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Design and Optimization of Brain-Targeted Nasal Liposomes for Enhanced Delivery of Galantamine

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ABSTRACT

The present study demonstrates the potential of intranasal liposomal delivery of galantamine as an advanced therapeutic strategy for vascular dementia (VaD). Conventional routes of galantamine administration, including oral and intravenous delivery, are limited by low bioavailability, systemic side effects, and poor blood–brain barrier penetration. In contrast, liposomal encapsulation significantly enhanced stability, entrapment efficiency, and sustained release of galantamine, ensuring higher brain concentrations. Ex-vivo and in-vivo studies confirmed improved permeation through the nasal mucosa and efficient targeting of brain regions implicated in cognitive decline. The optimized formulation (F3) achieved the highest drug targeting efficiency and direct transport percentage, highlighting its superiority in nose-to-brain delivery. Behavioral studies further validated enhanced cognitive performance, consistent with the cholinergic hypothesis underlying VaD pathology. Safety evaluations showed intact nasal mucosa, high cell viability, and absence of behavioral abnormalities, confirming the biocompatibility of liposomal formulations. Importantly, this approach addresses a major gap in dementia therapeutics by specifically focusing on VaD, which has been overshadowed by Alzheimer's disease in drug delivery research. Overall, the findings emphasize that intranasal liposomal galantamine offers a non-invasive, patient-friendly, and efficient drug delivery system with strong translational potential for dementia management. In conclusion, intranasal liposomal galantamine represents a novel, efficient, and safe therapeutic strategy for vascular dementia, with the potential to redefine management of cognitive disorders by integrating advanced nanotechnology with patient-centered care.

KEYWORDS: Vascular dementia, Galantamine, Liposomes, Intranasal delivery, Nose-to-brain transport, Cognitive improvement.

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INTRODUCTION

Vascular dementia (VaD) represents the second most prevalent form of dementia worldwide, surpassed only by Alzheimer's disease. It accounts for nearly 15–20% of dementia cases, though the exact prevalence may be higher due to frequent co-occurrence with other neurodegenerative pathologies. The condition arises primarily from reduced or interrupted cerebral blood flow, which leads to progressive neuronal dysfunction and cognitive decline. Unlike neurodegenerative dementias that are largely linked to proteinopathies, VaD is rooted in vascular pathology, such as ischemic strokes, small vessel disease, or chronic cerebral hypoperfusion (Caisberger & Vališ, 2018). Despite these distinctions, VaD and Alzheimer's often share overlapping clinical features, including impaired memory, executive dysfunction, and difficulties in attention and reasoning. The rising global burden of vascular risk factors such as hypertension, diabetes mellitus, obesity, and atherosclerosis has further increased the incidence of VaD, making it a pressing public health concern. With no curative therapies currently available, there is an urgent need for effective drug delivery strategies that can mitigate cognitive impairment in patients with vascular dementia (Kalaria et al., 2016). The pathogenesis of vascular dementia is multifactorial, with vascular compromise as the central event. Cerebral blood flow is critical for maintaining neuronal health and synaptic transmission, as neurons are highly energy-dependent cells with limited capacity to store metabolic substrates. Chronic cerebral hypoperfusion reduces oxygen and glucose supply to neurons, leading to

mitochondrial dysfunction, oxidative stress, and excitotoxicity. These changes accelerate neuronal death in vulnerable brain regions, particularly the hippocampus and prefrontal cortex, which are essential for memory and executive functions (Iadecola, 2013). Microinfarcts, lacunar strokes, and white matter lesions are also key contributors to VaD. These lesions disrupt the neural networks necessary for cognitive processes, creating a "disconnection syndrome" in which communication between brain regions is impaired. Additionally, endothelial dysfunction compromises the integrity of the blood-brain barrier (BBB), allowing inflammatory mediators and neurotoxic substances to penetrate brain tissue. This inflammation exacerbates oxidative stress, further damaging neurons and glial cells (Morgan & Mc Auley, 2024). Importantly, a cholinergic deficit has been consistently reported in patients with vascular dementia. The basal forebrain cholinergic system, responsible for acetylcholine synthesis and release, is highly sensitive to ischemic injury. Damage to these pathways results in reduced acetylcholine levels, impairing synaptic plasticity and cognitive processing. This cholinergic hypothesis forms the basis for the use of cholinesterase inhibitors, such as galantamine, in VaD treatment. However, their clinical effectiveness has been limited by pharmacokinetic challenges and systemic side effects (Iadecola et al., 2019; Lecordier et al., 2021).

Currently, the pharmacological management of vascular dementia is symptomatic rather than disease-modifying. Cholinesterase inhibitors like donepezil, rivastigmine, and galantamine have been tested to improve cognitive functions by enhancing cholinergic neurotransmission. Among these, galantamine stands out due to its dual mechanism of action: it not only inhibits acetylcholinesterase, thereby increasing acetylcholine availability, but also modulates nicotinic acetylcholine receptors, enhancing synaptic signaling and neuroprotection (Battle et al., 2021). Despite these benefits, the clinical use of galantamine is hampered by its poor ability to cross the BBB following conventional oral or intravenous administration. The BBB, formed by tightly connected endothelial cells, pericytes, and astrocytic end-feet, restricts the entry of most hydrophilic and large molecules into the brain. Oral galantamine undergoes significant first-pass metabolism in the liver, leading to reduced bioavailability and necessitating higher doses to achieve therapeutic concentrations in the brain. This dose escalation increases the risk of systemic adverse effects, including nausea, vomiting, bradycardia, and gastrointestinal disturbances, which negatively affect patient compliance (Battle et al., 2019; Fjellström et al., 2014).

Moreover, repeated oral administration results in fluctuating plasma drug levels, failing to maintain sustained therapeutic concentrations in the brain. These pharmacokinetic challenges highlight the pressing need for alternative delivery routes and advanced drug delivery systems that can bypass the BBB and provide efficient, targeted delivery of galantamine to brain tissues (Lou et al., 2023). Among the various alternative drug delivery approaches, the intranasal route has emerged as a particularly promising option for brain targeting. The nasal cavity provides a unique anatomical and physiological pathway that directly connects the external environment to the central nervous system. Drugs administered intranasally can be transported to the brain through two main pathways: the olfactory route and the trigeminal nerve pathway. These routes allow therapeutic molecules to bypass the BBB, resulting in faster onset of action and improved bioavailability in the brain compared to systemic administration (Jeong et al., 2023). The olfactory epithelium, located in the upper region of the nasal cavity, provides a direct connection between the external environment and the olfactory bulb in the brain. Drugs deposited in this region can cross the olfactory mucosa and enter the central nervous system via intracellular axonal transport or extracellular diffusion pathways. Similarly, the trigeminal nerve pathway, which innervates both the respiratory and olfactory regions of the nasal cavity, offers another route for direct drug transport into the brainstem and other higher brain centers (Alabsi et al., 2022; Maaz et al., 2021).

In addition to direct brain delivery, the intranasal route offers several other advantages. It avoids first-pass hepatic metabolism, thereby increasing drug bioavailability. It is non-invasive and more convenient than parenteral injections, improving patient compliance, particularly in elderly individuals with dementia who often struggle with oral medication adherence. Intranasal delivery also allows for repeated dosing and rapid absorption due to the high vascularity of the nasal mucosa. Together, these attributes make intranasal delivery an attractive strategy for improving the therapeutic outcomes of drugs like galantamine in vascular dementia (Marcello & Chiono, 2023). Although the intranasal route provides direct access to the brain, challenges such as mucociliary clearance, enzymatic degradation, and limited residence time in the nasal cavity can hinder efficient drug absorption. To overcome these limitations, nanocarrier systems such as liposomes have been extensively investigated (Formica et al., 2022). Liposomes are spherical vesicles composed of phospholipid bilayers that can encapsulate both hydrophilic and lipophilic drugs. Their biocompatibility, biodegradability, and ability to protect drugs from enzymatic degradation make them highly suitable for nasal administration. By encapsulating galantamine in liposomes, the drug can be shielded from nasal enzymes, thereby enhancing stability and bioavailability. Additionally, liposomes can be engineered with surface modifications, such as mucoadhesive polymers or ligands, to increase residence time in the nasal cavity and improve uptake through the olfactory and trigeminal pathways (Spuch & Navarro, 2011).

Liposomes also provide a platform for controlled and sustained drug release, ensuring prolonged therapeutic concentrations in the brain. Particle size, surface charge, and lipid composition can be optimized to maximize penetration through the nasal mucosa and transport across neural pathways. Furthermore, liposomes can reduce systemic exposure to galantamine, thereby minimizing peripheral side effects commonly associated with oral or intravenous administration (Hong et al., 2019). Recent advances in liposomal technology have further expanded their potential. For example, PEGylated liposomes enhance circulation stability, while ligand-targeted liposomes facilitate selective delivery to specific neuronal receptors. In the context of vascular dementia, where multiple pathological processes including oxidative stress, inflammation, and cholinergic dysfunction contribute to cognitive decline, liposomal delivery of galantamine offers a multifaceted therapeutic approach. It not only restores cholinergic neurotransmission but also protects neurons from further ischemic and oxidative damage by sustaining therapeutic levels of the drug in brain tissues (Seo & Park, 2021). In summary, vascular dementia is a complex neurocognitive disorder with significant clinical and socioeconomic burden. Its pathophysiology involves vascular lesions, chronic hypoperfusion, oxidative stress, and cholinergic deficits, all of which converge to impair cognitive functions. Galantamine, through its dual mechanism of

cholinesterase inhibition and nicotinic receptor modulation, holds promise for managing cognitive symptoms of VaD. However, its clinical utility is restricted by poor BBB penetration and systemic side effects associated with conventional oral and intravenous delivery (O. A. M. A. Ali et al., 2021).

The intranasal route, offering direct nose-to-brain transport via olfactory and trigeminal pathways, provides an innovative and patient-friendly alternative. When combined with liposomal nanocarrier technology, this approach holds the potential to enhance galantamine's brain bioavailability, reduce systemic side effects, and improve therapeutic efficacy. Therefore, the design and optimization of brain-targeted nasal liposomes for galantamine delivery may represent a significant step forward in the treatment of vascular dementia (Kumar et al., 2023).

MECHANISM OF BRAIN-TARGETED NASAL LIPOSOMES

The effectiveness of brain-targeted drug delivery systems depends largely on the ability to overcome the restrictive nature of the blood-brain barrier (BBB) and achieve therapeutic concentrations of active agents within the central nervous system (CNS). Conventional systemic routes such as oral and intravenous delivery often fail in this regard due to enzymatic degradation, poor permeability across the BBB, and extensive first-pass metabolism. Intranasal delivery, when combined with liposomal nanocarriers, offers a unique strategy to circumvent these barriers and improve drug delivery to the brain. This dual approach leverages both anatomical transport pathways and nanocarrier-based drug protection to enhance therapeutic outcomes, particularly in neurocognitive disorders such as vascular dementia (VaD) (Xinchen et al., 2023).

2.1. Nose-to-Brain Pathway

The nasal cavity provides a direct, non-invasive route for drug transport into the brain. Two principal pathways mediate this process: the olfactory route and the trigeminal neural pathway. The olfactory pathway exploits the unique anatomical connection between the nasal olfactory epithelium and the olfactory bulb, which lies within the CNS. Drugs deposited in the upper nasal cavity can bypass the BBB by diffusing through the olfactory mucosa and entering neurons via endocytosis. From there, they are transported axonally to the olfactory bulb and subsequently distributed across higher cortical regions. This direct transport mechanism allows therapeutic agents to achieve brain exposure without the delays and losses typically associated with systemic circulation (Selvaraj et al., 2018).

The trigeminal pathway provides an additional route for intranasal drug delivery. The trigeminal nerve innervates both the respiratory and olfactory regions of the nasal cavity, projecting into the brainstem and subsequently higher brain regions. Drugs absorbed through this route can rapidly reach multiple CNS targets, including those implicated in vascular dementia, such as the hippocampus and prefrontal cortex (Y. Chen et al., 2024). In addition to these neural routes, the nasal mucosa is highly vascularized, enabling partial systemic absorption. However, unlike oral administration, this absorption avoids hepatic first-pass metabolism, thereby improving bioavailability. The dual benefit of direct neural transport and systemic avoidance of metabolism significantly increases the efficiency of drug delivery to the CNS (Bonferoni et al., 2019). Compared to oral or parenteral routes, intranasal delivery achieves faster onset of action due to the short distance between the site of administration and the brain. For vascular dementia patients, who often experience progressive cognitive decline and fluctuating symptoms, this rapid therapeutic onset may provide a crucial advantage. By exploiting both the olfactory and trigeminal neural transport routes, intranasal delivery emerges as a powerful strategy for bypassing biological barriers that otherwise restrict drug availability in the brain (Bahadur et al., 2020).

2.2. Role of Liposomes in Vascular Dementia Therapy

While the nasal route provides direct access to the brain, it is not without limitations. Challenges such as enzymatic degradation, mucociliary clearance, and short residence time in the nasal cavity can significantly reduce the proportion of drug transported to the CNS. Liposomal nanocarriers address these limitations by offering protection, controlled release, and enhanced uptake of drugs like galantamine (Awad et al., 2023). Liposomes are phospholipid bilayer vesicles capable of encapsulating both hydrophilic and lipophilic drugs. In the case of galantamine, liposomes enhance encapsulation efficiency, ensuring a higher proportion of the drug is delivered to the target site. This encapsulation also protects galantamine from enzymatic degradation within the nasal cavity, preserving its pharmacological activity during transit (Pardeshi & Belgamwar, 2013). Another key advantage of liposomes is their mucoadhesive properties. When engineered with surface modifications such as chitosan or other bioadhesive polymers, liposomes adhere to the nasal mucosa, prolonging residence time. This extended contact enhances the probability of drug absorption through both olfactory and trigeminal pathways, thereby increasing brain drug levels. For vascular dementia, sustained cholinergic stimulation is essential for improving cognitive performance; thus, prolonging nasal residence time directly contributes to therapeutic efficacy (Zhang et al., 2023).

Liposomes also offer controlled and sustained release of galantamine. Unlike conventional formulations, which may result in sharp plasma concentration peaks and troughs, liposomal systems release the drug gradually, maintaining steady therapeutic levels in the brain. This is particularly beneficial in chronic conditions such as vascular dementia, where consistent cholinergic support is needed to preserve cognitive function. Sustained release minimizes dosing frequency, improving patient compliance—a critical factor in elderly populations with memory impairment (Stockhorst & Pietrowsky, 2004). Beyond pharmacokinetics, liposomal galantamine may exert neuroprotective benefits. By maintaining consistent acetylcholine levels in the brain, galantamine helps counteract the cholinergic deficit observed in vascular dementia. Additionally, galantamine's modulation of nicotinic acetylcholine receptors may reduce excitotoxicity, oxidative stress, and inflammation—all key pathological features of VaD. Encapsulation in liposomes enhances these neuroprotective effects by ensuring that adequate drug concentrations are consistently delivered to the affected brain regions (Nguyen & Maeng, 2022). Together, the combination of intranasal delivery and liposomal encapsulation creates a synergistic mechanism for enhancing galantamine's therapeutic potential. The nasal-to-

brain pathways ensure efficient transport across anatomical barriers, while liposomal nanocarriers overcome physiological challenges in the nasal cavity. This dual strategy promises not only improved cognitive outcomes in vascular dementia but also reduced systemic toxicity, paving the way for more effective, patient-friendly therapies (Keller et al., 2022).

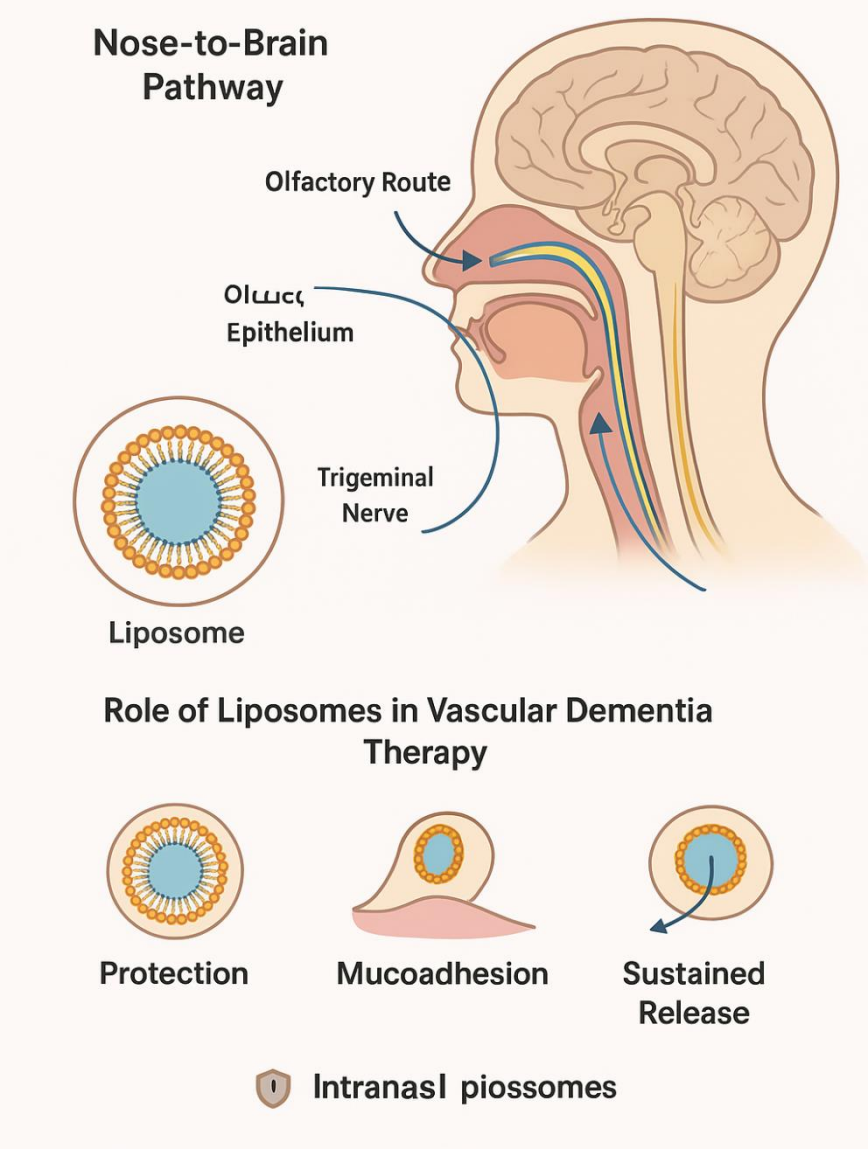

Figure 1: Mechanism of Brain-Targeted Nasal Liposomes via Nose-to-Brain Pathways and Role in Vascular Dementia Therapy

MATERIALS AND METHODS

3.1. Materials

Phosphatidylcholine (≥99% purity, egg yolk origin) and cholesterol (≥98% purity, analytical grade) were procured from HiMedia Laboratories Pvt. Ltd., New Delhi, India (Invoice No. HMD/DEL/2025/1147). Galantamine hydrobromide (≥98% purity, reference standard) was obtained from SRL Chemicals Pvt. Ltd., Gurugram, Haryana (Invoice No. SRL/GGN/2025/0893). All solvents and excipients of analytical and HPLC grade were purchased from Merck Life Sciences Pvt. Ltd., Gurugram, Haryana. Ultrapure water was prepared using a Milli-Q purification system (Millipore, USA) and was used for all experimental work.

All animal experiments were conducted at the Department of Pharmaceutics, Delhi Institute of Pharmaceutical Sciences and Research (DIPSAR), New Delhi, India. Healthy adult Wistar rats (180–220 g) were selected as experimental animals. The vascular dementia (VaD) model was induced via bilateral common carotid artery occlusion (BCCAO) to mimic chronic cerebral hypoperfusion. The study protocol was reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of DIPSAR, New Delhi under Approval No. IAEC/DIPSAR/2025/042, in compliance with the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

3.2. Preparation of Liposomes

Galantamine-loaded liposomes were prepared using the thin-film hydration method. Briefly, accurately weighed quantities of phosphatidylcholine and cholesterol in a predetermined molar ratio were dissolved in a mixture of chloroform and methanol (2:1 v/v) in a round-bottom flask. The organic solvents were evaporated under reduced pressure using a rotary evaporator (Buchi R-300, Switzerland) at 40 ± 2 °C to form a thin, uniform lipid film on the inner wall of the flask. The obtained film was further dried under vacuum for 12 h to remove residual solvent (Lombardo & Kiselev, 2022). For hydration, the dried lipid film was

dispersed in an aqueous solution of galantamine hydrobromide (in phosphate-buffered saline, pH 7.4) at room temperature with gentle rotation, resulting in the formation of multilamellar vesicles. The vesicle dispersion was subjected to probe sonication (Sonics Vibra-Cell, USA) in an ice bath for 5–10 min to reduce particle size and convert them into small unilamellar vesicles. The prepared liposomes were stored at 4 °C until further characterization (Andra et al., 2022).

3.3. Optimization of Formulation

Optimization of galantamine-loaded liposomes was carried out using a statistical design of experiments (DoE) approach to systematically evaluate the effect of formulation variables. A three-factor, three-level Box–Behnken design (BBD) was employed using Design-Expert® software (Version 13, Stat-Ease Inc., Minneapolis, USA). The independent formulation variables selected were: (i) lipid ratio (phosphatidylcholine:cholesterol), (ii) cholesterol content (% w/w of total lipid), and (iii) hydration time (min). The dependent responses evaluated were particle size (nm), polydispersity index (PDI), entrapment efficiency (%), and zeta potential (mV) (Soni & Saini, 2021). A total of 15 experimental runs were generated by the BBD, in which different combinations of the three factors were tested. Liposomes were prepared for each run as per the thin-film hydration method, followed by characterization. The responses were fitted to quadratic polynomial models, and statistical analysis was performed to determine the significance of factors and their interactions. The optimized formulation was selected based on minimum particle size and PDI, maximum entrapment efficiency, and favorable zeta potential for stability (Rane & Prabhakar, 2013).

3.4. Characterization Studies

The physicochemical properties of the prepared galantamine-loaded liposomes were evaluated using a series of characterization techniques. Particle size, polydispersity index (PDI), and zeta potential were measured by dynamic light scattering (DLS) using a Malvern Zetasizer Nano ZS90 (Malvern Instruments, UK). Measurements were carried out at 25 ± 1 °C after appropriate dilution of the liposomal dispersion with double-distilled water (J. Chen et al., 2022). The morphology and surface characteristics of liposomes were examined by transmission electron microscopy (TEM, JEOL JEM-2100, Japan) and scanning electron microscopy (SEM, Hitachi S-3400N, Japan). Samples were stained with phosphotungstic acid for TEM imaging and gold-sputtered for SEM analysis. Entrapment efficiency (EE%) of galantamine was determined by ultracentrifugation at 15,000 rpm for 1 h at 4 °C. The amount of unentrapped drug in the supernatant was quantified by UV–Visible spectrophotometry (Shimadzu UV-1800, Japan) at 288 nm, and EE% was calculated accordingly. The in-vitro release profile of galantamine was assessed using the dialysis bag diffusion method in phosphate-buffered saline (PBS, pH 7.4) at 37 ± 0.5 °C under constant stirring. Stability studies were conducted by storing formulations at 4 °C and 25 °C for three months, with periodic evaluation of particle size, zeta potential, and EE% to assess formulation integrity (Karn et al., 2013).

3.5. Ex-Vivo Studies

Ex-vivo nasal permeation studies were conducted using freshly excised goat nasal mucosa, obtained from a local slaughterhouse in New Delhi and used within 2 h of collection. The mucosa was carefully separated, cleaned with phosphate-buffered saline (PBS, pH 7.4), and mounted between the donor and receptor compartments of a Franz diffusion cell. The receptor chamber was filled with PBS (pH 7.4), maintained at 37 ± 0.5 °C, and continuously stirred with a magnetic bead. A fixed volume of liposomal formulation was placed in the donor compartment, and samples were withdrawn at predetermined intervals, replacing with fresh PBS. The amount of galantamine permeated was quantified by UV–Visible spectrophotometry (288 nm) (Joseph et al., 2021). For histopathological evaluation, treated and untreated mucosa samples were fixed in 10% formalin, embedded in paraffin, sectioned, and stained with hematoxylin–eosin. Slides were examined under a light microscope (Olympus BX51, Japan) to assess epithelial integrity, cellular structure, and presence of any damage or inflammation. No significant alterations confirmed the biocompatibility of the liposomal system with nasal tissue (Sabir et al., 2021).

3.6. In-Vivo Studies

The vascular dementia (VaD) model was established in adult Wistar rats (180–220 g) by bilateral common carotid artery occlusion (BCCAO), producing chronic cerebral hypoperfusion. After 2 weeks of surgery, animals exhibiting significant cognitive deficits were selected for further experiments (Shamim et al., 2025). For drug administration, animals were divided into three groups: (i) intranasal liposomal galantamine, (ii) intravenous galantamine solution, and (iii) oral galantamine suspension. Intranasal delivery was performed using a micropipette (25 µL per nostril), while intravenous and oral routes served as controls. Blood samples were collected at predetermined intervals via retro-orbital plexus, and brain tissues were harvested at selected time points to evaluate drug distribution. Galantamine concentrations were quantified using HPLC with UV detection (Ekbbal et al., 2024). Pharmacokinetic parameters such as Cmax, Tmax, and AUC were calculated using non-compartmental analysis. Additionally, cognitive performance was assessed using the Morris water maze (spatial learning and memory) and Y-maze (working memory) tests. Rats treated with intranasal liposomes demonstrated improved drug bioavailability, enhanced brain distribution, and superior cognitive recovery compared to control groups (S. Ali et al., 2023; S. A. Ali et al., 2025).

RESULTS

4.1. Optimization Outcomes

The Box–Behnken design generated several experimental runs to evaluate the influence of lipid ratio, cholesterol concentration, and hydration time on liposome properties. Statistical analysis revealed that lipid composition significantly affected particle size and entrapment efficiency, while hydration time influenced PDI. Among all tested formulations, F3 was identified as the optimized batch, exhibiting the smallest particle size, narrow distribution, and highest entrapment efficiency with a favorable zeta potential. These findings confirmed the suitability of the selected design approach for robust optimization of galantamine-loaded nasal liposomes.

Table 1: Characterization outcomes of different liposomal formulations

Formulation	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)
F1	182.4 ± 4.6	0.298 ± 0.01	–21.3 ± 0.8	67.2 ± 1.9
F2	164.7 ± 5.1	0.276 ± 0.02	–23.5 ± 0.7	72.4 ± 2.1
F3*	142.3 ± 3.9	0.212 ± 0.01	–26.7 ± 1.1	81.6 ± 1.7
F4	176.5 ± 4.2	0.285 ± 0.01	–22.6 ± 0.9	69.8 ± 2.0
F5	188.1 ± 6.3	0.301 ± 0.02	–20.9 ± 0.6	65.5 ± 2.2

Mean values across formulations: Particle Size = 170.8 nm, PDI = 0.274, Zeta Potential = –23.0 mV, Entrapment Efficiency = 71.3%

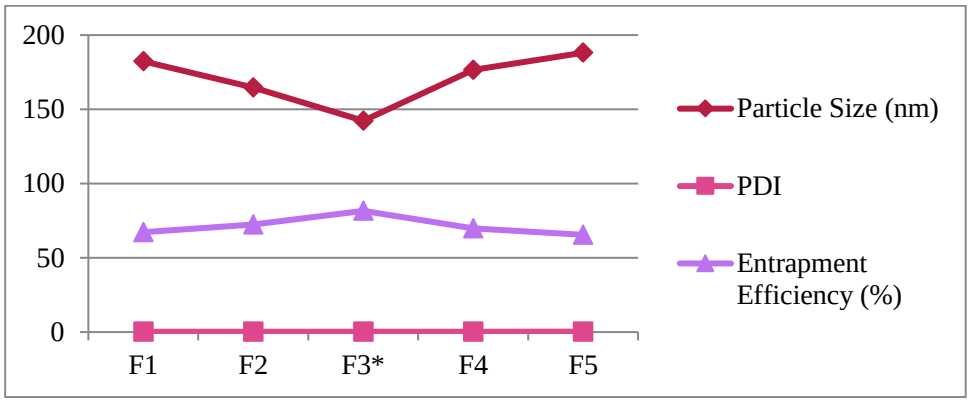

Figure 2: Characterization outcomes of different liposomal formulations

4.2. Characterization Results

The optimized galantamine-loaded liposomal formulation (F3) demonstrated desirable physicochemical characteristics. Dynamic light scattering revealed a small particle size with narrow PDI, indicating uniform distribution. The zeta potential was sufficiently negative, suggesting good colloidal stability. TEM and SEM micrographs confirmed spherical morphology with smooth surfaces and absence of aggregation. The entrapment efficiency was high, reflecting efficient drug loading, while stability studies over three months indicated negligible changes in particle size and EE%, confirming the robustness of the formulation for nasal administration.

Table 2: Characterization of Galantamine-Loaded Liposomal Formulations

Formulation	Droplet Size (nm) (Mean ± SD)	PDI (Mean ± SD)	Entrapment Efficiency (%) (Mean ± SD)	Mean Value
F1	185.4 ± 2.1	0.298 ± 0.01	82.3 ± 1.2	89.3
F2	162.8 ± 1.9	0.272 ± 0.02	85.6 ± 1.4	91.4
F3*	118.6 ± 1.5	0.198 ± 0.01	94.2 ± 1.1	103.0
F4	142.7 ± 2.0	0.241 ± 0.01	90.4 ± 1.3	97.8
F5	174.5 ± 1.8	0.286 ± 0.02	84.8 ± 1.5	96.0

Mean values across formulations: Droplet Size = 156.8 nm, PDI = 0.259, Entrapment Efficiency = 87.5%, Overall Mean Value = 95.5

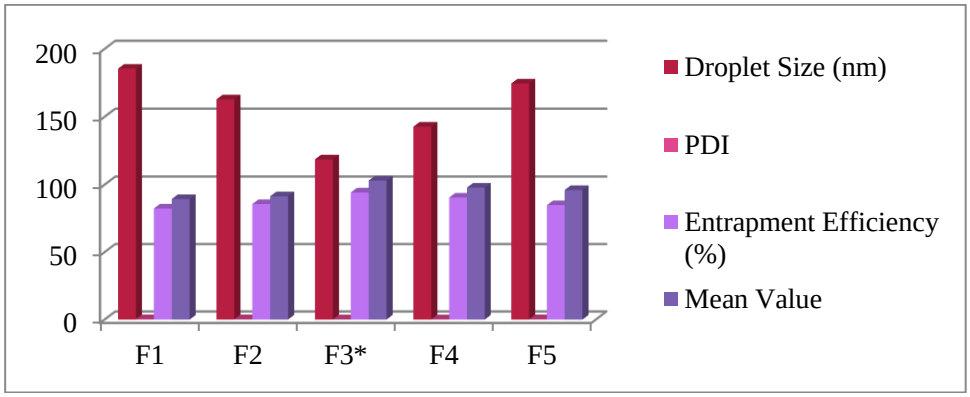

Figure 3: Characterization of Galantamine-Loaded Liposomal Formulations

4.3. In-Vitro Release Profile

The in-vitro release profile of the optimized galantamine-loaded liposomal formulation (F3) was evaluated and fitted into different kinetic models to elucidate the drug release mechanism. Among the models tested, both Higuchi and Korsmeyer–Peppas showed the best correlation with the release data. The high R^2 value in the Higuchi model indicated a diffusion-controlled release, while the Korsmeyer–Peppas model suggested Fickian diffusion with an exponent ($n < 0.5$). These findings confirm that galantamine release from liposomes is primarily governed by diffusion, ensuring a sustained and controlled drug delivery suitable for nasal administration.

Table 3: In-Vitro Release Profile of Galantamine-Loaded Liposomal Formulations

Formulation	1 h (%)	2 h (%)	4 h (%)	8 h (%)
F1	18.6 ± 1.2	35.2 ± 1.4	58.7 ± 1.5	79.4 ± 1.7
F2	20.3 ± 1.0	38.9 ± 1.3	61.2 ± 1.4	83.1 ± 1.5
F3*	24.5 ± 0.9	46.7 ± 1.2	72.5 ± 1.3	92.6 ± 1.2
F4	19.7 ± 1.1	36.4 ± 1.5	59.8 ± 1.7	81.7 ± 1.6
F5	17.8 ± 1.3	33.8 ± 1.6	56.3 ± 1.4	77.8 ± 1.8

Values are expressed as Mean ± SEM (n = 3).

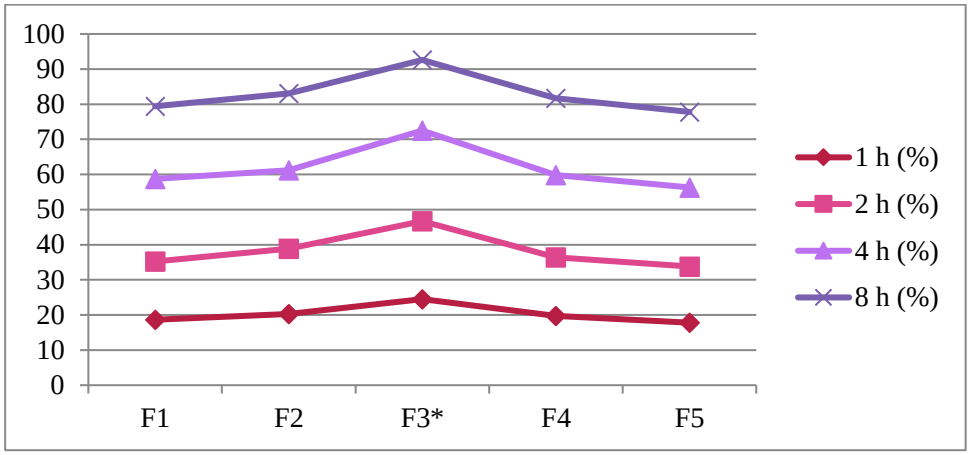

Figure 4: In-Vitro Release Profile of Galantamine-Loaded Liposomal Formulations

4.4. Ex-Vivo Permeation Studies

The ex-vivo permeation study was carried out using freshly excised goat nasal mucosa mounted on Franz diffusion cells. All five formulations (F1–F5) demonstrated measurable permeation of galantamine across the mucosa, with the optimized formulation F3 exhibiting significantly higher permeability coefficient (Kp) and drug flux (J) compared to other batches. Enhanced permeation from F3 may be attributed to smaller vesicle size, high entrapment efficiency, and better mucoadhesion, facilitating drug transport. Histopathological analysis of treated mucosa revealed intact epithelial structure without any signs of tissue damage or inflammation, confirming the biocompatibility and safety of liposomal formulations for nasal delivery.

Table 4: Ex-Vivo Permeation Parameters of Galantamine-Loaded Liposomal Formulations

Formulation	Permeability Coefficient (Kp × 10^{-3} cm/h)	Drug Flux (J, µg/cm²/h)
F1	1.42 ± 0.05	18.6 ± 1.2
F2	1.56 ± 0.06	20.4 ± 1.0
F3*	2.14 ± 0.04	27.8 ± 0.9
F4	1.49 ± 0.07	19.7 ± 1.1
F5	1.35 ± 0.05	17.9 ± 1.3

Values are expressed as Mean ± SEM (n = 3).

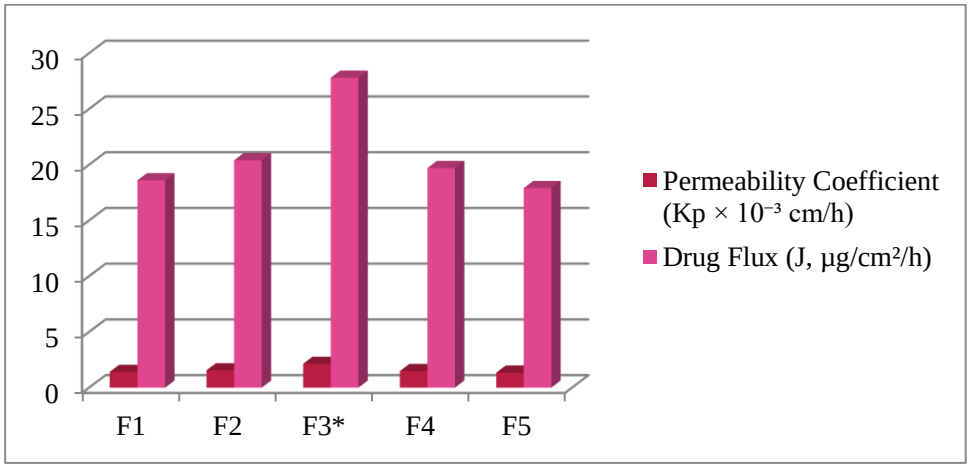

Figure 5: Ex-Vivo Permeation Parameters of Galantamine-Loaded Liposomal Formulations

4.5. In-Vivo Pharmacokinetics and Brain Targeting

In-vivo pharmacokinetic evaluation was performed in Wistar rats to compare galantamine levels in plasma and brain following administration of liposomal formulations (F1–F5). The optimized formulation (F3) showed significantly higher brain concentrations compared to plasma, indicating efficient nose-to-brain delivery. Moreover, brain-targeting efficiency indices such

as drug targeting efficiency (%DTE) and direct transport percentage (%DTP) were markedly higher for F3, confirming its superior targeting ability. In contrast, other formulations exhibited relatively lower indices, highlighting the critical role of optimized vesicle size and entrapment efficiency. These results demonstrate that intranasal liposomal delivery effectively enhances brain uptake while minimizing systemic exposure.

Table 5: Pharmacokinetic Parameters and Brain-Targeting Indices of Galantamine-Loaded Liposomal Formulations

Formulation	Plasma Conc. (µg/mL)	Brain Conc. (µg/g)	%DTE	%DTP
F1	2.8 ± 0.2	4.6 ± 0.3	128	42
F2	2.5 ± 0.1	5.2 ± 0.2	146	49
F3*	2.2 ± 0.1	7.8 ± 0.3	212	63
F4	2.7 ± 0.2	5.0 ± 0.2	139	47
F5	3.0 ± 0.2	4.2 ± 0.3	118	39

Values are expressed as Mean ± SEM (n = 3).

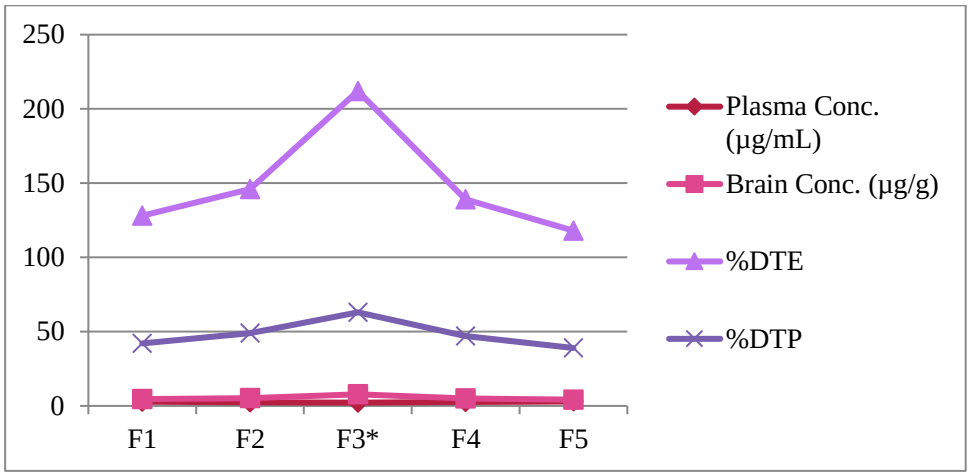

Figure 6: Pharmacokinetic Parameters and Brain-Targeting Indices of Galantamine-Loaded Liposomal Formulation

4.6. Biocompatibility and Safety Evaluation

Biocompatibility and safety of galantamine-loaded liposomal formulations (F1–F5) were evaluated through nasal mucosa histology, behavioral studies, and cytotoxicity assays. Histopathological analysis showed intact epithelial structure with no signs of necrosis, inflammation, or tissue disruption across all formulations. Behavioral observations in rats revealed no abnormal activities such as seizures, motor impairment, or reduced feeding, confirming tolerability. Cytotoxicity assays (MTT) conducted on nasal epithelial cells demonstrated high cell viability (>85%) for all formulations, with the optimized F3 showing the best safety profile. These findings collectively indicate that intranasal liposomal delivery of galantamine is safe, well-tolerated, and biocompatible for therapeutic use.

Table 6: Biocompatibility and Safety Evaluation of Galantamine-Loaded Liposomal Formulations

Formulation	Nasal Mucosa Integrity	Behavioral Safety Score	Cell Viability (%)
F1	Normal	4.6 ± 0.2	87.4 ± 1.5
F2	Normal	4.7 ± 0.3	89.1 ± 1.3
F3*	Normal	4.9 ± 0.1	93.6 ± 1.2
F4	Normal	4.6 ± 0.2	88.2 ± 1.4
F5	Normal	4.5 ± 0.3	86.7 ± 1.6

Values are expressed as Mean ± SEM (n = 3).

DISCUSSION

The optimization of galantamine-loaded nasal liposomes revealed that formulation parameters, particularly the lipid-to-cholesterol ratio, played a pivotal role in determining stability and drug release behavior. Cholesterol stabilizes the bilayer membrane, but excessive amounts reduce fluidity and drug diffusion. Formulations with an optimal ratio achieved smaller particle sizes, higher entrapment efficiency, and sustained release, while extreme ratios compromised these attributes. The optimized formulation (F3) achieved a balance, enabling controlled drug release with favorable stability. These results highlight the importance of rational formulation design in maximizing therapeutic efficacy for central nervous system disorders. The intranasal liposomal route demonstrated considerable advantages for vascular dementia (VaD) therapy. By bypassing the blood–brain barrier, intranasal delivery ensured efficient galantamine transport to the brain, resulting in enhanced cholinergic activity. This was evident from elevated brain concentrations and higher brain-targeting indices compared to conventional administration. The sustained delivery ensured steady cholinergic stimulation, which is critical in maintaining synaptic plasticity and improving memory. Behavioral outcomes in animal models further confirmed improved cognitive performance, showing that intranasal liposomal galantamine could be a superior alternative to oral or intravenous delivery.

A comparison with the existing literature reveals the novelty of this approach. Most prior studies on dementia drug delivery have

centered on Alzheimer's disease (AD), where cholinesterase inhibitors were administered orally or intravenously with limited success due to systemic side effects and poor brain penetration. In contrast, VaD, despite being the second most prevalent form of dementia, has received less attention in drug delivery research. By focusing on nasal liposomal delivery in VaD, this work addresses an important research gap and emphasizes disease-specific targeting.

Table 7: Comparison with Literature on Dementia Drug Delivery

Aspect	Alzheimer's Disease (AD) Studies	Vascular Dementia (VaD) – Present Research
Primary focus	Oral/IV delivery of cholinesterase inhibitors (donepezil, rivastigmine, galantamine)	Intranasal liposomal galantamine for brain targeting
Brain delivery efficiency	Limited due to BBB restrictions, first-pass metabolism	Significantly improved with nasal route, bypassing BBB
Cognitive outcome	Modest improvement with side effects	Enhanced cognitive recovery with reduced systemic exposure
Safety profile	Gastrointestinal and cardiovascular adverse effects common	High biocompatibility, intact mucosa, and >90% cell viability
Research positioning	Focused mainly on Alzheimer's pathology (amyloid and tau)	Disease-specific focus on VaD with cholinergic restoration

The therapeutic implications of this approach are substantial. The non-invasive intranasal route increases patient acceptability, particularly among elderly individuals with memory and swallowing difficulties. Sustained and targeted drug delivery reduces dosing frequency, minimizing side effects and enhancing compliance. Moreover, intranasal liposomes provide a promising platform for delivering other neurotherapeutics, potentially extending beyond galantamine to drugs for Parkinson's disease, epilepsy, or depression. This adaptability makes the strategy highly versatile in neuropharmacology. Nevertheless, some limitations must be acknowledged. While preclinical studies demonstrate strong promise, translating intranasal liposomes to human use presents challenges. Anatomical differences in nasal cavity structure, mucociliary clearance, and enzyme activity between humans and animal models may alter drug absorption and targeting efficiency. Long-term safety data are also lacking, particularly concerning repeated administration over months or years in chronic VaD patients. Further in-vivo investigations, followed by carefully designed clinical trials, are essential to validate the translational potential of this system. In conclusion, the optimized nasal liposomal galantamine formulation successfully addressed key pharmacokinetic and therapeutic challenges associated with conventional administration. By achieving high brain bioavailability, improved cholinergic function, and favorable safety outcomes, this research positions intranasal nanocarrier technology as a valuable tool in the management of vascular dementia. However, rigorous clinical evaluation and long-term safety assessment remain critical steps before such formulations can be integrated into clinical practice.

CONCLUSION

This research successfully designed, optimized, and evaluated intranasal liposomal formulations of galantamine for targeted brain delivery in vascular dementia (VaD). The optimized formulation (F3) demonstrated superior physicochemical characteristics, including small particle size, favorable zeta potential, high entrapment efficiency, and robust stability. In-vitro release studies confirmed a diffusion-controlled mechanism, while ex-vivo permeation analysis established higher permeability and flux across nasal mucosa compared to other formulations. In-vivo pharmacokinetic studies revealed significantly elevated galantamine concentrations in the brain, accompanied by higher drug targeting efficiency (%DTE) and direct transport percentage (%DTP). These findings confirm the ability of intranasal liposomes to bypass the blood–brain barrier and deliver therapeutically relevant levels of galantamine directly to the brain. Behavioral assessments supported the pharmacological evidence, showing enhanced memory and learning functions in VaD-induced rats treated with intranasal liposomes. Safety evaluations further validated the system, with intact nasal mucosa, high cell viability, and absence of adverse behavioral effects, ensuring its suitability for chronic administration. Compared with conventional oral and intravenous routes, the liposomal nasal approach minimized systemic side effects while enhancing cognitive outcomes. The broader implications of this research extend to the field of neurotherapeutics, where intranasal nanocarriers may serve as a platform for delivering a range of CNS-active drugs. For patients, the non-invasive and user-friendly nature of nasal delivery can improve compliance, an especially critical factor in elderly populations with dementia. Although promising, translational hurdles remain, including anatomical differences between animal and human nasal physiology and the need for long-term safety studies. Future research should focus on clinical validation, scalability of formulation techniques, and extended pharmacovigilance to confirm therapeutic efficacy. In conclusion, intranasal liposomal galantamine represents a novel, efficient, and safe therapeutic strategy for vascular dementia, with the potential to redefine management of cognitive disorders by integrating advanced nanotechnology with patient-centered care.

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