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Chapter 6: Intra-nasal Nano drug delivery system: a non-invasive gateway to the brain

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Abstract

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disease and there are currently limited treatment options available for the disease as a result of the blood–brain barrier which causes passage restriction for more than 99% of the therapeutic agents leading to central nervous system. Classic orally or parenterally administered treatments like acetylcholinesterase inhibitors and N-methyl-D-aspartate antagonists provide symptomatic benefit with poor bioavailability and low brain penetration. Over the past years, intranasal (IN) drug delivery has gained much attention and has been found as a potential non-invasive route to avoid BBB through direct nose-to-brain routes via olfactory and trigeminal nerves. This strategy has been further evolved by nanotechnology for the design of structurally tailored nanocarriers, such as polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanostructured lipid carriers, nanoemulsions, dendrimers, and biological carriers, to protect the drug from enzymatic degradation, urinary dilution, or rapid nasal clearance, improving mucosa adhesion, and promoting the controlled and targeted CNS delivery. Preclinical studies show that nasal nano-formulation of known and repositioning molecules, such as donepezil, rivastigmine, galantamine, sitagliptin, and insulin, display better brain uptake, lower oxidative stress, and improve cognitive performance in AD models. Preliminary clinical trials conducted with intranasal insulin have also indicated positive effects on memory and daily function in patients, especially in non-ApoE4 carriers. Notwithstanding these benefits, there exist physiological barriers such as mucociliary clearance, enzymatic degradation, limited dosing volume, etc., which are the major hurdles. Mucoadhesive polymers, in situ gelling systems, permeation enhancers, enzyme inhibitors, and others are being investigated to improve delivery. More recently, unique intranasal devices like the precision olfactory delivery technology have also been developed to enhance drug deposition in the anterior nasal cavity and the extent of brain targeting.

Keywords: *Alzheimer's disease, Intranasal delivery, Blood–brain barrier, Nanocarriers, Nose-to-brain transport, Neurotherapeutics*

1. Introduction

Neurodegenerative diseases including Alzheimer's disease are becoming epidemic and represent a great healthcare burden. Getting therapeutics to the brain is notoriously challenging because of the blood-brain barrier (BBB), which prohibits >99% of drugs[1]. Conventional (oral or parenteral) treatments in AD are generally only symptomatic (acetylcholinesterase inhibitors, memantine) with low bioavailability and poor central nervous system penetration[2]. As such, there is great interest in alternative pathways that skirt the BBB. The intranasal (IN) route offers a non-invasive possibility for drug delivery right into the brain[3],[4]. Drugs can reach the brain via olfactory and trigeminal nerve pathways in the nasal mucosa without first-pass metabolism or systemic effects[1]. It has been shown that intranasal administration provides quick action, comfortable feeling to the patients and lag of peripheral side effects[3],[5]. In practice, "Nasya" therapy (intranasal administration of herbal preparations) has been effectively used for brain disorders in the Ayurvedic medicine tradition, re- emphasising its viable historical utility[4]. Contemporary research now employs nanocarriers (lipid or polymer-based nanoparticles, nano-emulsions, dendrimers, etc.) to further improve this path[2],[3]. In total, intranasal nanoparticles are a novel "nano-brain" revolution in AD therapy allowing focused and regulated administration of destined small molecules, peptides, proteins, and even cells in the brain[3],[5].

1.1 Anatomy of the Nasal-to-Brain Pathways

The human nasal cavity is partitioned by a septum into left and right passages, each having three epithelial areas:

(i) the anterior vestibule (squamous epithelium)

(ii) mid-respiratory area (ciliated pseudostratified epithelium)

(iii) the posterior olfactory area (neuroepithelium)[1],[5]

The mucosa in the nasal cavity is covered by respiratory epithelium and the nasal mucosa is richly vascularized allowing for some systemic absorption[2]. The olfactory epithelium is smaller and is positioned in the upper posterior cavity, and is responsible for the function of the bipolar olfactory receptor neurons projecting the axons to olfactory bulb in the brain transfer cribriform plate[1],[4]. This anatomic structure offers a direct avenue to the brain. Olfactory mucosal: drugs deposited

on the olfactory mucosa are absorbed either by olfactory neurons or by paracellular/perineural pathways and migrate (both neurally and via perivascular spaces) to the olfactory bulb and other brain sites[5,6]. The trigeminal nerve, too, which is mainly mediated by the ophthalmic and maxillar branches and the trigeminal ganglion in its afferentation, is the 2nd channel: molecules could travel along trigeminal axons, get access to brainstem nuclei (pons) and, in turn, penetrate into the CNS[4,7].

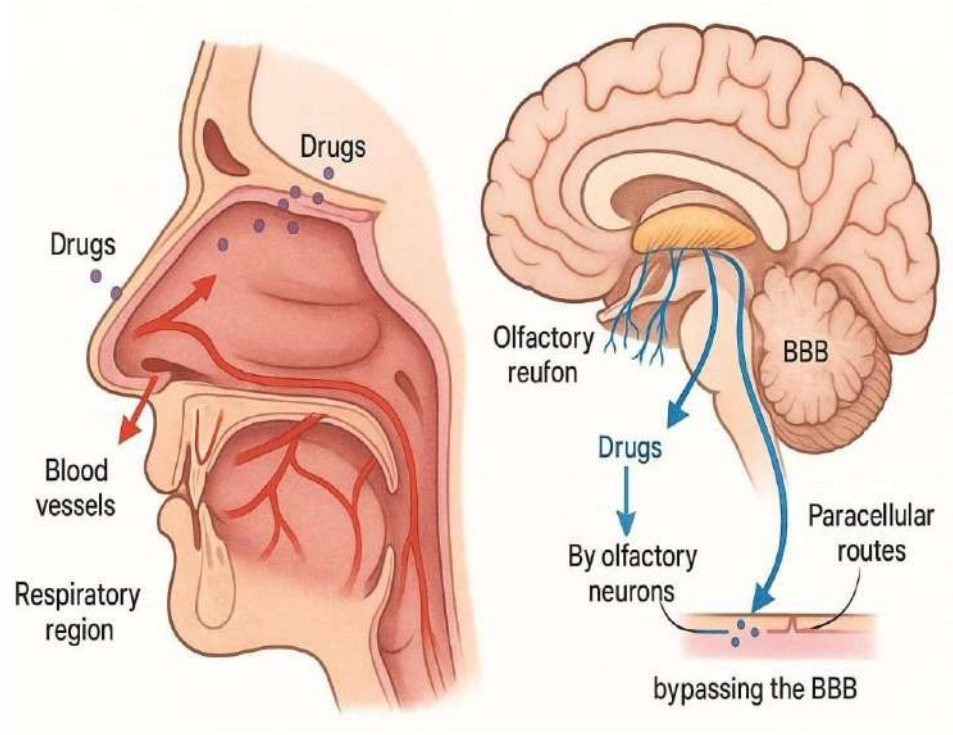

Figure 6.1: Anatomy and routes of intranasal delivery to the brain.

Drugs in the nasal vestibule and respiratory region can enter blood vessels or trigeminal nerves to reach the CNS via the brainstem. Drugs in the olfactory region can be taken up by olfactory neurons or paracellular routes to the olfactory bulb and forebrain, bypassing the BBB.

Therefore, drug molecules or nano-carrriers delivered intranasally could have access to the brain on multiple pathways. They can migrate intracellularly in neurons (slow: hours–days) or extracellularly in perineural/perivascular channels (faster)[5,6]. Additionally, small molecules are sometimes able to penetrate the

olfactory epithelium and subsequently blend into the cerebrospinal fluid (CSF) spaces[8]. The consequence is an increased uptake of the brain by the olfactory and trigeminal pathways, with a systemic absorption from the respiratory tree with the same characteristics than by-passing first-pass metabolism[9]. In rodents, the olfactory region accounts for a greater ratio of the nasal cavity volume (rat: 3350 mm^2/cm^3 vs human: 820 mm^2/cm^3); therefore, animal models are more sensitive to intranasal administration[10]. However, human studies show that focusing on the upper part of the nasal cavity is capable of delivering drugs to the brain[11].

1.2 Advantages of intranasal delivery

The intranasal route is a non-invasive route, which overcomes many drawbacks of other techniques. Intranasal delivery circumvents the BBB efficiently by administering drugs to the nasal mucosa, that had long been an obstacle of the CNS[12]. This can result in a very high degree of central bioavailability, animal and human studies for example demonstrating that olfactory/trigeminal targeting of the CNS can result in brain levels significantly higher than by peripheral routes for the same dose[13]. Peripheral exposure does not readily occur because the drug does not have to cross the bloodstream and BBB. In this way, intranasal delivery may minimize systemic side effects and toxicity of CNS drugs[13]. An attractant of this vaccine format is patient compliance since intranasal sprays, gels, or powders can be self-administered and do not necessitate needles or invasive procedures[14]. Nasal sprays have a fast onset of action due to the anatomy of the nasal mucosa, which is highly vascularized and thin[15]. This is useful in acute/crisis scenarios (e.g. opioid overdose rescue therapies or seizure) and may confer benefits for patients with AD who have swallowing challenges[16]. Sufficient enough, Ayurveda, the ancient Indian medicinal system, has long claimed intranasal drug administration Nasya to be an efficient “practical, non-invasive, rapid and simple” brain delivery route too[7]. The recent clinical trials exploit this advantage; for example, intranasal application of neuropeptides and insulin is being evaluated for memory improvement in AD, with minimal systemic accumulation[17]. In comparison with oral administration, intranasal administration bypasses first-pass hepatic metabolism entirely, which is an additional advantage of effective brain dose delivery. Advantages of intranasal delivery are, in conclusion, the following: simple, requiring less invasive methods while providing a more direct access to the CNS; [less application risks, settings-independent applicability, potential of self-application; quicker uptake; fewer peripheral side effects[9],[18].

Table 6.1 : Routes of drug delivery to the brain

Route	BBB Bypass	Invasiveness	Advantages
Intranasal	Yes	Non-invasive	Direct nose-brain; rapid onset; low systemic exposure
Oral	No	Non-invasive	Easy administration; but extensive first-pass metabolism
Intravenous	No	Invasive	High plasma levels; limited BBB penetration; systemic toxicity
Intrathecal	Yes	Invasive	Bypass BBB completely; used in specialized cases
Intracerebral	Yes	Highly invasive	Direct CNS delivery; used only in research/rare therapy

The inflammation of the BBB made by LTD4 could exclude the MSG from brain parenchyma, then, the specific MSG cytotoxicity to neurons would not take place. Invasive delivery routes (intrathecal, intracerebral) also circumvent the BBB but are invasive because of the need for surgical interventions.

1.3 Physiological Barriers and Formulation Strategies

Intranasal delivery, while the most optimistic, has its own challenges. Physiological and anatomical barriers in the nose may restrict drug uptake. First, the vestibule and valve of the nose effectively limit delivery to the olfactory mucosa (the second problem appears to be caused by using standard sprays which are commonly not deposited within the shortest possible distance from the turbinate – i.e. anterior nose – they most probably do not reach the olfactory mucosa)[19]. The deposited drugs or particles are subsequently cleared by mucociliary to the throat. These enzymes (peptidases, proteases) in the nasal mucosa may also break down peptide or protein drugs before they are absorbed[20]. In addition, tight junctions between epithelial cells restrict passive paracellular transport of large molecules, and efflux transporters, such as P-glycoprotein, can pump some drugs back into the lumen. Perhaps even more remarkably, formulators must overcome additional obstacles, including the low surface area of our own olfactory mucosa, the nose mucus interfering as another barrier, and constricted formulation volumes (~100–150 µL per nostril)[17].

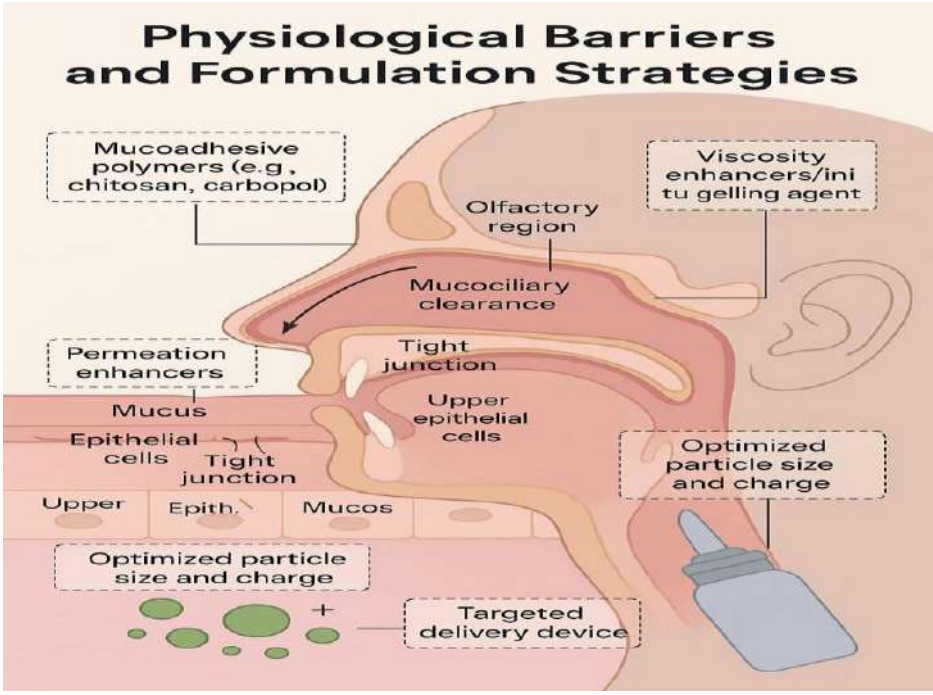

Figure 6.2: Physiological Barriers and Formulation Strategies for Intranasal Delivery.

Specialized formulations and apparatuses are, however, required to overcome these obstacles. Common strategies are:

1.3.1 Mucoadhesive polymers (e.g. chitosan, carbopol, hyaluronic acid) for increasing the residency time on the mucosa; it is indeed known that chitosan can open tight junctions and has been proved that it can increase nose-to-brain uptake. For instance, chitosan nanoparticles of sitagliptin delivered about 5 times the free drug to the brain[18].

1.3.2 Viscosity enhancers/in situ gelling agents (thermosensitive or ion-sensitive hydrogels), which transform into gel in the nasal cavity, are used to help minimize the clearance[19].

1.3.3 Permeation enhancers, which are compounds that selectively extract lipids from the cell membranes or reversibly alter the structure of the lipid matrix, resulting in enhanced drug permeation through the membrane, such as cyclodextrins, bile salts, surfactants or fatty acids that can affect the barrier function cells by modify the lipid-protein organization of the membrane or directly interfere with the local bilayer structure. Many permeation enhancers also inhibit transcellular or enzymatic barriers[19].

1.3.4 Co-administered enzyme inhibitors for the protection of peptides/proteins. (v) Particle size and charge tuning: ultra small (<200 nm) particles may facilitate deeper penetration through mucosa, and the positive surface charge (e.g., chitosan's amine groups) may precipitates for enhanced adhesion to the negatively charged mucus and the cell membranes[18].

1.3.5 Targeted devices: specialised nebulisers or breath-actuated sprayers may increase deposition into the olfactory region[19].

Table 6.2: Physiological barriers within the nose cavity and strategies to improve nose-to-brain uptake.

Barrier	Strategy to Overcome	Example/Notes
Nasal valve/vestibule	Specialized delivery (optimum head position, breathe-actuated sprays)	Use of olfactory-targeted devices (vianase, optinose)
Mucociliary clearance	Mucoadhesive formulation (chitosan, carbopol) or gels	Chitosan NPs;poloxamers for in situ gel; dlower drainage
Enzymatic degradation	Enzyme inhibitors; encapsulation in nanoparticles	Protease inhibitors; lipid nanoparticles carriers
Epithelial tight junctions	Absorption enhancer; transient opener	Chitosan opens junction; cyclodextrins; surfactants
Limited olfactory surface	Targeted deposition (devices, nasal sprays)	Breath-powered devices to deliver to upper nasal cavity
Small permissible volume	Concentrated formulations; nanoparticles to carry more drug	High potency APIs; multi-dose regimes

Successful approaches have included the use of mucoadhesive gels or polymers (e.g. chitosan) to reduce clearance, permeation enhancers to perturb tight junctions, enzyme inhibitors or encapsulation within nanoparticles to protect labile drugs, and formulations administered to the olfactory region using devices.

1.4 Intranasal Nanocarriers: Types and Features

Nanotechnology provides an effective way to overcome the challenges related to formulation, and to improve the BTT from the nose to the brain. Nanocarriers may load therapeutic agents by encapsulation or conjugation, modulating the drug release and protecting from degradation. They can be functionalized to bind mucus or neural pathways, as well as to incorporate imaging or targeting ligands. Multiple nanocarrier types have been investigated for intranasal brain.

1.5.1 Polymeric nanoparticles:

Biodegradable polymers (e.g. PLGA, polycaprolactone, polysaccharides chitosan or alginate) can be employed to make either nanospheres or nano-capsules. These particles (50–300 nm) enable high drug content and long-term release. NPs of chitosan are particularly advantageous, as the positive charge elongates the residence time in the nose and increases tight junctions opening. For example, intranasal delivery of galantamine with chitosan NPs in rats significantly decreased levels of oxidative stress and TNF-α in the brain compared with the free drug. Polymeric NPs can also be surface-coated (e.g., PEGylation for the avoidance of clearance; lectins or peptides for receptor targeting) to improve their brain uptake[20].

1.5.2 Lipid based nanocarriers:

Lipid derivatives or analogs like, liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have been widely used for intranasal delivery. SLNs and NLCs contain physiological lipids and emulsifiers; NLCs in particular have a blend of solid with liquid matrix which allows higher drug entrapment and avoids drug extrusion. Nasal enzymes can be bypassed by encapsulating payloads in lipid NPs, which can also improve permeation. They are biocompatible and usually GRAS-acceptable. For instance, insulin or peptides may be packed in liposomes or nano-micelles as a carrier for transporting through nasal route. Particle agglomeration on storage or low viscosity is the possible disadvantage that can be compensated by the addition of stabilizers or by the encapsulation of NPs in gels[20].

1.5.3 Nano-emulsions and microemulsions:

Oil-in-water emulsions with droplet sizes less than 100 nm have been developed for nasal delivery. They have a large surface area, which can improve drug absorption. We note that donepezil nano-emulsions for intranasal administration with successful absorption has also been formulated for rapid uptake. Emulsifying or surfactant agents employed, however, must be non-irritating to the nasal mucosa.

1.5.4 Vesicular systems (niosomes, transfersomes):

These resemble liposomes but are composed of non- ionic surfactants which can also fuse with membrane and release drugs. They provide nasal formulation flexibility[21].

1.5.5 Dendrimers and polymeric micelles:

Hyperbranched dendrimers (e.g. PAMAM) with well-designed size and charge can

encapsulate or bind drugs. They can be surface functionalized (e.g. with targeting ligands). Nasal delivery of lipophilic drugs into micelles (10–100 nm) of amphiphilic copolymers. For nose-to-brain use, both are experimental[22].

1.5.6 Inorganic nanoparticles:

Gold NPs, silica NPs and quantum dots (QDs) have been largely investigated for imaging and theranostics. Their use for drug delivery is restricted by toxicity, yet surface-modified gold NPs could be used to deliver small molecules or peptides intranasally in the future[22].

1.5.7 Biological carriers (exosomes, virus-like particles):

Exosomes (vesicles of 30–150 nm, naturally secreted by cells) are reported to be able to cross the nasal mucosa and have been experimentally used for siRNA or drug delivery. Virus-like particles (lacking genetic material) also mediate the release of neurotrophic factors. These are still largely experimental[23].

Table 6.3 : Highlights the main types of nanocarriers, their composition, and key pros or cons regarding intranasal CNS delivery.

Nanocarrier	Composition / Example	Advantages	Limitations
Polymeric NPs	PLGA, chitosan, alginate, PEG-PLGA	Biodegradable; tunable release; chitosan = mucoadhesive	Potential cytotoxicity; mucosal clearance
Solid lipid/NLCs	Physiological lipids + surfactants	Protects drugs from enzymes; high biocompatibility; high loading	May aggregate; require stabilizers
Liposomes/Niosomes	Phospholipids or surfactants	Encapsulate hydrophilic/lipophilic; membrane fusion potential	Stability issues; short shelf-life
Nanoemulsions	Oil, surfactant, water (droplets <100 nm)	High surface area; rapid uptake; easy to sterilize	Use of surfactants may irritate mucosa
Denderimers	Branched polymers (e.g. PAMAM)	Monodisperse; functionalizable surface; high loading	Complex synthesis; potential toxicity

Micelles	Amphiphilic copolymers (e.g. PLUR, PEG-PLA)	Solubilize hydrophobic drugs; small size	Dilution stability ; lower loading capacity
Inorganic NPs	Gold, silica, quantum dots	Imaging; surface functionalization	Safety/toxicity concerns
Biological carriers	Exosomes, viral capsids	Natural targeting; low immunogenic (exosomes)	Complexity; manufacturing challenges

Typical nanocarriers for nasal drug delivery to the brain. Polymeric nanoparticles (PLGA, chitosan, etc.) and lipid-based carriers (SLN, NLCs, liposomes) are the most common, as they are degradable and may protect the payload. Each system comes with its own drawbacks: e.g. solid lipid NPs require careful formulation or they might aggregate in biological fluids, polymeric NPs release poorly in biological fluids and need extensive toxicity screening. Chitosan NPs are remarkable for their muco-adhesivity and tight junction opening.

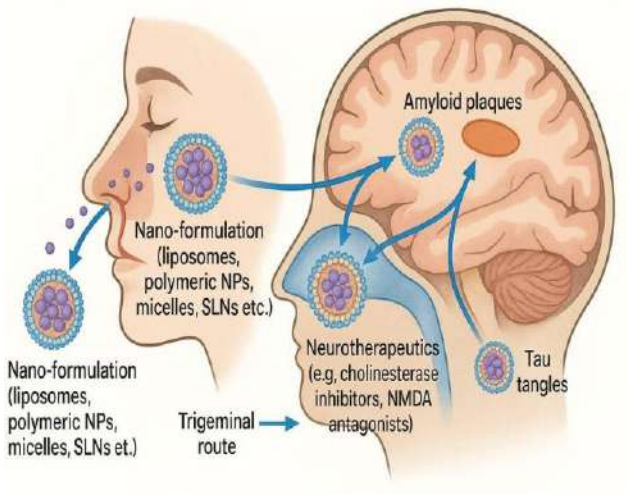

Figure 6.3 : Intranasal nanocarriers targeting the Alzheimer's brain.

1.5 Transport Mechanisms of Nanocarriers

NP when administered through the nasal route may take advantage of several transport mechanisms for entering the brain. Some drugs may go into capillaries of the respiratory mucosa and then into the blood and on to the brain, but this is often only a small percent of the total neural pathways. The most important nose-to-brain routes for nanocarriers that bypass the BBB are as follows;

(a) Olfactory transport: MNPs enter either through olfactory neurons or directly through the olfactory epithelium ➔ lamina propria ➔olfactory bulb.

(b) Trigeminal route: in which particles can enter the respiratory epithelium and are adsorbed by endings of the trigeminal nerves (maxillary nerve) and may be transferred to the brainstem[24].

Larger size-range (especially 50–200 nm) of IN-nanocarriers are vehicles enter brain mostly by means of perineural/perivascular routes rather than slow intracellular one. Indeed, animal studies have demonstrated that nanoparticle carriers can reach the olfactory bulb and the brainstem within minutes to hours of nasal dosing. For instance, polymeric nano-micelles mediating siRNA and cell-penetrating peptides were able to target neurons in the brain through the olfactory and trigeminal nerves. The CNS deposition is typically higher for IN nanocarriers than for free drug, an effect captured by a study reporting upwards of >4-fold higher concentrations in olfactory regions and pons for IN nano- formulations in contrast to IN free drug, which was consistent with nose–brain direct entry (9). By virtue of this selective delivery, the systemic dose may be reduced and it might be possible to achieve therapeutically relevant brain concentrations more efficiently (i.e., at lower drug exposure) than with peripheral exposure. Paracellular pathways are also involved: drugs (or nanocarrier) soluble in water can diffuse between epithelial cells, penetrate inside the lamina propria, gain entry in CSF across the cribriform plate and spread through the glymphatic (perivascular) system. Medications can also penetrate the subarachnoid cisterns and spread across the brain through the circulation of the CSF. Some transcellular paths (endocytosis across epithelia) are mentioned too. In brief, INP can be transported to the brain through a combination of olfactory/trigeminal nerve and bulk flow in neural perivascular spaces. Crucially, the relative contributions differ: olfactory transfer is fast but confined in scope, whereas trigeminal transfer is slower and can reach multiple brain structures, including more caudal areas. Despite external control of internalization processes, a strategy of optimizing particle size, surface properties, and formulation (conjugation to cell-penetrating peptides or bio-adhesives) can help to bias one pathway over another to increase targeting[24].

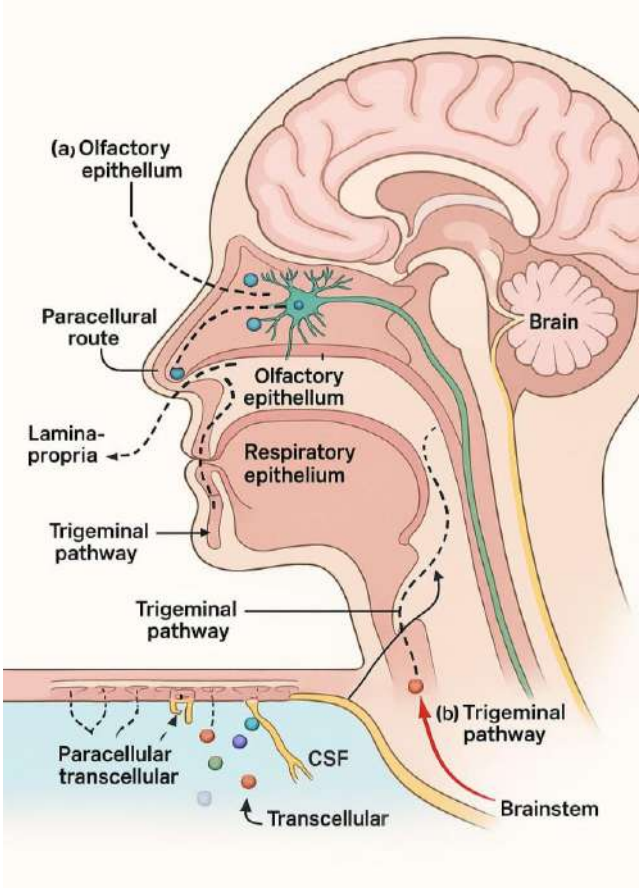

Figure 6.4 : Transport Mechanisms of Intranasal Nanocarriers to the Brain. Schematic representation of olfactory and trigeminal neural pathways, along with paracellular and transcellular routes, facilitating targeted nanoparticle delivery.

1.6 Intranasal Devices for CNS Targeting

Besides appropriate formulations, the nose-to-brain delivery is also determined by the delivery vehicles. Conventional nasal sprays frequently deposit the medicament in the front or respiratory regions but miss the olfactory region. Special instruments have been developed to increase drug deposition in the upper nose (olfactory region) and to prevent it being swallowed or inhaled into the lungs. As an example, the via Nase/Precision Olfactory Delivery™ (POD) device (Impel neuro pharma) utilizes pressurized propellant (HFA gas) to create ultrafine aerosol with the potential to achieve approximately up to ~45% dose delivery to the olfactory epithelium. The Optinose device uses the exhalation of the patient through a mouthpiece to close the soft palate and generate positive pressure, separating delivered spray and the nasal cavity, and directing it to the upper posterior nasal vault Atomizers such as mucosal

atomization devices (MADs) are air powered and can generate an aerosol mist, which may be useful if delivery of a larger molecule such as a peptide is desired. New kinds of insufflators in form of gel or powder are appearing in which the formulations are powders or in situ gelling liquids that allow their residence to be extended[25].

Devices have also been investigated in clinical trials for the CNS applications. For example, the Via Nase IPOD device was utilized in the intranasal insulin trials for Alzheimer's (SNIFF and MemAID) by targeting an aerosol even closer by the upper nasal mucosa. In studies of imaging to measure how much settled near the top of the nose, the device with a propellant, made by Impel, had deposition of approximately 45 percent in the upper nasal cavity. Optinose has been investigated for migraine and other neurological uses, and trials show that it is better at delivering midazolam to the olfactory region than a conventional pump. Thus, sophisticated delivery systems are essential for IN nano-drug- delivery platform[26].

Table 6.4 : Intranasal drug delivery devices

Device/Example	Delivery Mechanism	Key features	Notes
Standard nasal spray	Manual pump or squeeze (liquid)	Simple; widespread use	Usually deposits in lower/middle nasal cavity; no targeting.
Breath actuated sprayer	User exhales to drive spray	Closes soft palate; targets upper nasal cavity	OptiNose™ is a common example.
Impel POD/ ViaNase	HFA-propellant aerosol	High deposition in olfactory region	FDA-cleared for intranasal CNS delivery.
Atomizer (MAD)	Compressed gas creates mist	Fine droplets; penetrates deep nasal passages	Often used for emergency peptides.

Standard jet nebulizer	Compressed air mesh	Generates small droplets; used in research	Less targeted; mainly for systemic deposition.
Intranasal gel applicator	Syringe or dropper	Adheres to mucosa; prolongs contact	Requires appropriate gelling polymers.

Intranasal drug delivery devices. More specialized systems (e.g., Impel's POD, Optinose™) are focused on optimizing deposition in the olfactory region, whereas a standard nasal pump does not target the administration of liquid or spray to a particular area. Selection of device is based on the type of formulation (liquid or powder) and the site of deposition in the nasal cavity.

1.7 Intranasal Nanotherapy in Alzheimer's Disease

The pathological process of AD includes amyloid-β plaques, tau tangles, synapse loss and neuroinflammation. Existing oral/injectable drug agents (e.g. donepezil, rivastigmine, memantine) provide only modest symptomatic benefit, partially as a result of suboptimal brain delivery. Intranasal nano-delivery holds the potential of achieving higher therapeutic concentrations in the brain and reduced systemic action[27],[28].

Many preclinical studies show that intranasal nano-formulations can enhance drug biodistribution and efficiency in AD models. As an example, intranasal delivery of 9-cis-retinoic acid (a neuroprotective ligand) to an AD transgenic mouse significantly reduced Aβ plaque formation and improved synaptic function. Nanocarriers allow improved brain penetration of conventional AD drugs: rivastigmine (an acetylcholinesterase inhibitor) loaded into in situ-gelling nanostructured lipid carriers (NLCs), delivered nasally to mice, resulted in higher brain concentrations and better memory than iv delivery 701. NLC gel encased donepezil and administered intranasally provided three times more brain exposure compared to oral tablets (≈1.26× AUC) in rats. They also said nasally delivering existing medicines, such as Parkinson's drug ropinirole or sitagliptin for diabetes, could be a faster approach, adding that in the case of sitagliptin, it was encapsulated with chitosan nanoparticles in rats, making it almost 5x more likely to reach the brain compared to free drug, which they indicated could have cognitive benefits[29],[30],[31].

Intranasal insulin is likely the most extensively researched example. Insulin affects neuromodulation and cognition within the brain, however the T_2DMSC cannot easily penetrate the BBB. Other Routes of Administration -Intranasal insulin in clinical trials with early AD or MCI has demonstrated improvements in verbal memory and daily function (mainly in patients without ApoE4 allele). e.g., the "SNIFF" trial, where insulin administered intranasally led to modest enhancement of memory in AD patients. Significantly, intranasal insulin produces these effects without increasing blood glucose, with no hypoglycaemia[32].

Additional types of intranasal Nano-therapies for AD are currently being examined, including neurotrophic factors (BDNF, for example), anti-amyloid antibodies, and anti-inflammatory peptides. In preclinical studies, intranasal administration of NGF- or BDNF-loaded NPs has demonstrated neuroprotective effects. For instance, intranasal nerve growth factor (NGF) decreased amyloid pathology in AD mice (Finger et al., connected with AD diagnosis). Drug repurposing is also addressed: GLP-1 analogues (e.g. exenatide) administered intranasally enhanced glucose metabolism and decreased neuroinflammation in AD models. Finally,

vaccines or gene therapies may be administered intranasally via viral vectors or DNA-loaded nanoparticles, providing a new frontier[31]

Table 6.5 : Intranasal nano-formulations studied for Alzheimer's therapy

Drug/Therapy	Formulation	Model/Context	Key Outcome
Insulin	Aqueous nasal spray	AD patient	Improved verbal memory and reduced Aβ in ApoE4– AD subjects
Rivastigmine	NLC based nasal gel	AD mouse model	↑Brain drug concentration and cognition vs IV solution
Donepezil	NLC based gel	Rat	1.26× higher brain AUC than oral tablet
9-cis Retinoic Acid	Intranasal solution	AD transgenic mouse	↓Aβ plaques; improved synaptic function
Sitagliptin	Chitosan	AD rat model	5-fold ↑brain concentration vs free drug

Several promises in selected studies are that nose-to-brain nano-delivery of therapeutic drugs (e.g., AChE inhibitors, insulin) leads to pronounced increases in brain uptake and therapeutic effects in AD models or patients.

The increasing evidence indicates that the intranasal nano-drug delivery system can improve the poor brain uptake of conventional AD medications. Indeed, it has been reported that the use of intranasal NLC or NP preparations of cholinesterase inhibitors (e.g., rivastigmine, donepezil) led to better brain targeting and cognitive results than conventional ones as observed in studies. The DECREASE in the levels of oxidative stress markers (MDA, TNF-α) in the brains of AD rats following galantamine–chitosan NP administration also confirmed the neuroprotective effects. Nasal antibodies (anti-β- amyloid) are also being preclinically tested with the idea of clearing plaques without IV infusion.

Although several strategies are in animal or early phases, intranasal distinctive CNS access renders it a highly appealing approach to new AD therapies[7].

1.8Safety and regulatory considerations

Safety of intranasal route is overall good and long-term safety has yet to be assured. The buccal and nasal mucosa are relatively tolerant to many agents, but repeated exposure to irritants (surfactants, solvents) can injure the overlying epithelium. And there is data that nasal formulations can be less toxic than systemic. In fact, a review states that intranasal drug delivery demonstrates to be as safe or safer than the systemic dose in animal or human preclinical trials. However, any new nano-formulation according to regulatory approval must undergo testing for cytotoxicity, immunogenicity, how the olfactory system is affected as well as nasal irritation. For instance, large amounts of lipid surfactants may irritate the nose. Chronic use might also prejudice olfaction or mucociliary function. As such, biodegradable, biocompatible materials (such as GRAS lipids, chitosan) are desirable.

Standardized toxicity studies are essential; a recent review warned that some NP components (e.g., some stabilizers or cationic polymers) might incite nasal inflammation or CNS oxidative stress if not adequately selected.

Furthermore, with intranasal devices, it is necessary to validate that the intended dose can be repeatedly delivered to the olfactory region. Clinical trials have occasionally been plagued by faulty devices — one intranasal insulin study had to change devices midway through the trial because they were malfunctioning. Formulation volume, droplet size and particle charge need to be standardized to ensure consistent intracerebral dosing. Regulatory: No nasal nano-drugs for CNS currently have approval (IN vaccines like FluMist and axotrophin in trials affirm the feasibility). Full

approval in the future, therefore, will depend on more substantive safety and effectiveness data in AD patients[32].

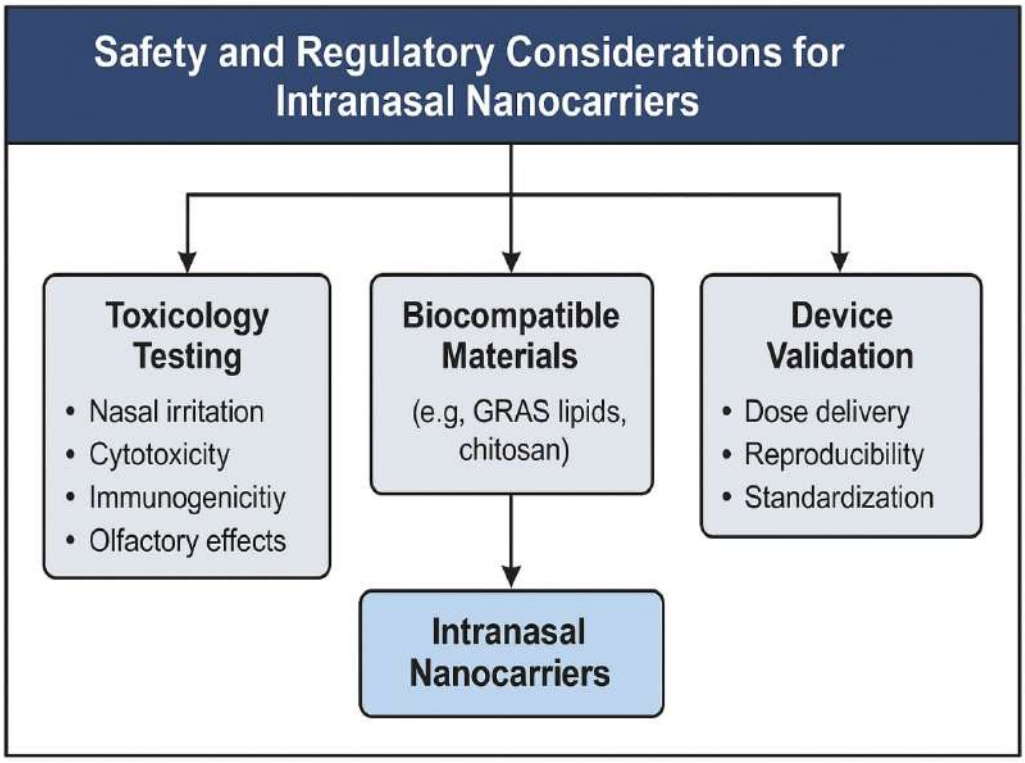

Figure 6.5 : Safety and regulatory consideration for intra nano-carriers**.**

Conclusion and future perspective

Nanocarriers intranasally emerge as a non-invasive opportunity to developing future treatments for ADs. As discussed earlier, the particular structure of the nose allows drugs to transport directly to the CNS, and nanotechnology can be a solution to the problems associated with nasal administration. Intranasal nano-formulations of existing AD medications, neuropeptides and novel therapeutics have significantly improved brain targeting and have shown exciting cognitive outcomes in models and preliminary clinical trials. The benefits are unmatched bypassing the blood-brain barrier, decreasing systemic toxicity and enabling chronic outpatient therapy. Next steps in this regard include optimizing formulations for maximal olfactory deposition, demonstrating long-term safety for the mucosa, and rigorous clinical trial testing. Incorporation of more advanced imaging will facilitate refinement of delivery approaches. Tailored devices-based on the anatomy of the nose-and dual-targeting systems (e.g., receptor ligand plus penetration enhancer) could enhance efficacy

further. On the regulatory level, clear guidelines on intranasal nano-medicines are needed. It's a nano-brain revolution in Alzheimer's, and the vision is becoming real. By surmounting the restrictive traditional pathways, intranasal nano-drug delivery draws us closer to effective treatments of this devastating disease.

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Conflicts of Interest

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