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INTRANASAL DRUG DELIVERY FOR CNS DISORDER: FORMULATION AND TARGETING CHALLENGES

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ABSTRACT

The strategy facilitates rapid drug onset, reduces systemic negative consequences, and enables transportation of molecules ranging from small lipophilic compounds to peptides and biologics. Clinically approved IN drugs for CNS indications include esketamine for treatment-resistant depression, midazolam and diazepam for seizure clusters, and zavegepant for acute migraine. Investigational programs, particularly intranasal insulin for Alzheimer's disease, highlight the potential for neurodegenerative conditions. This review summarizes nasal anatomy, mechanisms of intranasal to CNS transport, physico-chemical properties, formulation, considerations, approved and investigational drugs, limitations, and future perspectives. Overall, Intranasal medication administration is increasingly recognized as an effective encouraging approach for treating central nervous system disorders.

KEYWORDS: CNS Disorder, physico-chemical properties, nervous system.

INTRODUCTION

For therapeutic purposes, nasal administration has been employed since ancient times. Since the respiratory system is a major contactzone, it serves as a gateway for the environment, not just for pathogenic organisms like viruses and bacteria, but additionally for possible therapies. Over the last century, the application of Drugs administered intranasally (IN) were primarily limited to treating the external signs of infectious disease or seasonal rhinitis/illnesses associated with breathing system, as to as instance. Conclusion delivery by way of the nasal passage method increased in popularity in the 20th century well-known as a different approach to treating systemic symptoms like in indications related to the heart. The potential for administered medications in to central nervous system by 1991, Airways in the nose were finally investigated. William Intellectual property right application For a technique of administering drugs via was made by Frey II to treat brain neurological conditions.[1]

The nasal route is simple to get to practical, dependable, and endothelial-porous membrane and an epithelium that is highly vascularized allows for the quick soaking up of substances into the body's bloodstream, steering clear of initial pass in liver removal. Furthermore, intranasal medication administration allows for dose reduction, quick achievement of therapeutic blood-concentrations, a faster start to reduce adverse effects and pharmacological activity.[2,3] According to reports,In general, lipophilic medications are well absorbed from the pharmacokinetic profiles in the nasal cavity, which are frequently the same as those acquired following an intravenous injection with nearly 100% bioavailability.[4]

Insulin, calcitonin, desmopressin, buserelin, growth hormone, luteinizing hormone, and hormone releaseAdreno-corticotrophic hormone and hormone areA few peptides that have been effectively given by nasal administration. In addition to these steroids (estradiol, corticosteroids, testosterone, progesterone, etc.).[5,6] antihypertensives (nitroglycerine, nifedipine, analgesics (propranolol, hydralazine, etc.), Antibiotics, antivirals, and buprenorphine.[7] have been demonstrated to have significant systemic effects. when given through the nasal passage. Regarding nasal a variety of drug delivery methods, including nasal mist, pump-action nasal applicators, suspensions, gel-based. products, microemulsions, heat-sensitive gels that stick to mucosal surfaces, powders have been investigated.[8] The feasibility of nasal medication delivery during the preceding few decades, route has garnered increased interest from doctors and scientists working in the pharmaceutical sector.

The nasal cavity's structural characteristics and the neurological connections between the nose and the brain

The vestibule, respiratory region, and olfactory region are the three primary zones that make up the highly specialized architecture of the nostrils. It is the vestibule located at the nose's outermost opening, has very little effect on how well drugs are absorbed. The primary site of nasal medication intake involves the airways area. because it has the largest absorptive surface—roughly 160 cm² in humans—and contains Columnar epithelial cells with and without cilia, basal cells, and Mucus-producing goblet cells In contrast, the olfactory region is only 10 cm² in size and is made up of Basic cells, sensory neurons, including sensory neurons. These bipolar neurons send signals straight from the nasal epithelial towards the smelling lobe.[9] The part after it provides a more thorough explanation about the sensory transporter structure.

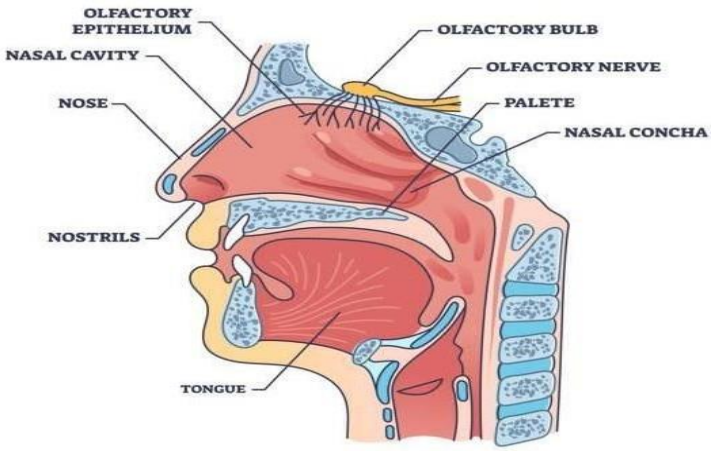

Figure 1: Nasal cavity.

Olfactory Pathway

The olfactory epithelium, sometimes known as the olfactory mucosa, contains the olfactory receptor neurons involved in signal detection, which can be reached by therapeutic compounds administered intranasally. Signal transduction

takes place in these neurons at the cilia, which are the receptor cells' distal extensions. Both transcellular transport and paracellular transport are two ways that compounds can enter olfactory receptor neurons. Enabling paracellular diffusion of substances is largely dependent on the structure and integrity of the nasal epithelial barrier, which is supported by tight junctions, adherens junctions, desmosomes, and the intercellular spaces.[10]

Trigeminal Process

Within the posterior brain, this nerve projects to areas like the medulla, pons, and portions of the spinal cord. Compounds can travel along the trigeminal nerve after intranasal administration by intracellular axonal transport or endocytosis. The ophthalmic, maxillary, and mandibular divisions make up The biggest nerve in the brain and number five in order is the trigeminal nerve. Because they extend into the nasal mucosa, neurons from these optical and maxillary branches are essential in facilitating the transport of pharmaceuticals from the nasal cavity to the brain. Furthermore, there is a functional overlap between these transport pathways since some trigeminal fibers end in the olfactory bulbs.[11]

Systemic Pathway

The delivery of medications administered intranasally to the brain is also significantly influenced by blood circulation. Because the respiratory epithelium has a denser vascular network than the olfactory region, a portion of the administered dose enters the systemic circulation.[12] The breathing region's blend of enclosed and unbroken endothelium elements facilitates this vascular uptake, Compared to hydrophilic or high-molecular-weight substances, small, lipophilic compounds are especially effective at entering the blood and crossing the blood and getting past the blood-brain barrier. Additionally, this countercurrent exchange system facilitates the quick delivery of systemically absorbed medications to the nervous system and the skull by allowing them to enter the nasal vasculature and swiftly reach the carotid arteries.

Processes Involved in Brain Drug Uptake

Over the past few decades, scientists have thoroughly investigated the possibility of using olfactory neurons as a direct method of delivering medication to the brain and cerebrospinal fluid. At this moment, we recognize that the methods by which medications are absorbed the most are through two distinct routes from the nervous system to the nose. Paths first acts as a systemic mechanism through which a portion of the medication enters the bloodstream.by the respiratory epithelium's abundant vasculature and then passes through, brain’s endothelial barrier to deliver substances to neural tissue. The other is olfactory pathway, which allows the medication to be directly delivered without going through the BBB to brain tissue. Drugs everywhere Olfactory epithelial cells may simply move slowly through the small space between cells or through the cell membrane, either via endocytosis or vesicle carriers.[13,14] To facilitate the direct flow of drugs into the respiratory tract into the brain, three main mechanisms are put forth. While the other two of these pathways take place extracellularly outside of cells, one of them is dependent on intracellular transport.[15]

The intracellular, neuron-mediated route is comparatively slow and may require several hours for molecules to reach the olfactory bulb after administration, as it involves processes linked to olfactory function. In this mechanism, olfactory epithelial neurons internalize substances— often through endocytosis—and carry them along their axons to the sense of smell.

Prior to arriving at the bulb that senses smell in the first extracellular route, drugs move through the intercellular gaps that surround olfactory neurons. Compounds can get around the blood– brain barrier by moving along the trigeminal nerve branches, which is the second extracellular route. These agents can spread further into deeper brain regions once they have reached the olfactory bulb or trigeminal areas. Additionally, some of the dose may be absorbed systemically via the nasal mucosa, enter the bloodstream, and proceed to the nervous system in general.

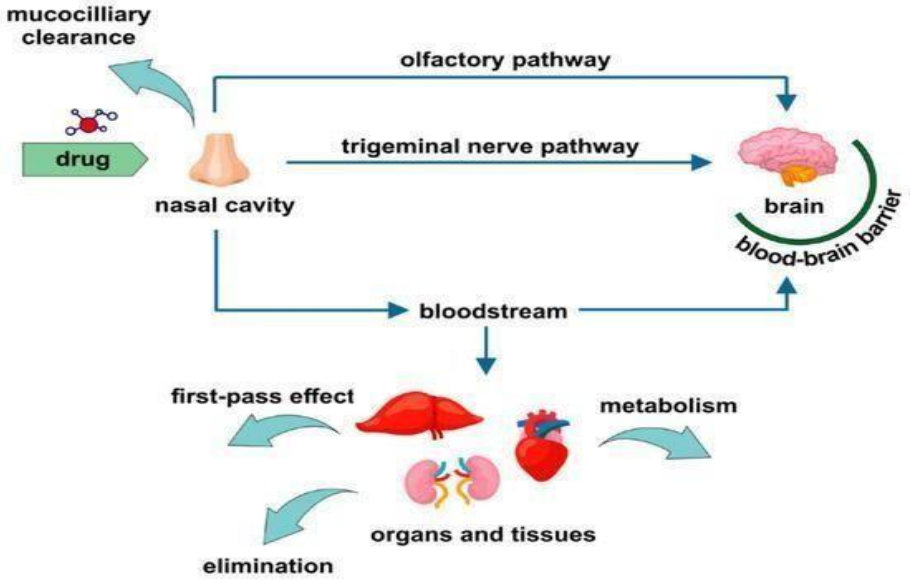

Figure 2: Process involved in Brain Drug Uptake.

Benefits of administering drugs via the nasal route[16,17,18]

Because of the highly vascularized nasal mucosa, the medication is absorbed quickly. The action begins quickly.

It is simple, noninvasive, and easy for patients to administer.

It stops the medication from breaking down in the digestive system.

The medication avoids the liver metabolism that typically takes place during first-pass processing.

The nasal bioavailability of small drug molecules is high.

Medication candidates that aren't suitable for oral administration may be administered through the nose with success.

Use the parenteral route instead, particularly for Peptides and proteins. A long-term, convenient path for patient therapy.

The bioavailability has improved.

The low dosage reduces side effects.

There is an improvement in patient compliance and convenience. It is possible to administer it yourself.

Straightforward entry into the bloodstream and CNS is feasible.

Reduces the chance of overdosing Lacks a sophisticated formulation/necessity

Limitations Related to Nasal Medication Administration

Delivering high molecular weight molecules (usually more than ~1 kDa) is ineffective with this method.

Certain illness states can have an adverse effect on the efficacy of nasal drug delivery. The impermeability of this path varies significantly between species.

Natural defensive systems, including cilia as well as intestinal clearance movement, can influence how well drugs pass through the nasal membrane.

Some drugs, such as azelastine and budesonide, can cause nasal mucosal irritation.

The mechanisms involved are still not fully understood, and there are currently only a few experimental models available.

The potential for systemic toxicity and the safety of absorption-enhancing agents are still debatable.

The gastrointestinal tract has more surface area for absorption than the nasal cavity.

It is more inconvenient than the oral method due to the possibility of nasal irritation.

Enzyme- induced barrier to drug permeability.

Characteristics of the "perfect" medication amenable to nasal dosing[19]

An ideal nasal drug candidate should dissolve well in water so the required dose can be delivered effectively within a 25–150 µL volume through the nasal route.

Proper nasal absorption characteristics.

The medication does not cause nasal irritation.

An appropriate clinical justification for nasal administration forms, like a quick start to action. The dose should be small—typically under 25 mg per administration.

The medication should not produce any harmful or irritating substances within the nasal cavity. It should be free from strong or unpleasant odors.

The formulation needs to maintain good stability over its shelf life.

The novel approaches used to improve the uptake of the drugs include

Mucoadhesive formulation

The implementation of mucoadhesive polymers within intranasal preparations increase duration about mucosal contact, length of time that the dosage forms are inside the cavities of the nose. Different formulations composed of mucoadhesive polymers can be such as nasal gel, mucoadhesive powder, microsuch as nanoemulsion or emulsion.

Mucoadhesive polymer examples

Derivatives of cellulose: carboxymethyl cellulose (CMC), HPC, hydroxypropyl cellulose, Both carboxymethyl methyl cellulose (CMC) and methyl cellulose (MC) etc. Carbopol 971 P, Carbopol 934 P, and other polyacrylates 974 P carbopol Starch (starch from maize).

Powders

Drug dosage forms for nasal administration in powder form provide a number of benefits regarding liquid formulations as a powder, drugs resistance to chemical change improved, There is no need for a preservative in the formulation, and it is able to give higher dosages of medications. The powder form is it works well with a variety of non-peptide medications for medications that contain peptides.[20]

Nasal gel

Consequently, the use related to nasal powder products rise. Patient adherence, particularly when flavor, aroma about Drug delivery is unacceptable. Following communication with the nasal mucosa, powders made of polymers are thought to absorb water from the nasal cavity, then create a viscous gel mucus. Following that, free polymer chains entering the ciliary movement may be impeded by tissue fissures, which will lengthen the duration of the medications' retention in the nasal cavity.[21]

Microemulsions

Clear, stable mixes of the two phases that are kept stable by surfactants as well as co-surfactants are known as microemulsions. They have a strong ability to dissolve medications and can maintain their physical stability for extended periods of time because of their nanoscale droplet size. These qualities caused extensive research into the usage of small particles as transporters for better permeability and absorption of medications with low water solubility. Additionally, they can be modified for focused or monitored administration, increasing the efficacy of treatment and lowering undesirable systemic effects.[22]

Advantages of Microemulsion in Nasal Drug Delivery

Enhanced Drug Absorption Bypass Blood brain barrier (BBB) Improved solubility of drug Rapid onset of action.

For example

When administered intranasally as opposed to orally or intravenously, diazepam, sumatriptan microemulsions have compared better brain delivery and a quicker onset.[23,24] When used intranasally, risperidone microemulsion enhanced therapeutic action and brain targeting.[23]

Nano emulsions

Rizatriptan administered intranasally using a nanoemulsionBenzoate, an antimicrobial medication that targets the nose to the brain, has created with support from water-containing pseudo-ternary phase diagrams, lipophilic-hydrophilic surfactants, various proportions of mucoadhesive polymers, such as carbopol , HPMC980.[25] Risperidone administered intranasally revealed that notable amount By using an intranasal mucoadhesive nanoemulsion, risperidone was transported to the brain swiftly and effectively.

Phospholipid vesicles

Liposomes are minute, ball-shaped structures composed of lipid layer, concentric lipid monolayered or several bilayers, grouped enveloping a watery core in the middle. They're composed of nontoxic, natural, biodegradable, and components like phospholipids, which can naturally mimic occurring membranes of cells. They might have cholesterol in them as a membrane stabilizer, and could contain traces of agents that charge. They might include cholesterol as a component a stabilizer for membranes, can contain trace molecules that make charges. With these advantageous structural features, Liposomes can encapsulate medications with a variety of the latter of which are present inside lipophilicities/lipid double layer coupled with hydrophilic constituents that are stored in the watery center. Amphiphilic medications may bind to the bilayer's polar head region. The use of liposomes has been examined as transporters of different pharmaceutically active substances like chelating agents, antimicrobial medications, antineoplastic genetic materials, steroids, agents, vaccines. Liposomes offer a productive medication delivery system since they are able to modify the pharmacodynamics and pharmacokinetics of drugs that were trapped. Additionally, liposomes can be coated with a variety of thousands of polyethylene glycol (PEG) strands to prolong the duration of blood circulation.[26]

Nanoparticles

By overcoming extracellular transport barriers such as P-glycoprotein efflux. This would enhance the drug's CNS availability. An elevated relative surface area indicates that the drug will be released by these vectors. quicker than a larger equivalent, a desirable characteristic where Pain must be managed immediately. Their small size potentially make it possible for nanoparticles to travel As mentioned earlier, substances can reach the brain via transcellular

transport through olfactory neurons, utilizing either the sustentacular or neuronal endocytic pathways within the olfactory membrane. By changing the surface of the nanoparticles, one could several drugs are supplied specifically to the brain and spinal cord using the same "platform" distribution technique that has been acknowledged, comprehensively explained biophysical properties and mechanism(s)into the brain.[27] Studies revealed nasal circulation was improved by modifying the surface nanoparticles and targeted cancer cells with gene therapy.[28]

Nasal spray

The nasal spray settles in the nasal atrium anteriorly extend the duration of residence, while the drops are scattered along the nasal cavity's length. Nasal sprays deposit closer to the front, increasing the capability of providing compounds to the brain. At what time diazepam is given intranasally using nasal spray, Because it produces a rapid effect, this approach may be particularly valuable for the emergency management of status epilepticus. Formulations for solutions, suspensions can both be made into sprays for the nose. Because of the accessibility of A nasal spray with metered dose pumps and actuators can provide precise dosage between 25, 200 µm. The size of the particles and shape of the medication, the viscosity of the formulation dictates which pump and actuator to use. assembly.[29]

Noisome

Structurally, they are similar to liposomes but consist of unique comp Surfactant vesicles that are not ionic. They form through the self-organization of non-ionic amphiphilic molecules along with supplementary lipid-based surfactants in an aquatic environment. Are tiny, lamellar structures created by mixing a non-ionic surfactant with cholesterol and the alkyl or diallyl polyglycerol ether Class After which it is hydrated in aqueous media, producing closed bilayer systems such as aqueous liposomes. Noisome dispersions can show signs of fusion, aggregation, leaking or hydrolysing medications that are encapsulated, thus restricting the dispersion's shelf life.

Noisome are being researched extensively as a low-cost substitute unrelated to liposomes in terms of biology. The surfactants biosome are non-immunogenic, biodegradable, and biocompatible. It possesses improved chemical stability, increased accessibility, comparatively inexpensive niosomes in comparison to liposomes, making storage simpler, which encourages exploitation. Niosomes as phospholipid substitutes. In theory A specific class must be present for biosomal formulation to occur of an aqueous system, an amphiphile.[30,31]

Obstacles in Intranasal Medication Administration Systems

Considerable interest has been shown in the intranasal route as a substitute for oral, parenteral medication delivery. Its benefits include extensive vascularization, a wide absorptive surface, and the ability to transport drugs directly between the central nervous system as well as the nasal region, bypassing the barrier between the brain and blood. Nevertheless, its effectiveness is limited by various physiological, anatomical, and biochemical obstacles.

Barriers that are both biological and physical

The sensory as well as respiratory regions make up the nasal passages. Medication can only go into the brain directly using the olfactory region, which only occupies about 10% of the lining of the nose. Furthermore, the nasal mucosa's tight junctions prevent big, water-soluble molecules from passing through, which reduces the permeability and absorption of drugs.[32]

Mucociliary Clearance

Mucous lining of the nose is coated with mucus, lined with cilia that consistently move toward nasopharynx, helping to remove foreign particles. This natural defense, known as mucociliary clearance, significantly limits how long drugs can remain in the interior of the nose. This often leads to reduced bioavailability and poorer drug absorption.[33]

Enzymatic Barrier

Carboxylesterases, proteolytic enzymes, multiple cytochrome P450 isoforms are among the many metabolic enzymes found in the nasal epithelium. Certain medications, particularly peptides and proteins, can be broken down by these enzymes prior to being absorbed into the bloodstream. Enzymatic degradation is therefore still a significant obstacle in nasal drug delivery.[34]

Formulation and Physicochemical Barriers

Drugs that are unstable, have a high molecular weight, or are poorly soluble have trouble passing through the nasal epithelium. Absorption efficiency is greatly influenced by the formulation's physicochemical characteristics, including pH, viscosity, and particle size. Novel formulations like liposomes, nanoemulsion and nanoparticle have been created to enhance the solubility, and absorption of the medication via the nasal route.[35]

Pathological and Environmental Barriers

The physiology of the nasal passages can be changed through the nose conditions like congestion, sinusitis, or rhinitis, which can impact how well drugs are absorbed. Environmental conditions, including temperature, humidity, air pollution, can influence drug delivery by altering mucosal permeability and the efficiency of mucociliary activity.[36]

Polymers with mucoadhesive properties applied in nasal drug delivery

Chemically Modified Cellulose

Cellulose derivatives, due to their excellent mucoadhesive characteristics, can considerably extend a medication's duration in the nostrils.[37] In addition, their high viscosity upon hydration helps sustain the release of the medication within the nasal environment.[37,38] For these reasons, enhanced bioavailability and better intranasal absorption can result from the Implementation of celluloses as an absorption enhancer.

Numerous references demonstrate the effectiveness of celluloses in boosting the nasal absorption efficiency of hydrophilic agents as well as small hydrophobic macromolecules [Table 1].

Table 1: E.g. of cellulose.

Mucoadhesive Polymers	Therapeutic agent	Delivery form	Authority
Carboxymethylcellulose sodium	Apomorphine	Fine particles	Ugwoke MI et al.[42]
Crystalline cellulose	Toradol	Aerosol	Quadir M et al.[43]
Crystalline cellulose	Lupron Depot	Fine particles	Suzuki Y et al .[44]
Cellulose, hydroxypropyl ether	Hydroxy tyramine	Solution	Ikeda K et al.[45]
Cellulose, hydroxypropyl ether	Mefeclorazine	Semisolid formulation	Zaki NM et al.[37]

Polyacrylates

These substances have been extensively studied for various medicinal product routes, primarily nasal, because of their exceptional adhesive and formation of gel properties. Administration polyacrylate-based polymers, such as carbomers and polycarbophil, which come in different viscosities and levels of cross-linking, are frequently used in mucoadhesive nasal drug delivery formulations.[39]

Bio adhesive polymers	Therapeutic agent	Delivery form	Authority
Polyacrylate polymer 971P	APO	Fine particles	UgWoke MI et al.[46]
Carbopol 934P	Levonorgestrel	Liquid	Shahiwala et al.[47]
Polyacrylate polymer 981P combined with DM β-CD	Mefeclorazine	Fine particles	Quadi M et al.[48]
Carbopol 934/HPC	Mefeclorazine	Powder	Cellens C et al.[49]

Starch

Table 2 E.g. Of polysaccharide Starch is among the most widely used mucoadhesive carriers for using the nose to brain administer prescription drugs. It has been discovered to improve the absorption of small hydrophobic medications as well as hydrophilic macromolecules. The most popular type of waxy maize starch is drum-dried pharmaceutical use, due to its superior bio adhesive properties compared to other starch varieties.[40]

Table 3: E.g. of starch.

Mucoadhesive Polymers	Therapeutic agent	Delivery form	Authority
DSM	Apomorphine hydrochloride	Fine particles	Ugwoke MI et al.[46]
DSM/STDHF	Gentamicin	Fine particles	Illum L et al.[48]
DDMW	Hydrogel system	Fine particles	Illum L et al.[48]

Chitin derivative

Commonly known as chitin, linear cationic polymer derived from the degradation of cellulose, a structural polymer found in large quantities in the shells of crustaceans like crabs, shrimp, and lobsters. Neutral and alkaline solutions do not dissolve chitosan. conditions because of the NH_2 clusters formed during acetylation. But it could react with both organic and inorganic acids, including acetic, lactic, hydrochloric, and glutamic acids, to produce water-soluble salts. According to toxicity assessments, chitosan demonstrates a high safety threshold, with Paul and Garside (2000) reporting an LD_{50} of more than 16 g/kg in mice. Chitosan is now frequently utilized as an agent in many medication delivery methods, such as nasal, oral, ocula,, implantable, parenteral, and transdermal formulations, due to its affordability, high biocompatibility, and biodegradability.[41]

Table 4: Example of chitin derivatives.

Mucoadhesive Polymers	Therapeutic agent	Delivery form	Authority
Chitosan	Tetra-substituted methyl pyrazine Insulin	Liquefied substance	Mei D et al.[51]
Chitosan	Pancreatic hormone insulin	Liquefied substance	Illum L et al.[41]
Deacetylated chitin	Progestin contraceptive	Liquefied substance	Shahiwala A et al.[47]
Deacetylated chitin	FITC–Dextran 4k	Liquefied substance	Miyamoto M et al.[51]
Deacetylated chitin	Mefeclorazine	Liquid	Zaki NM et al.[37]

Recent break thoughts

Lipid-based nanocarriers: SLNs and NLCs administered intranasally show promise for Through the blood-brain barrier, neurodegenerative and neuro-oncological disorders.[53]

Lipid and polymeric carriers: Intranasal micelles, liposomes, polymeric nanoparticles, SLNs, and NLCs enhance brain bioavailability.[54]

Biologics for Alzheimer's: Non-invasive nasal delivery of medication to the mind is possible with antigenic compounds, as well as gene treatments.[55]

Macromolecular nanoparticles: Size, charge, coatings, and targeting affect nasal mucosa penetration and brain uptake.[56]

Challenges & future research: Device design and human translation remain key hurdles in CNS intranasal delivery.[57]

Imaging agents: Intranasal delivery can also be used for diagnostic imaging of the brain.[58]
Levodopa for Parkinson's: Intranasal nanocarriers offer nose-to-brain transport for Parkinson's therapy.[59]
Atomization devices: Novel nasal devices improve CNS delivery and onset of drugs like dexmedetomidine.[60]

CONCLUSION

Compared to conventional delivery methods, this approach minimizes systemic adverse effects and allows for faster therapeutic action by avoiding the blood–brain barrier. However, challenges such as mucociliary clearance, enzymatic breakdown, limited absorption area, and individual differences in nasal anatomy still limit its effectiveness.

To address these issues, advanced nanocarrier systems—including liposomes, nanoemulsions, noisome, polymeric nanoparticles, and in situ gels—are being designed to enhance drug stability, prolong residence time, and improve brain-targeting efficiency. Additionally, optimizing factors like mucoadhesive properties, particle size, and surface charge is crucial for maximizing drug delivery to the CNS.

Intranasal delivery is a practical and patient-friendly substitute for CNS medication delivery. It is anticipated that this strategy will become a crucial platform for upcoming CNS treatments as nanotechnology, bioadhesive materials, and nose-to-brain targeting techniques continue to advance.

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