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Intranasal Nano-Enabled Therapies for Alzheimer's Disease: A Comprehensive Review of Nose-to-Brain Pathways, Smart Lipid–Polymer Hybrid Carriers, and Clinical Translation

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ABSTRACT

Alzheimer disease (AD) is now affecting over 55 million individuals across the globe, and it has a yearly cost that is as high as the gross domestic product of most of the middle-sized countries. Approved pharmacotherapies, mainly acetylcholinesterase (AChE) inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, have short-lived symptomatic effects and achieve low brain exposure because >98% of small molecules fail to cross the blood–brain barrier (BBB).The intranasal route of nose-to-brain (N2B) delivery is also used to circumvent the BBB by olfactory and trigeminal pathways to provide a rapid exposure of central nervous system (CNS) with negligible systemic toxicity. Nonetheless, mucociliary clearance, epithelial atrophy (age-related) and the absence of standardized formulationcharacterization frameworks have impeded the process of translation. In this review, recent advances in the field of smart nano-composite carriers, particularly, mucoadhesive, thermoresponsive lipid-polymer hybrids hydrogels, in AD treatment, are summarized. The emphasis is on design rationale, critical quality attributes, in-vivo performance and regulation with consideration to dual-cargo strategies, which are symptomatic and disease-modifying agents' combinations.In parallel, the regulatory landscape has shifted: lecanemab (Leqembi) gained EU authorisation in April 2025 and donanemab (Kisunla) received US FDA approval in July 2024 with a positive CHMP opinion in July 2025, underscoring the therapeutic momentum in AD monoclonal antibodies even as delivery challenges remain.

KEYWORDS: Alzheimer disease, intranasal delivery, nose to brain delivery, nanoparticle, lipid polymer hybrid nanocarriers, mucoadhesive hydrogels, thermoresponsive gels, Blood brain barrier, cholinesterase inhibitors, clinical practice

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INTRODUCTION

AD is the leading cause of dementia, accounting for an estimated 60–70% of cases worldwide, with ~55 million people currently living with dementia and numbers projected to rise sharply by 2050 (WHO, 2025; Alzheimer's Association, 2025; Prince et al. 2015; Villarejo-Galende et al. 2021). Admittedly, there is a slow increase in the diagnosis and care pathways, but mortality due to AD increased by 145 % in 2019 compared to 2000, exceeding the increase in mortality in heart disease and cancer (Li et al. 2022). The total spending of direct medical costs, the informal caregiving and the losses in productivity reach beyond USD 1 trillion every year, which is likely to increase twofold by the next decade (Alzheimer Association, 2016). These distressing statistics point out a great need to have therapeutics which not only improve cognition and behavior but also prevent neurodegeneration.The 2025 Alzheimer's Disease Facts and Figures also highlights accelerating care and economic burdens, reinforcing the need for disease-modifying strategies. (Alzheimer's Association, 2025).The first-line AChE inhibitors, donepezil, rivastigmine and galantamine, temporarily increase the level of acetylcholine in the synapse and do not affect the course of the disease, often causing gastrointestinal and cardiac side-effects (Giacobini 2004; Masuda 2004). Memantine is a NMDA antagonist that can have a modest effect on activities of daily living but exhibits very inconsistent oral bioavailability (Food and Drug Administration 2019). Anti-amyloid monoclonal antibodies have seen mixed regulatory fortunes: while aducanumab remains controversial, lecanemab (Leqembi) secured EU authorisation in April 2025 following a positive re-examination in November 2024, and donanemab (Kisunla) was approved by the US FDA in July 2024 with a positive CHMP recommendation in July 2025. These approvals coexist with ongoing debates about benefit–risk balance, costs and appropriate patient selection. (EMA, 2024; European Commission/EMA, 2025; U.S. FDA, 2024; EMA, 2025).

NOSE TO THE BRAIN BIOLOGY IN THE ALZHEIMER DISEASE

The human nasal cavity provides a surface area of **~160 cm²**, yet only **a small fraction (≈5%) of the mucosa is olfactory epithelium**, which interfaces closely with the cranial nerves and cerebrospinal fluid spaces (Morrison & Costanzo, 1990; Crowe et al., 2018).With ageing and AD pathology, there is aggravation of epithelial thinning, decreased ciliary beat frequency and mucus rheology, which in combination impairs particulate transport (Quraishi et al. 1998; Bustamante-Marin & Ostrowski 2017). Neuroinflammation also compromises tight junction integrity, which paradoxically establishes micro-porous pathways to nanoscale carriers, and makes it vulnerable to irritants (Morrison & Costanzo 1990; Dando et al. 2014). Hence, the formulation strategies should be able to strike a balance between increased permeability and mucosal safety.Long-standing clinicopathological work and mechanistic syntheses point to olfactory pathway involvement in neurodegeneration, further motivating nose-to-brain strategies in AD (Morrison & Costanzo, 1990; Crowe et al., 2018; Scheltens et al., 2021).

Deposited material is cleared by mucociliary mechanism in 15 to 20 min, and this restricts residence and absorption of the drug (Bitter et al. 2011). Mucins are secreted in the form of negatively charged, viscoelastic hydrogel (approximately 5 wt %), which traps hydrophobic or positively charged particles with a diameter exceeding 300 nm (Groo & Lagarce 2014). Also, the lipophilic drugs can be metabolized by nasal esterases and cytochrome P450 isoforms prior to their reaching the neuronal pathways (Agu 2016). Polymers that are mucoadhesive e.g., chitosan and poloxamer 407 have an increased contact time through the formation of hydrogen bonding and hydrophobic regions with mucins (Giuliano et al. 2018; Brannigan & Khutoryanskiy 2019).

The three major pathways of drug migration to the brain parenchyma are: (i) the intracellular axonal transport along the olfactory nerves (hours-days), (ii) the paracellular diffusion through sustentacular cells (minutes-hours) and (iii) the bulk flow through the perivascular trigeminal nerve channels (minutes) (Crowe et al. 2018; Wang et al. 2019). Particle size < 200 nm and the hydrophilicity of the surface are favorable to transport by paracellular pathway, and ligand-decorated, deformable vesicles can usurp the process of receptor-mediated endocytosis to deliver cargo to the axons (Bonaccorso et al. 2017). Nanoparticle based on hybrid lipid-polymer particles embedded in thermo-responsive gels take the advantage of fast perivascular convection during the first moments of administration and slow release of cargo to allow sustained uptake in axons, providing the benefit of dual kinetics.

Table 1. Key anatomical and physiological challenges for intranasal delivery in Alzheimer's disease

Challenge	Pathophysiological feature in AD	Practical consequence for formulation	Design counter-strategy
Epithelial thinning	Age-related atrophy; amyloid-β deposition	Reduced surface area for absorption	Use ultra-penetrative NPs (< 150 nm)
Decreased ciliary beat frequency	Oxidative stress impairs dynein motors	Faster mucociliary clearance	Incorporate mucoadhesive polymers (chitosan, poloxamer 407)
Altered mucus viscoelasticity	↑ Cross-linked mucins, ↓ water content	Higher diffusion resistance	Employ mucus-penetrating coatings (PEG, poloxamine)
Neuroinflammation	Cytokine-mediated TJ disruption	Potential toxicity, variable permeability	Add anti-inflammatory excipients; safety profiling

Source: Adapted from Crowe et al. 2018; Sobiesk & Ismail 2022; Bustamante-Marin & Ostrowski 2017; Brannigan & Khutoryanskiy 2019.

THERAPEUTIC CARGO LANDSCAPE FOR INTRANASAL DELIVERY IN AD

The traditional cholinesterase inhibitors are still the most clinically advanced cargos to be used by the intranasal (IN) route. Liposomal donepezil elevated drug concentrations in the hippocampus by 6-fold and prevented scopolamine-induced amnesia in rodents and a rivastigmine nanoemulsion enhanced escape latency in the Morris-water-maze by 41 % compared with the same dose of drug as an oral form (Yang et al. 2013; Kaur et al. 2020). The pro-drug of galantamine Gln-1062 that is aimed at concealing gastrointestinal irritancy had a 14-fold increased brain-to-plasma ratio following IN administration in a Phase-I trial (Bakker et al. 2020). Despite the fact that these molecules are still symptomatic in nature, the fast onset and low peripheral exposure that IN carriers offer could make a meaningful impact on quality-of-life in moderate AD, where compliance with oral medications is notoriously low (Masuda 2004).Newer work with donepezil nanostructured lipid carriers in thermoresponsive in-situ gel has reported favourable PK/PD characterisation and nose-to-brain targeting in preclinical models, supporting this carrier class for rapid-onset symptomatic relief. (Sonawane &Pokharkar, 2024).

Disease modifying potential has been demonstrated by insulin, neurotrophic peptides and anti-A antibodies, which are all classically excluded by the BBB. Peripheral glucose was not affected by regular-acting IN insulin, which enhanced verbal memory in amnestic-MCI patients (Craft et al. 2017). The IN delivery of aducanumab nano-suspensions is in pre-clinical development, which is expected to minimize the 40 % infusion-related ARIA occurrence noted systemically (Aduhelm(r) prescribing information 2022). In the same way, intranasal APH-1105, which is a hydrophobic alpha-secretase modulator chitosan-based nanoparticle, has reached Phase-II (NCT03806478). All these illustrations show that IN technology has the ability to recycle big, fragile molecules by preventing systemic proteolysis and hepatic clearance.Comprehensive 2024 overviews of nanotechnology-enabled nose-to-brain delivery consolidate design rules for improving transport across olfactory/trigeminal pathways and mitigating mucociliary losses. (Huang et al., 2024).

Antioxidant and anti-amyloid properties are shown by complex plant-derived molecules (resveratrol, berberine), but they have poor solubility in water (brick-dust), and they are extensively metabolized in the first pass (Rao et al. 2020; Akbar et al. 2021). The nanostructured lipid carriers (NLC) with the encapsulation of resveratrol and embedded in ion-sensitive gel increased brain area under the curve (AUC) 4.8-fold and reduced Abeta-induced oxidative markers in rats (Rajput & Butani 2019). The repurposed drug pioglitazone also showed the same effects when developed in the form of IN nanolipid carriers (Jojo et al. 2019). The combination of multi-target pharmacology and the local delivery of CNS drugs may be the key to bringing the pleiotropic phytoconstituents into clinically useful applications.

Emerging biological carriers.

Intranasal extracellular vesicles (EVs/exosomes) are gaining traction for CNS indications and have shown functional benefit in brain injury and neuroinflammation models when administered intranasally, positioning EVs as potential AD cargo vehicles. (Ikeda et al., 2024; Rossi et al., 2025).

Table 2. Selected intranasal cargos under pre-clinical or clinical evaluation for AD

Cargo (class)	Carrier type	Stage	Key efficacy outcome	Ref.
Donepezil (AChEi)	Liposomes in thermogel	Pre-clinical	↑ Brain C_{max} 6×; memory restoration	Yang et al. 2013
Rivastigmine (AChEi)	Nanoemulsion	Pre-clinical	41 % faster maze learning	Kaur et al. 2020
Galantamine pro-drug (Gln-1062)	Solution	Phase I	Brain:plasma ↑14×, good tolerability	Bakker et al. 2020
Insulin (peptide)	Solution	Phase II/III	Improved ADAS-Cog by 4 pts at 4 mo	Craft et al. 2017
APH-1105 (α-secretase mod.)	Chitosan NP	Phase IIa	Ongoing (NCT03806478)	Aphios 2021
Resveratrol	NLC + ION gel	Pre-clinical	Brain AUC ↑4.8×; ↓ROS & Aβ	Rajput & Butani 2019

Source: References cited in table.

FORMULATION STRATEGIES ENABLING EFFECTIVE N2B DELIVERY

The most prevalent ones in current pipelines are liposomes, solid-lipid nanoparticles (SLN) and NLC, which are more biocompatible and capable of encapsulating both types of drugs hydrophilic and lipophilic ones (Bulbake et al. 2017; Cunha et al. 2021). The size of the vesicles (80150 nm) promotes paracellular diffusion, whereas the glycoproteins of the mucus are less able to opsonize vesicles due to PEGylation of the surface (Groo & Lagarce 2014). After the neuronal uptake, endosomal escape may as well take place through charge-reversible lipid incorporation and subsequent pH-dependent endosomal escape, a new approach with siRNA and CRISPR cargos. Nevertheless, the plain lipid vesicles are dogged by physical instability and burst release, which stimulates combining with polymers or gels.Design frameworks published in 2024–2025 summarise best practices for hybrid nano-in-gel systems, ligand-targeted carriers, and mucus-penetrating surface chemistries tailored to N2B transport. (Huang et al., 2024; Duong et al., 2025).

The particles made of chitosan, PLGA and Eudragit RL-100 have the property of long residence time in the nose via electrostatic mucoadhesion and swelling (Nagpal et al. 2013; Corsaro et al. 2022). The polymer:drug ratio and polydispersity of the formulation are formulation variables that have direct effects on olfactory deposition and toxicity; optimized rivastigmine-chitosan NPs (z-average = 120 nm; PDI = 0.19) reversed the cognitive impairment in rabbits without the destruction of nasal epithelium (Fazil et al. 2012). However, dense polymer matrices may take a long time to release drugs, and this may be a disadvantage because it would take time before therapeutic effects are realized, which would be inappropriate during acute agitation incidents of AD.

The synergy of the high rate of diffusion of nano-lipid carriers and residence time of in-situ gels has jumpstarted a paradigm of design. Poloxamer 407 is a sol-gel transition substance with a temperature of approximately 32 C, and it creates a depot in which the liposomes are trapped, but can move freely through the micellar network (Mura et al. 2018). A donepezil-NLC/poloxamer formulation was able to achieve a 12 h therapeutic level in the brain and only needed 67 % of the total dose compared to oral tablets (Rajput & Butani 2018). The key to the success is to have rheological synergy, as above 22 % w/v of poloxamer can stiffen to a level of blocking the olfactory pathways, whereas at a concentration of below 16 % it will drip into the nasopharynx (Giuliano et al. 2018).

According to the draft guidance of the FDA on locally acting nasal drug products, the control of spray pattern, droplet size distribution (< 10 % RSD) and formulation pH (4.5 6.5) is required to ensure a low level of ciliotoxicity (FDA 2021).For quality and equivalence testing, two key references now guide inhalation/nasal products: the US FDA OINDP BA/BE guidance (2020) and the EMA's revised *Guideline on the pharmaceutical quality of inhalation and nasal medicinal products* (final revision published 14 July 2025; initial draft 12 Feb 2024). (FDA, 2020; EMA, 2024; EMA, 2025). In the nano-in-gel systems, other important quality attributes (CQAs) are as follows: gelation temperature (T sol-gel), storage modulus (G eff 100 Pa to retain) and nanoparticle integrity at 3 months at 25 o C/60 % RH. Scalable production uses high-pressure homogenization of lipid NPs and subsequent poloxamer powder-based continuous twin-screw mixing without breaking the cold chain of cargos that are sensitive to the cold. The use of central composite designs and multivariate data analysis in a Quality-by-Design (QbD) workflow has cut the batch-to-batch variability of pioglitazone NLC down to 6 % after having been 18 % (Patel et al. 2021). Pre-clinical work on the development of such parameters to enable investigational new drug (IND) readiness and de-risking of clinical translation.

Table 3. Influence of carrier attributes on transport pathways

Attribute	Preferred range	Dominant N2B pathway enabled	Supporting evidence
Particle size	80–150 nm	Paracellular & perivascular	Bonaccorso et al. 2017
ζ-potential	−10 to +10 mV (PEGylated)	Mucus penetration without entrapment	Groo & Mircheva 2014
Surface ligand	TfR/ICAM-1 peptides	Receptor-mediated axonal transport	Bourganis et al. 2018
Gelation T°	30–34 °C	Depot formation at nasal surface	Giuliano et al. 2018

Source: References cited in table.

Table 4. Critical quality attributes and analytical assays for IN nano-in-gel products

CQA	Target spec	Primary assay	Regulatory note
Nanoparticle size/PDI	100 ± 20 nm / ≤0.25	Dynamic light scattering	ISO 22412 (2019)
Drug loading	≥ 5 % w/w	HPLC-UV (ICH Q2)	Content uniformity
Gel T_{sol-gel}	30–34 °C	Oscillatory rheology	Must not clog device
Spray plume angle	30–60°	Laser imaging	FDA nasal guidance
Endotoxin	< 0.25 EU mL⁻¹	LAL test	Parenteral standards

Source: Bulbake et al. 2017; FDA 2021; ISO 22412 — consolidated.

IN-VIVO PHARMACOKINETICS AND PHARMACODYNAMICS OF INTRANASAL SYSTEMS

Intranasal (IN) nanocarriers Enhanced penetration of the cerebro-cortex is characteristically achieved within 15min-30min, which is as fast as an intravenous infusion but without systemic spikes. When the Rivastigmine chitosan nanoparticles were administered in rat hippocampus, a Tmax of 18 4 min was observed as opposed to oral solution where the Tmax was 75 8 min (Fazil et al. 2012). The brain-to-plasma AUC of donepezil nano-lipogels was 6-fold higher, which confirms that it preferentially partitions through olfactory and trigeminal pathways (Rajput & Butani 2018). Such kinetics benefits are reflected in the accelerated cognitive rescue: in scopolamine amnesia model, IN rivastigmine reduced escape latency by 41 % whereas at the same oral dose, rescue was ineffective during 2 h (Kaur et al. 2020). This evidence highlights the great advantage of reducing the loss on the first pass and the use of epithelial transcytosis to enhance the onset of therapy, which is highly desirable in sundowning agitation or acute behavioral flares of Alzheimer disease (Kales et al. 2019).

Besides brief spikes, optimized formulations maintain drugs in the cholinergic IC₅₀ suburban range 8-12 h, and that is enough to attain twice-daily dosing. The poloxamer-407 lipogel that bears donepezil maintained the cortical concentrations of 45 +/- 6 ng g -1 up to 12 h compared to oral tablets which dropped below 10 ng g -1 in 6 h (Rajput & Butani 2018). According to gamma-scintigraphy and confocal microscopy, the distribution of 80 to 150 nm PEGylated vesicles is along perivascular Virchow-Robin spaces and reaches hippocampus, amygdala and entorhinal cortices, the regions involved in memory encoding (Bonaccorso et al. 2017). Charge-reversal peptides also facilitate axonal transport to more distal nuclei, which was shown with transferrin-decorated liposomes that increased the levels of drugs in thalamus 3.2-fold compared to non-targeted controls (Bourganis et al. 2018). Together, abnormal slow kinetics and biased deposition leave a pharmacologically relevant footprint on the AD- susceptible areas of the brain.

A good modulation of biomarkers is a symbol of improved exposure. Intranasal insulin had a normalizing effect on CSF A₄₂/tau ratios and ADAS-Cog scores improved by 4 points after four months without causing peripheral hypoglycaemia (Craft et al. 2017). Hippocampal acetylcholine was replenished to 92 % of naive levels and the lipid-peroxidation markers were decreased by 38 % with rivastigmine liposomes (Yang et al. 2013). In a similar fashion, NLC of resveratrol reduced malondialdehyde in the cortical homogenates and elevated SOD-1 expression, which signifies a combined antioxidant and cholinergic rescue (Rajput & Butani 2019). A synthesis of the neurotransmitter equilibrium, anti-inflammatory cytokine changes and synaptic plasticity signs thereby certifies the functional aptitude of IN delivery platforms.

Table 5. Comparative pharmacokinetic parameters of selected intranasal vs. conventional formulations

Drug / carrier	Route	Brain C_{max} (ng g^{-1})	T_{max} (min)	Brain : plasma AUC	Key citation
Rivastigmine / chitosan NP	IN	128 ± 11	18 ± 4	5.7	Fazil et al. 2012
Rivastigmine / oral sol.	PO	34 ± 6	75 ± 8	1.0	Fazil et al. 2012
Donepezil / lipogel	IN	152 ± 13	22 ± 5	6.2	Rajput & Butani 2018
Donepezil / tablet	PO	47 ± 9	70 ± 10	1.3	Rajput & Butani 2018
Insulin (regular)	IN	—*	15 ± 3	4.1	Craft et al. 2017

*Peptide concentrations measured as CSF immunoreactivity rather than mass units.
Source: studies listed in table.

SAFETY, TOXICOLOGY AND CLINICAL TRANSLATION

In histopathology of >20 rodent studies, low rates of epithelial erosion are demonstrated in formulation pH of 4.5-6.5 and a concentration of surfactants less than 0.02 % w/v (Bitter et al. 2011). The gels made of poloxamer maintain ciliary beating in excess of 80 % of the baseline, whereas cellulose derivatives of higher viscosity (30 %) can slow down clearance (Giuliano et al. 2018). Reversible goblet-cell hypertrophy was observed only after chronic 90-day dosing of chitosan NPs in rabbits, and it was mild (Nagpal et al. 2013). Nevertheless, the choice of excipients is important: the presence of benzalkonium chloride in 0.01 % or more leads to ciliostasis and should be avoided in chronic AD treatments. The use of a tiered in-vitro/in-silico assessment involving human nasal-epithelial chips and Quantitative Structure-Toxicity Relationship modelling has diminished the need to use animal inhalation studies in accordance with the 3Rs principle (Movia et al. 2020).

Because of the sub-200 nm size and neutral surface, lipid nanoparticles do not sequester in the liver by hepatic Kupffer-cells, and highly first-pass-metabolized drugs have systemic bioavailability <5 % (Bulbake et al. 2017). Poloxamer 407 has acute single-dose LD 50 values greater than 5 g kg -1 and the polymer is USP GRAS-graded (Singh-Joy & McLain 2008). The oxidative stress associated with nanoparticles is alleviated by the addition of 42 % of the reactive-oxygen-species formed in human neuroblastoma cells by adding either alpha-tocopherol or cholesterol into bilayers (Oberdorster et al. 2005; Ross et al. 2018). Notably, no QTc prolongation or cholinergic bradyarrhythmia was found in elderly volunteers when a 4-mg donepezil IN spray was used, which is common when using oral therapy (Morgan & Soh 2017).

There are 14 clinical trials that are registered and are aimed at AD using the nasal route (Table 6). Gln-1062 has dose-proportional pharmacokinetics and a similar number of gastrointestinal adverse events as oral galantamine, but with lower gastrointestinal adverse events (Bakker et al. 2020). The IN insulin detemir (NCT01595646) was tested in phase-II randomized study, where significant benefits were seen in delayed recall of stories after 120 days particularly in APOE-e4 carriers. Rivastigmine IN spray (ACTRN12614001313628) was shown to possess 78 % absolute bioavailability, which assisted in setting up a Phase-III. In the meantime, nano-particulate APH-1105 is testing cognitive effects at 24 weeks; its adaptive design will also provide data on how best to dose and in the real world (Aphios 2021). It is particularly interesting that European regulators demand histological evidence of the integrity of the olfactory bulb after treatment, which is an obstacle that has not been overcome with certain polymeric systems.

The device and formulation development has been co-developed and this has turned out to be a key to successful translation. Aptar CPS multi dose device with uni direction check valve and metered swirl nozzle is now used in insulin, sumatriptan and rivastigmine nasal products which sets precedent of complex nanocarrier approval (ONZETRA 2016; Morgan & Soh 2017).Recent manufacturer documentation consolidates the Unidose (UDS) platform's track record across FDA/EMA-approved nasal medicines and highlights design features (primeless actuation, 360° use) relevant to adherence in older adults. (Aptar Pharma, 2025). ICH M13 is also harmonized bioequivalence guidelines of complex parenteral/nasal products which will simplify generic pathways as well. However, the evidence of clinical benefit, i.e., the decrease in caregiver burden or a postponed nursing-home stay, is required to show the marketplace that the increased manufacturing cost is worth it (Younis et al. 2022). Phase-III data on insulin and rivastigmine sprays are maturing, so the next five years will probably witness the first nano-enabled, intranasal disease-modifier against Alzheimer disease, which pre-clinical development has promised two decades ago.

Table 6. Selected registered clinical trials of intranasal therapeutics for Alzheimer's disease

Identifier	Cargo / formulation	Phase	Population	Primary endpoint	Status (per registry)
NCT05081219	Insulin + Empagliflozin spray	II	Mild AD	ADAS-Cog change (6 mo)	Completed.
NCT01595646	Insulin detemir spray	II	Amnestic MCI	Delayed recall	Completed.
ACTRN12614001313628	Rivastigmine spray	I	Healthy ≥60 y	PK/safety	Completed (ANZCTR). PK/bioavailability published.
NCT03806478	APH-1105 chitosan NP (intranasal)	IIa	Mild–moderate AD	CDR-SB score	Unknown / not yet recruiting (registry not recently updated).
NCT02503501	Glulisine spray	II	Mild AD/MCI	ADAS-Cog	Terminated.
NCT01547169	Insulin aspart spray	II	Mild AD	Cerebral glucose uptake	Completed.

Notes.

- You asked to "update/confirm these rows exactly":
- NCT05081219 — requested "Recruiting"; current registry–linked sources show Completed (primary completion in 2024). I've reflected that change.
- ACTRN12614001313628 — Completed on ANZCTR; PK/bioavailability results reported in *Br J Clin Pharmacol* (Morgan & Soh, 2016).

FUTURE DIRECTIONS AND OUTSTANDING CHALLENGES

Despite the fact that the existing intranasal (IN) platforms significantly enhance Alzheimer-s disease (AD) pharmacotherapy, there are at least three variables of formulation that are under-investigated. First, carriers that respond to stimuli to achieve on-demand release (limiting off-target exposure) could be used, i.e., stimuli-responsive carriers that use the slightly acidic micro-environment of AD plaques (pH 6.5) (Zhang et al. 2019). Secondly, in-situ forming bio-orthogonal lattices e.g. thiol-ene click cross-linked poloxamer gels provide thermal stability during shipping and gel quickly (seconds) at intranasal temperature and have residence times greater than 8 h, as well as resist mucociliary shear (Russo & Villa 2019). Third, nano-assemblies co-loaded with acetylcholinesterase inhibitors (e.g., rivastigmine) and anti-oxidants (e.g., resveratrol) can target parallel pathways in AD synergistically; rodent evidence indicates that such nano-assemblies have been reported to enhance the Morris-water-maze performance by 1.6-fold than each of the drugs alone (Kulkarni et al. 2021). These concepts require orthogonal analytical pipelines to be translated: differential scanning calorimetry to study gelation kinetics, nanoparticle tracking analysis to control polydispersity and advanced synchrotron SAXS to study structural evolution in real time (Kuznetsova et al. 2022). The merger of materials science and neuro-pharmaceutics is thus ready to spawn the second generation of IN therapies that have programmable pharmacology.

The greatest translational barrier is the species variation in nasal cavity geometries, thickness of the epithelial layer and the area of the olfactory surface. Rodents have an olfactory area of 50 % of nasal mucosa (compared to 10 % in humans) that increases the apparent nose-to-brain uptake (Morrison & Costanzo 1990). Computational fluid dynamics and 3-D-printed, patient-specific nasal replicas can be used to predict deposition patterns of candidate sprays, which can then be used to inform the angle of nozzle, the geometry of plumes and the actuation force (Agu 2016). There is also the availability of human in-vitro mucosa chips that include differentiated ciliated and goblet cells, which currently allow high-throughput permeability and ciliotoxicity to be screened and replace >40 % of animal studies, and have also led to faster Investigational New Drug submissions (Movia et al. 2020). Regulatory convergence is also going that way: a US-FDA draft guidance on the issue of complex generics (nasal and inhalation) (2022) favours the utilisation of population pharmacokinetic modelling rather than large Phase-I trials, provided that very good in vitro-in vivo correlations are obtained. The standardization of these approaches in ICH will reduce the bench-to-bedside times of the process, which currently takes 8-10 years, to the projected 5-6 years, which is vital as the prevalence of AD is increasing worldwide (Li et al. 2022).The EMA's revised quality guideline for inhalation and nasal products (finalised July 2025) codifies lifecycle and device considerations and is expected to smooth EU pathways for complex nasal generics and hybrids when strong IVIVC and modelling are provided. (EMA, 2025).

The future IN systems should be in a position to react to the variability in nasal physiology (e.g. septal deviation, rhinitis), pharmacogenomics (APOE-4 status, P-gp expression). Electromechanical nebulisers with impedance sensors can be smart and capable of mapping the nasal airway of the user in real time and dynamically changing aerosol velocity to maximize olfactory deposition regardless of anatomical variation (Bakker et al. 2020). Parallel to this, Bluetooth-connected digital therapeutics devices that capture actuation times, connect to caregiver apps, deliver adherence analytics and remote titration have also been developed. On the pharmacology front, polygenic-risk-driven dosing algorithms can adjust the range of micro-dose delivered; e.g. APOE-e4 carriers respond to IN insulin more, so they may have a lower cognitive-efficacy dose threshold (Craft et al. 2017). These hardware-software-biology elements combined into a single connected therapeutic package will transform AD management into a continuous, responsive neuro-support system rather than the intermittent symptomatic relief paradigm, which is in line with the new paradigm of precision neurology that is home-based.

Table 7. Research priorities and anticipated timeline for next-generation intranasal Alzheimer's therapeutics

Priority theme	Key experimental milestones	Expected completion*	Translational impact
pH-triggered nano-gels	Synthesize acid-labile linkers; validate plaque-selective release in 3xTg-AD mice	2026	Targeted reduction of amyloid burden
Human mucosa-chip validation	Correlate permeability vs. clinical PK for 5 benchmark drugs	2025	Replace 60 % of animal nasal-toxicology tests
Smart nebuliser prototyping	Complete ergonomic & aerosol performance studies in ≥100 elders	2027	Personalized deposition → higher response rates

*Consensus estimates from EU-IMI NEURONOSE consortium and NIH Blueprint calls 2023–24.*Source: compiled from Agrawal et al. 2022; Younis et al. 2022; regulatory white papers.*

CONCLUSIONS

The totality of the reviewed evidence presented throughout the four sections evidences that intranasal nano-enabled delivery is no longer a hypothetical curiosity but an evolving therapeutic modality with the potential to overcome the blood brain barrier, reach region selective distribution of drugs and induce clinically relevant neuro-cognitive improvements in Alzheimer disease. Innovative formulations-chitosan nanoparticles of rivastigmine, poloxamer lipogels of donepezil and insulin sprays show up to six-fold increases of brain bioavailability and better behavioural effects with reduced systemic adverse effects typical of oral cholinesterase inhibitors. The safety profiles are also promising provided that the concentration of excipients is not in excess of the limits of ciliotoxicity and that the particle size/charge has been optimised to prevent oxidative and reticulo-endothelial risks. The regulatory paths have moved to Phase-III trials and the growth has been spurred by the device-formulation co-packages and standardized bioequivalence frameworks.

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