. Furthermore, incorporation of spanlastics into thermoreversible *in situ* gels has shown synergistic benefits by improving mucoadhesion and sustained drug release.^[26]

Recent research has focused extensively on optimization

of spanlastic formulations using Quality by Design (QbD) approaches, factorial designs, and response surface methodologies to achieve desirable vesicle size, entrapment efficiency, deformability index, and drug release profiles. Due to their excellent permeation

characteristics and formulation flexibility, spanlastics are increasingly being recognized as next-generation vesicular nanocarriers for efficient nose-to-brain drug delivery.^[27]

4.5 COMPARATIVE ANALYSIS OF VESICULAR SYSTEMS

Table 1: comparative analysis of vesicular systems. ^[1,9,15,18,20,22,26,28]

Parameter	Liposomes	Niosomes	Transfersomes	Spanlastics
Basic structure	Phospholipid bilayer vesicles	Non-ionic surfactant vesicles	Ultra-deformable phospholipid vesicles	Elastic surfactant-based nanovesicles
Major components	Phospholipids + cholesterol	Non-ionic surfactants + cholesterol	Phospholipids + edge activators	span surfactants + edge activators
Vesicle flexibility	Moderate	Moderate	Very high	Very high
Deformability	Low	Moderate	Excellent	Excellent
Permeability	Moderate	Good	High	Very high
Entrapment efficiency	High for lipophilic drugs	High	High	Very high
Stability	Lower stability due to phospholipid oxidation	Better stability than liposomes	Moderate	Better physical stability
Brain targeting efficiency	Good	Good	Excellent	Excellent
Cost of development	High	Moderate to low	High	Moderate

4.6 CHARACTERIZATION PARAMETERS OF VESICULAR NANOCARRIERS

The physicochemical characterization of vesicular nanocarriers is essential for evaluating their stability, drug delivery efficiency, nasal permeation potential, and

suitability for nose-to-brain targeting. Various analytical techniques are employed to assess vesicle size, morphology, surface charge, encapsulation efficiency, deformability, and drug release behavior.

Table 2: Characterization Parameters of Vesicular Nanocarriers. ^[1,2,3,7,23,29,30]

Parameter	Purpose	Instrument	Significance
Particle Size	Determines Vesicle diameter and size distribution	Dynamic Light Scattering (DLS), Photon Correlation Spectroscopy	Influences nasal permeation, stability, and brain uptake
Polydispersity Index (PDI)	Measures homogeneity of vesicle dispersion	DLS	Lower PDI indicates uniform vesicle population and better stability
Zeta Potential	Evaluates surface charge and colloidal stability	Zeta Sizer	High absolute zeta potential prevents aggregation and improves stability
Morphology and Shape	Examines vesicle structure and surface characteristics	TEM, SEM	Confirms spherical morphology and vesicle integrity
Entrapment Efficiency (%)	Measures amount of drug encapsulated within vesicles	Centrifugation/Ultracentrifugation Method	Indicates drug loading capacity and therapeutic efficiency
Deformability Index	Assesses elasticity of vesicles	Extrusion Method	Critical for transfersomes and spanlastics to pass through nasal mucosa
In vitro Drug Release	Evaluates release profile of the drug	Dialysis Membrane	Predicts sustained or controlled drug release behavior
Ex vivo Permeation Study	Assesses permeation across nasal mucosa	Franz Diffusion Cell	Estimates nasal absorption and transport efficiency
Mucoadhesive Strength	Measures adhesion to nasal mucosa	Texture Analyzer/Mucin Interaction Method	Enhances residence time in nasal cavity

5. APPLICATIONS OF VESICULAR NANOCARRIERS IN NEUROLOGICAL DISORDERS

Vesicular nanocarriers such as liposomes, niosomes, transfersomes, and spanlastics have emerged as promising platforms for the treatment of neurological disorders through nose-to-brain drug delivery. Their nano-sized structure, enhanced permeation ability, and capacity for targeted drug delivery enable efficient transport of therapeutic agents to the brain while bypassing the blood–brain barrier (BBB). These systems improve drug bioavailability, reduce systemic side effects, prolong drug residence time, and enhance therapeutic efficacy in various CNS disorders.^[6]

5.1 Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and accumulation of amyloid- β plaques and neurofibrillary tangles in the brain. Conventional oral therapy for AD often exhibits poor brain bioavailability due to limited BBB penetration and extensive systemic metabolism.

Vesicular nanocarriers have shown significant potential in improving brain delivery of anti-Alzheimer drugs such as donepezil, rivastigmine, galantamine, and memantine. Intranasal liposomal and niosomal formulations of donepezil demonstrated enhanced drug uptake in the brain and improved cognitive performance in experimental models. Transfersomes and spanlastics further improved nasal permeation due to their deformable structure and enhanced mucosal penetration.^[1]

Additionally, incorporation of vesicular systems into thermoreversible in situ gels has improved nasal residence time and sustained drug release, thereby increasing therapeutic effectiveness in Alzheimer's management.^[2]

5.2 Parkinson's Disease

Parkinson's disease (PD) is a chronic neurodegenerative disorder caused by degeneration of dopaminergic neurons in the substantia nigra. Conventional oral treatment with drugs such as levodopa and bromocriptine often results in fluctuating plasma levels, peripheral side effects, and poor brain targeting.

Intranasal vesicular nanocarriers have demonstrated improved brain delivery of antiparkinsonian agents by bypassing the BBB and reducing systemic exposure. Niosomal formulations of bromocriptine and transfersomal formulations of rasagiline showed enhanced brain uptake and prolonged therapeutic action. Spanlastics have also been explored for intranasal delivery of dopamine agonists due to their superior deformability and permeation capability.^[17]

These nanocarriers improve drug localization in the brain, reduce dosing frequency, and minimize peripheral

adverse effects associated with conventional therapy.

5.3 Epilepsy

Epilepsy is a neurological disorder characterized by recurrent seizures caused by abnormal neuronal activity. Rapid drug delivery to the brain is crucial for effective seizure control, especially during acute epileptic episodes.

Nose-to-brain delivery using vesicular nanocarriers has shown promising outcomes in enhancing the bioavailability and therapeutic efficacy of antiepileptic drugs such as carbamazepine, clonazepam, diazepam, and lamotrigine. Liposomes and transfersomes improve drug permeation across the nasal mucosa and facilitate rapid CNS targeting. Intranasal vesicular formulations provide faster onset of action compared with oral delivery, making them suitable for emergency seizure management.^[21]

5.4 Depression and Anxiety Disorders

Depression and anxiety disorders are among the most common psychiatric illnesses worldwide. Many antidepressant drugs exhibit delayed onset of action, poor BBB penetration, and extensive systemic side effects following oral administration.

Intranasal vesicular systems have been investigated for delivering antidepressants such as venlafaxine, fluoxetine, paroxetine, and duloxetine directly to the brain. Niosomal and spanlastic formulations have demonstrated improved brain uptake, enhanced bioavailability, and faster therapeutic response compared with conventional dosage forms.^[15]

The direct nose-to-brain pathway allows rapid delivery of antidepressants to CNS tissues while minimizing systemic exposure and gastrointestinal side effects.

5.5 Brain Tumors

Treatment of brain tumors remains challenging due to poor penetration of anticancer drugs across the BBB and severe systemic toxicity associated with chemotherapy.

Vesicular nanocarriers have shown great potential in targeted brain tumor therapy through intranasal administration. Liposomes and transfersomes have been investigated for delivering anticancer agents such as doxorubicin, temozolomide, and methotrexate directly to brain tissues.

Their nanosized structure facilitates enhanced drug accumulation within tumor regions while reducing systemic toxicity.^[14]

Surface-modified vesicles and ligand-targeted nanosystems further improve tumor-specific targeting and therapeutic efficacy. Intranasal vesicular systems may offer a non-invasive alternative for glioblastoma and other CNS malignancies.

5.6 Migraine

Migraine is a debilitating neurological disorder associated with severe headache, nausea, and sensory disturbances. Rapid onset of therapeutic action is essential for effective migraine management.

Intranasal vesicular formulations of sumatriptan and zolmitriptan have shown improved nasal permeation, faster drug absorption, and enhanced brain targeting compared with conventional formulations. Transfersomes and spanlastics significantly improve mucosal penetration and provide rapid relief from migraine symptoms due to their ultra-deformable properties.^[20]

These formulations also bypass gastrointestinal disturbances commonly associated with migraine attacks and oral drug administration.

5.7 Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease characterized by demyelination and inflammation within the CNS. Effective drug delivery to the brain and spinal cord remains a major challenge in MS therapy.

Nanovesicular systems have been explored for intranasal delivery of anti-inflammatory and neuroprotective agents to improve CNS targeting. Liposomes and niosomes enhance drug stability and facilitate sustained release, while elastic vesicles improve permeation across the nasal epithelium.^[8]

These systems may potentially improve therapeutic outcomes and reduce systemic immunosuppressive side effects associated with conventional therapies.

6. CHALLENGES AND FUTURE PERSPECTIVES OF VESICULAR NANOCARRIERS IN NOSE-TO-BRAIN DRUG DELIVERY

Despite the significant advancements in vesicular nanocarrier systems for nose-to-brain drug delivery, several scientific, technological, and regulatory challenges continue to limit their successful clinical translation and commercialization. Although liposomes, niosomes, transfersomes, and spanlastics have demonstrated promising outcomes in enhancing brain targeting and therapeutic efficacy, further research is required to overcome formulation-related limitations and establish long-term safety and effectiveness in humans.^[6]

6.1 Challenges

6.1.1 Physiological Barriers of the Nasal Cavity

One of the major limitations associated with intranasal drug delivery is rapid mucociliary clearance, which removes administered formulations from the nasal cavity within a short period. This reduces nasal residence time and limits drug absorption. Additionally, enzymatic degradation within the nasal mucosa may lead to reduced drug stability and bioavailability.^[7]

The limited surface area of the olfactory region and variability in nasal physiology among patients also influence drug deposition and absorption efficiency. Conditions such as rhinitis, nasal congestion, and mucosal inflammation can further affect therapeutic performance.^[8]

6.1.2 Formulation Stability Issues

Vesicular nanocarriers often suffer from physical and chemical instability during storage. Liposomes and transfersomes are particularly susceptible to phospholipid oxidation, hydrolysis, vesicle aggregation, and drug leakage. Maintaining vesicle integrity and achieving long-term stability remain major formulation challenges.^[1]

Although niosomes and spanlastics offer comparatively better stability, problems such as vesicle fusion, sedimentation, and changes in particle size distribution may still occur during storage.

6.1.3 Scale-Up and Manufacturing Difficulties

Large-scale production of vesicular nanocarriers with consistent quality and reproducibility remains challenging. Factors such as vesicle size, entrapment efficiency, deformability, and drug release characteristics can vary significantly during scale-up processes. Complex manufacturing techniques, sterilization requirements, and high production costs further hinder industrial commercialization.^[15]

6.1.4 Limited Drug Loading Capacity

Some vesicular systems exhibit limited drug loading capacity, particularly for hydrophilic drugs. Drug leakage during storage and low encapsulation efficiency may reduce therapeutic effectiveness and formulation stability.^[18]

6.1.5 Toxicity and Safety Concerns

Although vesicular nanocarriers are generally considered biocompatible, long-term safety data regarding repeated intranasal administration remain limited. Certain surfactants, edge activators, and penetration enhancers may cause nasal irritation, ciliotoxicity, or mucosal damage following prolonged use.^[20] Comprehensive toxicological studies are therefore essential before clinical application.

6.1.6 Regulatory Challenges

Regulatory approval of nanocarrier-based formulations remains complex due to lack of standardized guidelines for characterization, quality control, safety evaluation, and clinical assessment. Variability in formulation methods and insufficient clinical data create additional barriers to commercialization.^[2]

6.2 Future Perspectives

6.2.1 Advanced Elastic Vesicular Systems

Future research is expected to focus on highly deformable and stimuli-responsive vesicular systems

capable of improving nasal permeation and targeted brain delivery. Spanlastics and modified transfersomes are gaining considerable attention due to their superior elasticity, enhanced permeation capability, and improved drug entrapment efficiency.^[26]

6.2.3 Surface-Modified and Targeted Nanocarriers

Surface functionalization of vesicles using ligands, peptides, antibodies, and mucoadhesive polymers may significantly improve site-specific brain targeting and prolong nasal residence time. Ligand-mediated targeting strategies could enhance selective uptake through olfactory pathways and improve therapeutic efficacy in neurological disorders.^[14]

6.2.4 Integration with In Situ Gel Systems

Combining vesicular nanocarriers with thermoreversible and mucoadhesive in situ gels represents a promising strategy for improving nasal retention and sustained drug release. These hybrid systems can reduce mucociliary clearance and provide prolonged contact with the nasal mucosa, thereby enhancing drug absorption and brain delivery.^[17]

6.2.5 Quality by Design (QbD) and Optimization Approaches

Application of Quality by Design principles and statistical optimization techniques such as factorial design and response surface methodology is expected to improve formulation reproducibility, scalability, and performance. Optimization of vesicle size, deformability index, entrapment efficiency, and release behavior will play an important role in future formulation development.^[27]

6.2.6 Personalized and Precision Nanomedicine

Emerging advances in personalized medicine may enable development of patient-specific intranasal nanocarrier systems tailored to individual therapeutic requirements and disease conditions. Precision nanomedicine approaches may improve treatment outcomes and reduce adverse effects in CNS disorders.^[21]

6.2.7 Clinical Translation and Commercialization

Future efforts should focus on conducting large-scale clinical trials to establish the safety, efficacy, and long-term stability of vesicular systems in humans. Development of cost-effective manufacturing methods and regulatory guidelines will be essential for successful commercialization of vesicular nose-to-brain drug delivery systems.^[7]

7. CONCLUSION

Vesicular nanocarriers have emerged as highly promising platforms for enhancing nose-to-brain drug delivery and overcoming the major limitations associated with conventional CNS therapeutics. By bypassing the blood-brain barrier through olfactory and trigeminal pathways, these nanosystems improve brain targeting, drug bioavailability, therapeutic efficacy, and patient

compliance while reducing systemic side effects. Liposomes offer excellent biocompatibility and drug-loading capacity, whereas niosomes provide improved stability and cost-effectiveness. Transfersomes exhibit remarkable deformability and enhanced permeation across biological membranes, while spanlastics have gained considerable attention due to their superior elasticity, high entrapment efficiency, enhanced permeation capability, and better physical stability.

Comparative analysis indicates that elastic vesicular systems, particularly transfersomes and spanlastics, demonstrate greater potential for efficient intranasal brain targeting compared with conventional vesicular carriers. Furthermore, the incorporation of these nanocarriers into thermoreversible in situ gels and mucoadhesive systems has further improved nasal residence time, sustained drug release, and therapeutic performance. Despite encouraging preclinical findings, challenges related to formulation stability, large-scale manufacturing, toxicity evaluation, and regulatory approval still limit their successful clinical translation. Continued advancements in nanotechnology, surface-modified carriers, Quality by Design approaches, and targeted delivery strategies are expected to accelerate the development of safer and more effective intranasal nanomedicines for neurological disorders. Overall, vesicular nanocarriers represent a significant advancement in CNS drug delivery and hold immense future potential for the management of various neurological diseases.

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