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RECENT ADVANCES IN TRANSFEROSOME-BASED NASAL DRUG DELIVERY SYSTEMS: A DECADE IN REVIEW (2015–2025)

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ABSTRACT

Intranasal drug delivery has emerged as a non invasive and clinically attractive route for both systemic and central nervous system (CNS) targeted therapy, largely because it bypasses hepatic first pass metabolism and, via the olfactory and trigeminal neural pathways, offers a route that circumvents the blood brain barrier. Among the nanocarriers explored for this purpose, transferosomes (also spelled transfersomes) ultra deformable, edge activator modified phospholipid vesicles first described by Cevc and Blume for transdermal use have attracted growing interest over the last decade as vehicles for nose to brain and local nasal delivery. Their elastic bilayer allows them to squeeze through nasal mucus and paracellular pores, improve mucoadhesion when incorporated into in situ gels, protect labile drugs, and enhance both entrapment efficiency and permeation relative to conventional liposomes. This review synthesises advances reported between 2015 and 2025 in transferosome composition, fabrication, characterization, and their nasal application across neurodegenerative disease, psychiatric disorders, migraine, infection, oncology, and antiviral therapy, with a focus on formulation design (thin film hydration, reverse phase evaporation, and Box–Behnken/quality by design optimisation), *in-situ* gelling strategies, and *in vivo* pharmacokinetic/brain targeting outcomes such as drug targeting efficiency (DTE%) and direct transport percentage (DTP%). Persistent translational challenges including scale up, long term physical stability, standardisation of deformability testing, and regulatory ambiguity are also discussed, together with emerging directions such as hybrid transferosomal systems, stimuli responsive gels, and surface functionalization for olfactory targeting.

KEYWORDS: Transferosomes, Nasal Drug Delivery, Nose To Brain Delivery, Ultra Deformable Vesicles, *In-Situ* Gel, Edge Activator, CNS Targeting.

INTRODUCTION

The nasal cavity has evolved, over the past two decades, from a route reserved mainly for local treatment of allergic rhinitis and congestion into a versatile portal for systemic and CNS drug delivery. Its large, highly vascularised mucosal surface area, porous endothelial membrane, avoidance of gastrointestinal degradation and hepatic first pass metabolism, and direct anatomical continuity with the brain through the olfactory and trigeminal nerves make it an especially attractive route for peptides, proteins, and small molecules with poor oral bioavailability.[1-7] However, the nasal route is also constrained by a small dosing volume (100–150 µL per nostril), rapid mucociliary clearance (typically 15–20 minutes), enzymatic degradation, and a restricted olfactory surface area representing only about 3–10% of the total nasal mucosa in humans.[2,7] These limitations have driven the development of nanocarrier based strategies capable of prolonging nasal residence time, protecting the payload, and enhancing transmucosal and neuronal transport. Transferosomes were originally conceived in the early 1990s by Cevc and colleagues as ultra deformable liposomes for transdermal delivery, distinguished from conventional liposomes by the incorporation of an "edge activator" typically a single chain surfactant or bile salt such as sodium cholate,

sodium deoxycholate, Span 60/80, or Tween 20/80 into the phospholipid bilayer.[3,8] This destabilising component increases bilayer flexibility, allowing the vesicle to deform and pass through pores considerably smaller than its own diameter under a hydration or osmotic gradient.[8,9] While this property was initially exploited to overcome the stratum corneum barrier in transdermal applications, the same deformability, together with the inherent mucoadhesive and permeation enhancing behaviour of phospholipid vesicles, has more recently been applied to the nasal mucosa, where it facilitates penetration through the mucus layer and tight junctions of the nasal epithelium.[9,10]

Over the last ten years (approximately 2015–2025), the literature on transferosomes has shifted markedly from predominantly transdermal and topical applications toward nasal and, in particular, nose to brain (N2B) delivery of CNS active drugs. This shift reflects both the persistent unmet need for non invasive brain targeted therapy in neurodegenerative and psychiatric disease, and the recognition that transferosomal deformability, when combined with mucoadhesive *in situ* gelling systems, can substantially improve nasal residence time and brain bioavailability.[11,12] This review consolidates this decade of progress, covering vesicle design and composition, preparation and characterization methodology, representative therapeutic applications, and the translational barriers that remain before transferosomal nasal products can progress toward clinical use.

The Nasal Route: Anatomy, Pathways, and Barriers to Delivery

The human nasal cavity is divided into the vestibule, the respiratory region, and the olfactory region. The respiratory region, lined by pseudostratified ciliated columnar epithelium and richly vascularised, is primarily responsible for systemic drug absorption, whereas the olfactory region located high in the nasal vault beneath the cribriform plate provides the principal anatomical gateway to the CNS.[2,13] Three main pathways have been proposed for nose to brain transport: (i) The olfactory nerve pathway, in which drug is taken up by olfactory sensory neurons or transported through the perineural/perivascular clefts surrounding these neurons directly into the olfactory bulb and cerebrospinal fluid (ii) The trigeminal nerve pathway, which innervates both the respiratory and olfactory epithelium and provides access to the brainstem and forebrain (iii) A minor systemic pathway via nasal vasculature, which is subject to the blood brain barrier.[13,14] Direct nose to brain transport via the olfactory route can occur within approximately 20 minutes, while the trigeminal route may take up to 1.7 hours.[13] Despite this anatomical advantage, several physiological barriers restrict effective nasal and N2B delivery. Mucociliary clearance rapidly transports unabsorbed material toward the nasopharynx, limiting the residence time of conventional formulations to only a few minutes.[14,15] The mucus gel layer itself is a viscoelastic, negatively charged barrier that can trap nanoparticles unless they are engineered for mucus penetration or mucoadhesion. Additionally, enzymatic activity (aminopeptidases, proteases), a restricted absorptive surface area in the olfactory region, and efflux transporters such as P-glycoprotein further reduce the fraction of dose reaching systemic or CNS circulation.[15,16] These constraints have collectively motivated the design of deformable, mucoadhesive nanocarriers among them transferosomes that can improve mucosal contact time and facilitate paracellular and transcellular transport.

Transferosomes: Composition, Structure, and Mechanism of Deformability

Structurally, transferosomes are single- or multi-lamellar vesicles composed of a phospholipid (commonly soybean or egg phosphatidylcholine, or the semi-synthetic Phospholipon® 90G) combined with an edge activator at a defined lipid-to-surfactant molar or weight ratio, often together with a small amount of ethanol as a co-solvent/fluidiser.[3,9] The edge activator destabilises the packing of the phospholipid bilayer, lowering its interfacial tension and increasing local curvature tolerance; this is the structural basis of the vesicle's characteristic elasticity, quantified experimentally as the "deformability index" through extrusion studies.[9,17] Common edge activators reported in nasal transferosome studies include sodium deoxycholate, sodium cholate, Span 60/80, Tween 20/80/85, and Cremophor® EL, each conferring different degrees of vesicle flexibility, size, and entrapment efficiency depending on their hydrophilic lipophilic balance.[17,18] For nasal application, the deformability of transferosomes is thought to assist penetration through the mucus gel network and paracellular tight junction spaces of the nasal epithelium, in a manner analogous to their penetration of intercellular lipid lamellae in the stratum corneum.[18,19] Because transferosomes retain a bilayer architecture with an aqueous core, they can accommodate both hydrophilic and lipophilic drugs hydrophilic molecules within the aqueous compartment and lipophilic molecules within the bilayer itself a versatility that has supported their use across drug classes ranging from small CNS-active molecules (rasagiline, mirtazapine, buspirone) to antibiotics (ofloxacin, cefepime) and natural polyphenols (resveratrol, quercetin, curcumin).[11,20,21] Cholesterol is typically avoided or minimised in transferosome formulations, since it rigidifies the bilayer and antagonises the fluidising action of the edge activator.[20]

Methods of Preparation

Several established techniques are used to fabricate transferosomes, most of which were adapted from classical liposome technology. The thin film hydration (rotary film evaporation) method remains the most widely reported approach: phospholipid and edge activator are dissolved in an organic solvent (commonly chloroform methanol), the solvent is removed under reduced pressure to form a thin lipid film, and the film is

hydrated with an aqueous buffer, typically followed by sonication or extrusion to control vesicle size.[17,22] Alternative methods include reverse phase evaporation, the ethanol/vortexing sonication method, the modified hand shaking method, and the freeze thaw method, each offering trade-offs in vesicle homogeneity, entrapment efficiency, and scalability.[22,23] Many recent nasal-focused studies additionally employ a design of experiments approach most commonly Box–Behnken or 3-factor definitive screening designs to statistically optimise the ratio of phospholipid to edge activator, sonication time, and drug loading against responses including vesicle size, polydispersity index (PDI), zeta potential, entrapment efficiency, and deformability index.[24,25,26] For nasal delivery, transferosomal dispersions are frequently incorporated into a secondary mucoadhesive or thermosensitive in-situ gelling vehicle (e.g., Pluronic®/Poloxamer 407 combined with Poloxamer 188, pectin, hydroxypropyl methylcellulose, or carbopol) to prolong nasal residence time and reduce post-administration run off, converting from a low viscosity solution at room temperature to a gel upon contact with the warmer, higher ionic strength nasal mucosa.[24,27]

Characterization of Nasal Transferosomes

Physicochemical characterization is essential to correlate formulation variables with *in vivo* nasal and brain targeting performance. Table 1 summarises the principal characterization parameters reported in the transferosomal nasal delivery literature of the last decade, along with the analytical techniques typically used and their functional relevance to nasal/N2B performance.[17,22,28]

Table 1: Key characterization parameters used in transferosomal nasal drug delivery studies (2015–2025).

Parameter	Typical Method	Relevance to Nasal/N2B Delivery
Vesicle size & PDI	Dynamic light scattering (DLS)	Sub-200 nm vesicles favour mucus penetration and olfactory epithelial uptake
Zeta potential	Electrophoretic light scattering	Indicates colloidal stability; moderate negative charge often improves mucoadhesion
Entrapment efficiency (EE%)	Ultracentrifugation/dialysis + UV or HPLC assay	Determines dose loaded per vesicle and influences therapeutic index
Deformability/elasticity index	Extrusion through defined-pore membrane filters	Core parameter distinguishing transferosomes from rigid liposomes
Vesicle morphology	TEM, SEM, cryo-TEM, AFM	Confirms spherical, unilamellar/multilamellar structure
In vitro release	Dialysis bag/Franz cell diffusion	Predicts sustained vs. burst release behaviour
Ex vivo nasal permeation	Excised sheep/goat/rat nasal mucosa in diffusion cell	Estimates transmucosal flux prior to in vivo study
Rheology/gelation temperature	Rotational viscometry, tube-inversion	Confirms sol–gel transition of in-situ gel near nasal temperature (~34 °C)
Mucoadhesion	Texture analyser, mucin-particle interaction assay	Predicts nasal residence time
Histopathology/ciliotoxicity	Light microscopy of nasal mucosa post-exposure	Assesses local nasal tolerability and safety
Drug targeting efficiency (DTE%) / direct transport percentage (DTP%)	AUC(brain)/AUC(plasma) ratio, IV vs IN comparison	Quantifies extent and directness of nose-to-brain transport

Advantages of Transferosomes for Nasal Delivery

- Ultra-deformability enables passage through the mucus gel layer and narrow paracellular spaces more effectively than conventional rigid liposomes.[9,18]
- Ability to co-encapsulate hydrophilic and lipophilic drugs owing to the bilayer/aqueous-core architecture.[20]
- High entrapment efficiency reported for several CNS drugs (often >70–95%), reducing dose requirements.[11,21]
- Biocompatible, biodegradable phospholipid-based composition with generally low nasal ciliotoxicity when optimised.[21,25]
- Compatibility with mucoadhesive in-situ gel platforms, extending nasal residence time beyond

that achievable with simple aqueous dispersions.[24,27]

- Demonstrated improvements in brain bioavailability, DTE%, and DTP% relative to intravenous or oral administration across multiple preclinical models.[11,29,30]

Recent Advances by Therapeutic Application (2015–2025)

Neurodegenerative Disease

Parkinson's disease and Alzheimer's disease have been prominent targets for transferosomal nasal research given the need for chronic, non-invasive CNS dosing. ElShagea *et al.* developed a rasagiline mesylate-loaded transferosomal *in-situ* gel using phosphatidylcholine and sodium deoxycholate, optimised via Design-Expert software; the optimum formulation (~199 nm, 95.7% entrapment efficiency) incorporated into a Pluronic®/pectin thermosensitive gel achieved a brain bioavailability of 131% relative to intravenous solution, with DTE and DTP values of 304.5% and 67.2% respectively, alongside confirmed nasal mucosal biocompatibility.[11] Similarly, resveratrol loaded transferosomal *in-situ* gel, developed using a definitive screening design, achieved ~84 nm vesicles with 72.6% entrapment efficiency and demonstrated enhanced *ex vivo* nasal permeation and *in vivo* pharmacokinetic performance for potential neuroprotective use.[21] Quercetin loaded nanotransferosomal gel, reported in a two part study, showed 171 nm vesicles with 78.2% entrapment efficiency, high colloidal stability (zeta potential −32.6 mV), enhanced CT imaging confirmed brain accumulation, low cytotoxicity, and in the companion behavioural study significant antidepressant like and neuroprotective effects in a chronic stress rat model, supporting the dual antioxidant/CNS-targeting rationale for flavonoid transferosomes.[29,30]

Psychiatric and CNS Stimulant Disorders

Several groups have targeted psychiatric indications where oral bioavailability or first pass metabolism limits efficacy. A transferosome based intranasal delivery approach has been proposed for schizophrenia management, exploiting the rapid CNS access afforded by the nasal route to circumvent the delayed onset associated with oral antipsychotics.[31] Methylphenidate, used for attention-deficit/hyperactivity disorder, was formulated as transfersome based *in-situ* gel via thin-film hydration and Box–Behnken optimisation, achieving ~140 nm vesicles with 86% entrapment efficiency and negatively charged monodisperse vesicles suited to reduced dosing frequency in paediatric patients.[25] Mirtazapine, an antidepressant with only ~50% oral bioavailability due to first pass metabolism, was incorporated into transferosomes embedded within a thermoresponsive nasal gel; the optimised formulation (127 nm, −23.8 mV, 89% encapsulation efficiency) exhibited sustained release, six month cold storage stability, and improved brain targeting efficiency *in vivo*, with confirmed biocompatibility.[32] Earlier foundational work on buspirone hydrochloride transfersomal lyophilised gels and olanzapine transfersomal vesicles established the principle that vesicle elasticity correlates with the extent of intranasal to brain drug transport, a concept subsequently built upon by the newer *in-situ* gel based systems above.[33,34]

Migraine and Neurological Pain

Zolmitriptan, a triptan used for acute migraine, was among the earliest drugs formulated as nasal transfersomes, using a Box–Behnken design to optimise phospholipid/edge activator ratios for enhanced *in vitro* and *in vivo* nasal absorption compared with plain drug solution, exploiting the rapid onset achievable via nasal administration for an indication where speed of relief is clinically critical.[35] This early proof of concept has informed subsequent elastic vesicle (bilosome, transfersome analogue) migraine formulations designed to extend nasal mucociliary transit time and further improve brain bioavailability.[36]

Infectious Disease: Antibacterial and Antiviral Applications

Transferosomal nasal gels have also been applied to infections with CNS or respiratory involvement. Ofloxacin loaded transfersomal nanovesicles, optimised by Box–Behnken design, were developed for nose-to-brain delivery to improve management of bacterial meningitis, aiming to achieve therapeutic CNS antibiotic concentrations non-invasively.[37] Cefepime, a broad-spectrum cephalosporin, was similarly formulated as a thermosensitive transfersome-based in-situ gel (111 nm, 84% entrapment efficiency, deformability index 73) for intranasal brain-targeted delivery, with *in vitro*, *ex vivo*, and *in vivo* data supporting sustained release and enhanced transnasal penetration.[26] In the antiviral domain, a curcumin transferosome loaded thermosensitive intranasal *in-situ* gel was investigated as a prospective therapy against SARS-CoV-2, reflecting interest during and after the COVID-19 pandemic in nasally delivered nanocarriers capable of both local antiviral action and systemic/CNS anti-inflammatory effects of curcumin.[38]

Cardiovascular and Other Applications

Beyond CNS and infectious indications, nanotransfersomes of carvedilol, a beta-blocker with extensive hepatic first pass metabolism, were developed for intranasal delivery, with formulation, characterization, and *in vivo* evaluation demonstrating improved systemic bioavailability relative to oral administration.[39] These studies illustrate that the rationale for transferosomal nasal delivery circumventing first pass metabolism and achieving rapid onset extends beyond CNS targeted therapy to drugs for which conventional oral pharmacokinetics are suboptimal.

Table 2: Consolidates representative transferosomal nasal delivery studies published over the last decade, summarising composition, key physicochemical outcomes, and reported *in vivo* performance.

Drug (Indication)	Edge Activator / Key Excipients	Vesicle Size / EE%	Key In Vivo / Ex Vivo Outcome	References
Rasagiline mesylate (Parkinson's disease)	Sodium deoxycholate; Pluronic F-127/pectin in-situ gel	~199 nm / 95.7%	Brain bioavailability 131% vs IV; DTE 304.5%, DTP 67.2%	[11]
Resveratrol (neuroprotection)	Soya lecithin, permeation enhancers; mucoadhesive gel	83.8 nm / 72.6%	Enhanced ex vivo nasal permeation and brain pharmacokinetics	[21]
Quercetin (oxidative CNS injury / depression)	Edge activator screening; thermosensitive gel	171.4 nm / 78.2%	Increased brain gold-nanoparticle/CT accumulation; antidepressant-like effect in rats	[29,30]
Methylphenidate (ADHD)	Phospholipon 90G, Tween 80; in-situ gel	139.7 nm / 86%	Improved brain-targeted delivery profile in vitro/in vivo	[25]
Mirtazapine (depression)	Lecithin, Tween 80; thermoresponsive gel	127 nm / 89%	Sustained release; 6-month stability; improved brain-targeting efficiency	[32]
Zolmitriptan (migraine)	Box–Behnken-optimised surfactant blend	Sub-micron range	Enhanced nasal absorption vs plain drug solution	[35]
Ofloxacin (bacterial meningitis)	Box–Behnken-optimised edge activator	Nanometric range	Enhanced nose-to-brain pharmacokinetic profile	[37]
Cefepime (CNS infection)	Phospholipon 90G, Tween 80; thermosensitive gel	111.1 nm / 84%	Sustained release and enhanced trans-nasal penetration in vivo	[26]
Curcumin (antiviral, SARS-CoV-2)	Thermosensitive in-situ gel	Nanometric range	Proposed dual local antiviral / systemic anti-inflammatory action	[38]
Carvedilol (cardiovascular)	Nanotransfersome formulation	Nanometric range	Improved systemic bioavailability vs oral route	[39]

CONCLUSION

Over the past decade, transferosomes have progressed from a largely transdermal technology to a versatile platform actively explored for intranasal and nose-to-brain drug delivery. Their intrinsic deformability, capacity to co-encapsulate hydrophilic and lipophilic drugs, and compatibility with mucoadhesive in-situ gelling systems have supported consistent improvements in nasal permeation, brain bioavailability, and drug targeting indices across a broad range of CNS, infectious, and cardiovascular applications. Nonetheless, the field remains predominantly preclinical, and progress toward clinical translation will depend on resolving open questions around vesicle stability, standardised deformability characterization, scalable manufacturing, and the precise mechanism of nasal mucosal penetration. Addressing these gaps should allow transferosomal nasal systems to move from proof-of-concept rodent studies toward genuinely translatable non-invasive CNS and systemic therapies.

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