Chettinad Health City Medical Journal
Volume 14, Issue 1 - 2025, Pg. No. 88-97
Peer Reviewed & Open Access Journal

Review Article

Intranasal Drug Delivery System: An Innovative Approach

D Rushi Kumar Reddy[1], Suryaprakash Reddy C[2]

[1]Formulation Research and Development, Integrated Product Development Organisation, Dr Reddy's Laboratories Ltd, Bachupally, Hyderabad, Telangana, India
[2]Department of Pharmaceutics, Annamacharya College of Pharmacy, Rajampet, Affiliated to Jawaharlal Nehru Technological University, Andhra Pradesh, India
DOI: https://doi.org/10.24321/2278.2044.202512

I N F O

Corresponding Author:
D Rushi Kumar Reddy, Integrated Product Development Organisation, Dr Reddy's Laboratories Ltd, Bachupally, Hyderabad, Telangana, India
E-mail Id:
rishi0043@gmail.com
Orcid Id:
https://orcid.org/0009-0003-5080-3573
How to cite this article:
Reddy D R K, Reddy C S. Intranasal Drug Delivery System: An Innovative Approach. Chettinad Health City Med J. 2025;14(1):88-97.

Date of Submission: 2024-05-12
Date of Acceptance: 2025-01-09

A B S T R A C T

Drug delivery through the nose has been used for thousands of years. For medications like protein and peptides that have low oral bioavailability and are active at the microgram level, this is a helpful delivery system. The nasal mucosa's enormous surface area allows for a quick start of a therapeutic impact. The Ayurvedic medical system has acknowledged the possibility of an intranasal therapy that transports drugs avoiding the hepatic metabolic process and going straight to the central nerve system (CNS). The medications are inhaled through the nose for a localised or systemic effect. They are readily available and appropriate for self-medication. The nasal mucosa's enormous surface area allows for a direct distribution of therapeutic effects to the CNS with a quick commencement of action. The nasal drug delivery will be helpful for drugs that are unstable when taken orally due to considerable deterioration within the digestive system. Instead of parenteral therapy, the nasal route is beneficial for long-term treatment. Because the nasal mucosa is extremely permeable and vascularised, it can also be utilised for systemic therapy, as the medication enters the bloodstream immediately. They all work to increase patient comfort, convenience, and compliance.

Keywords: Nasal Absorption, Nasal Cavity, First-Pass Elimination, Intranasal Medication Delivery Method

Introduction

Nasal drug delivery has drawn a lot of interest recently because of its practical, promising, and trustworthy method of systemic drug administration, particularly for medications that cannot be taken orally and require injections.[1,2] Transmucosal nasal drug delivery has become a major player in novel drug delivery technology as a non-invasive method. This pathway circumvents the first-pass metabolism and has a big surface area, a microvascular endothelium with a high bloodstream. It is also easily accessible. Furthermore, due to the absence of enzyme activity in the stomach and pancreas, as well as disruption from the gastrointestinal tract, the nasal mucosa is more resistant to toxins than the gastrointestinal system. When nasal drug administration was first documented in history, it was exclusively used for topical medications meant to have localised effects. [3]To achieve both local and systemic effects, its application has expanded in recent years to embrace a wide range of targeted body locations.[4] Nasal drug distribution is also given special consideration in traditional medical systems, such as the Indian Ayurvedic system, which uses a well-known therapeutic method known as “Nasya karma”.

Difficulties with Drug Delivery to the Brain

Brain-Blood-Barrier

The brain’s thick Endothelial Cell (EC) layer and supporting base layer are surrounded by pinocytic vesicles and tight cell-to-cell junction proteins with particular transport mechanisms, which are components between the brain and blood (BBB). Pericytes and foot processes of the astrocyte, two cellular components that surround the endothelium, form an additional continuous layer that divides brain tissue from blood vessels.[5] The Virchow-Robin space, which is made up of the space between EC and the brain tissue surrounding penetrating arteries and venules, is home to perivascular macrophages, which perform specific CNS immune functions. Comprised of close contact, functional connections, and signalling between the neurovascular unit is a dynamic, functional unit that includes blood vessels, astrocytes, microglia, neurons, and pericytes. Understanding the neurovascular unit is necessary to comprehend how the brain works in both health and disease, including neuronal firing, synaptic plasticity, blood flow regulation, and damage response.[6]

The brain capillary is lined with a single specialised EC layer, which makes up the deepest luminal component of the neurovascular unit.[7] The BBB’s selective molecular permeability is increased by the greater number and quantity of mitochondria in this layer. The basement membrane, a lamina that is 30 to 40 nm thick and comprises pericytes and endothelial cells, encloses the cerebral capillaries. It is located directly adjacent to the astrocyte end-feet plasma membranes.

Pericytes surround the brain’s capillaries and microvessels and are found near astrocytes and neurons. The estimated ratio of pericytes to endothelial cells is 1:1.3. Through several signalling pathways, pericytes seem to be crucial for the BBB’s establishment and expansion throughout the control of tissue survival and during development.[8]

By revealing the capillaries, astrocytes engage with pericytes and microvascular endothelial cells, with their end foot protrusions. The maintenance of the BBB and the control of transmitter, metabolite, ion, and water concentrations outside of cells depend on astrocytes. They also serve as models for migrating neuronal streams and as stem cells throughout development. The relationship between astrocytes and neurons affects blood flow, neurotransmitter clearance, synaptic transmission, and neural plasticity.[9]

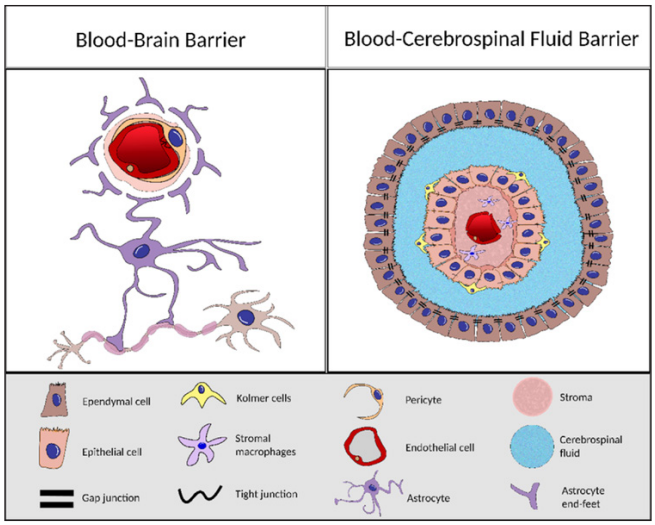

Figure 1.Blood-Cerebrospinal Fluid Barrier (BCSFB) and Blood-Brain Barrier (BBB)

Blood-Cerebrospinal Fluid Barrier (BCSFB)

The second barrier that a systemically administered medicine must cross before reaching the cerebrospinal fluid (CSF) is the blood-cerebrospinal fluid barrier (BCSFB) in the central nervous system (CNS). The BCSFB is located in the epithelium of the choroid plexus, which is designed to restrict the passage of molecules and cells into the CSF. This barrier is formed by the choroid plexus walls, which separate the blood from the CSF. Additionally, the arachnoid membrane, consisting of two layers, lies between the dura and pia mater on the outer surface of the brain. [10,11]It is made up of ependymal cells folding over on themselves. The subarachnoid gap, a component of the double layer, aids in CSF drainage. Tight connections stop chemicals from the blood from passing through the arachnoid membrane. A pictorial representation of the Blood-Brain Barrier and Blood-Cerebrospinal Fluid Barrier is shown in Figure 1. [12]

ISSN: 2278-2044
DOI: https://doi org/10.24321/2278.2044.202512

Three different types of barriers exist that restrict and tightly control access to the brain.

- **Physical Barrier:** With the biggest surface area (about 20 m^2), The majority of the blood-brain barrier is composed of densely packed, impermeable cells that are endothelial block paracellular transit. Additionally, there is no fenestration and a lower frequency of luminal side pinocytosis in the endothelium.[13] Tight junctional proteins, which bind the surrounding fenestrated capillaries with a monolayer of polarised epithelial cells, hold the barrier created by BCSFB together.
- **Transport/ Biological Barrier:** Numerous receptors and ion channels are expressed and functional, as the Transcellular transport is controlled by the influx/ efflux transport protein. P-gp, Breast Cancer Resistance Protein (BCRP), and Multidrug Resistance-associated Proteins (MRPs) are transporters connected to the ATP-binding cassette (ABC) membrane (ABCG2) is particularly crucial in reducing the permeability of several pharmaceutical medications. The most well-researched BBB transporter protein is P-gp.[14]
- **Metabolic Barrier/ Chemical Barrier:** Enzymes that catabolise substances might stop transcellular transfer. These transport and enzyme systems may also experience complex medication interactions, which could ultimately lead to toxicity or therapeutic failure.[15]

Nasal Route as an Administration Route for CNS Drug Delivery

Even though the nose route has historically been utilised to treat local symptoms, numerous studies have shown that intranasal (IN) medication administration can deliver therapeutic substances systemically. The highly perfused nasal cavity is one of the primary advantages of the nasal route, which facilitates quick systemic drug delivery and also avoids first-pass metabolism and drug extraction. This makes the nasal route an appealing option for drugs that would otherwise be administered parenterally or orally.[16] It was stated that neurological agents and macromolecules aimed at Alzheimer's disease may be delivered successfully, which was the first time a therapeutic agent had been delivered to a human following an IN injection. These studies presented a unique strategy for CNS medication administration that might avoid the BBB.

Nose Anatomy and Physiology

The nose is the main sense of smell and a vital respiratory organ. Two chambers of the nose are divided by the cartilaginous and bony nasal septum. These processes include the mucus and hairs lining the nasal canal, which collect inhaled particles and germs. Mucociliary clearance (MCC), immunological response, endogenous drug metabolism, and sound resonance are the nasal cavity's primary purposes. Anatomically, the human nasal cavity is situated between both the base of the skull and the roof of the mouth. The maxillary, inferior conchae, and ethmoid bones support the nasal cavity laterally.[17,18] An adult's nasal cavity has a surface area of around 150 cm^2 and may accommodate 15–20 mL. It is divided into two halves by the middle or nasal septum. Both parts move posteriorly to the nasopharynx after opening via the nostrils at the face. They are balanced. The nasal vestibule, atrium, olfactory region, and respiratory area make up each of the two symmetrical halves. The morphological and histological features of these areas set them apart.

Nasal Vestibule

The nasal vestibule is located just within the nostrils and is the most anterior portion of the nasal cavity, measuring around 0.6 cm^2. The vibrissae, or nasal hairs, in this area, filter the particles that are inhaled.[19] Histologically, a stratified squamous and keratinised epithelium including sebaceous glands covers this nasal region. However, the nasal vestibule is ideal for providing a strong defence against harmful environmental elements, it becomes extremely difficult to absorb things, including medications, in this area.

Atrium

The atrium is the space between the respiratory region and the nasal vestibule. Its front portion is made up of stratified squamous epithelium, while pseudo-stratified columnar cells with microvilli form its posterior region.[20]

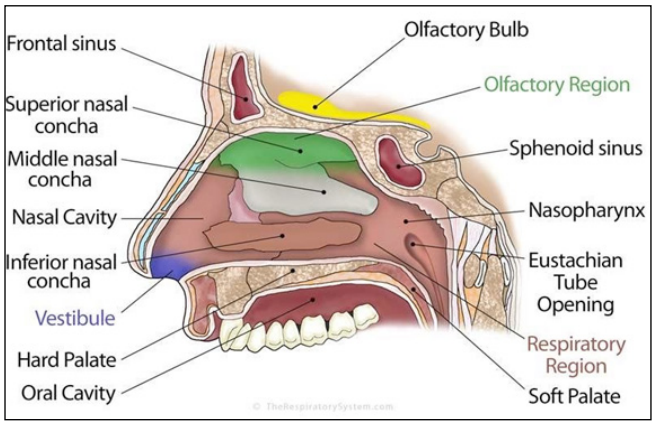

Figure 2.Anatomy of Nasal Cavity

Respiratory Area

Pictorial representation of Anatomy of nasal cavity is represented in Figure 2.[21] The nasal respiratory area, or conchae, which are divided into superior, middle, and inferior turbinates that extend from the lateral wall, make up the majority of the nasal cavity. They are responsible for regulating the humidity and temperature of the air we breathe. The gaps between them are known as meatus,

ISSN: 2278-2044
DOI: https://doi org/10.24321/2278.2044.202512

which are channels where air movement is generated, and they are there to guarantee that the inhaled air makes intimate touch with the mucosal surface of the respiratory system. The nasolacrimal ducts and the paranasal sinuses, which are air-filled chambers situated inside the face's bones and surrounding the nasal cavity, are received by the inferior and middle meatus. The nasal respiratory mucosa is made up of the lamina propria, basement membrane, and epithelium. It gives out medications in a methodical manner. Pseudostratified glands in the column that generate serous and mucus basal cells, goblet cells, and epithelial cells make up the nasal respiratory epithelium.[22] Microvilli and cilia are minute projections that cover the apical surface of most epithelial cells. Microvilli are required to increase the respiratory surface area, whereas cilia are required to transport mucus into the nasopharynx. The nasal epithelium is normally covered with a thin coating of mucus produced by goblet cells and secretory glands. Mucin, a glycoprotein that controls mucus viscosity, is present in these release granules. The layer of nasal mucus has a thickness of 5 µm and is made up of two layers: a viscous and dense layer on the exterior and a fluid and serous layer on the inside. Over 95% of the nasal mucus layer is composed of water and 3–5% mucin. Additionally, 2% of it contains bacterial metabolites, proteins, lipids, enzymes, antibodies, sloughed epithelial cells, and electrolytes. The nasal mucus layer must remain in place because mucin may bind large molecules like proteins and peptides. The base cells of the epithelium, the progenitors of other cell types, are found in the basement membrane, a more substantial collagen covering.

Olfactory Area

Situated on the nasal cavity's roof, the olfactory area stretches considerably along the lateral wall and septum. Only one part of the central nervous system is directly connected to the external environment, and that is the neural epithelium.[23] Specialised olfactory receptor cells, which are essential for the sense of smell, are found in the pseudo-stratified epithelium that comprises the olfactory region. This area contains tiny serous glands known as Bowman's glands, which release a fluid that acts as a solvent for foul-smelling substances.

Nasal Pathways to the Brain

The olfactory or trigeminal nerve routes are the main methods that which medications administered intravenously (IN) enter the brain and central nervous system (CNS). A modest function is also played by lymphatic circulation and diffusion into the cerebrospinal fluid (CSF).[24]

Olfactory Pathway

As shown in Figure 3 [25], therapeutic modalities enter the nose and go to also known as the olfactory epithelium or olfactory mucosa. The olfactory mucosa contains olfactory receptor neurons that do the transduction. The terminal projections of olfactory receptor neurons, called cilia, are where transduction takes place. Olfactory receptor neurons can receive substances through both paracellular and transcellular routes.[26] The nasal epithelium's integrity, tight junctions, adherent junctions, desmosomes, and intercellular gaps allow compounds to enter by paracellular transport.

The link between the nose and the brain is thought to be determined by the neurological pathway. Before reaching the olfactory bulb, which is situated on the surface of the brain, The axon and nerve bundle allow the medication molecules to cross the cribriform plate. The olfactory neurons allow the medicinal ingredient to reach the olfactory bulb and cerebrospinal fluid (CSF). By combining with the interstitial fluid, the medication might enter the brain from the cerebrospinal fluid (CSF). It just takes a few minutes for a drug that is administered by the nose to travel through the olfactory system and reach the brain. The intraneuronal and extra-neuronal routes are the two different ways that the olfactory neural route reaches the brain.[4] By use of the intra-neuronal route, which requires axonal transport, the active component may take hours or days to reach different parts of the brain. The active ingredient can enter the brain in a few minutes via both extra-neuronal and perineural routes. The olfactory neural network innervates deeper parts of the brain, including the cortex, cerebrum, and cerebellum.

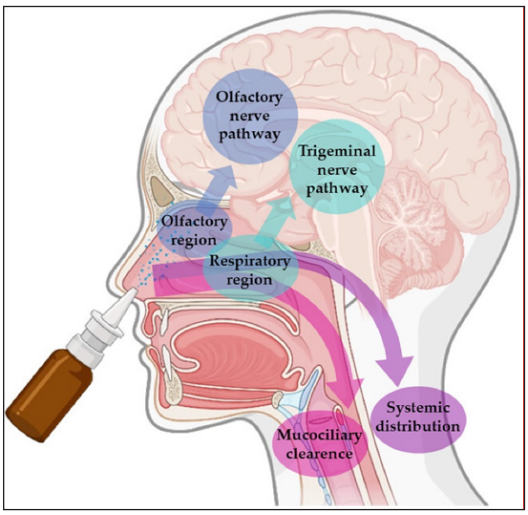

Figure 3.Entry of Drug through Nose-To-Brain Pathways

Trigeminal Pathway

The trigeminal nerve route links to the spinal cord, medulla, and pons after travelling via the back of the brain. There are two methods for delivering drugs through the nose: intracellular transfer (axonal transport) via endocytosis and

ISSN: 2278-2044
DOI: https://doi org/10.24321/2278.2044.202512

the trigeminal nerve pathway. The trigeminal nerve, the fifth and biggest cranial nerve, is made up of the ocular, maxillary, and mandibular branches. The ophthalmic and maxillary branches are essential for the passage of drugs from the nose to the brain because their neurons quickly cross the nasal mucosa.[27] The nasal mucosa is innervated by the maxillary branch of the trigeminal nerve, whereas the anterior nose and nasal mucosa are innervated by branches of the ophthalmic portion at the dorsal wall. The chemicals enter the nasal cavity through the mucosa and go to the respiratory and olfactory branches of the trigeminal nerves. They then go to the axonal pathway via the brain stem. A section of the trigeminal nerve that traverses the cribriform plate can also carry therapeutics from the nasal cavity to the forebrain.

Benefits of Nasal Drug Delivery[28,9]

1. The liver's first-pass metabolism is evaded.
2. a greater incidence of patient compliance than with parenteral procedures as accessible accessibility and needle-free drug delivery, which do not require skilled personnel, make self-medication easier.
3. It is possible to stop the gastrointestinal tract from breaking down drugs.
4. The nasal route can be used to improve the large medication compounds' bioavailability by using an absorption enhancer. It is simple to obtain both a quick start of the effect and quick medication absorption.
5. For small pharmacological compounds, the nasal route provides great absorption.
6. Nasal administration of medication results in low stability in GIT fluids.
7. Studies indicate that the nasal route can effectively replace the parenteral route, especially for drugs that comprise proteins and peptides.
8. This mode of delivery would be particularly appropriate for a polar drug that has problems being absorbed by the tongue.
9. Patients, particularly those undergoing long-term therapy, find it more convenient than parenteral medicine.

Disadvantages of Nasal Drug Delivery[30]

1. Compared to the gastrointestinal tract, the nasal cavity has a smaller surface area available for absorption.
2. Unlike the oral delivery approach, there is a chance of irritation.
3. The drug and other ingredients in the dosage form could harm the nasal mucosa's cilia irreversibly in addition to having adverse local effects.
4. The medicine may be mechanically lost into the lungs or other respiratory system components if the dosage form is administered incorrectly.
5. The membrane may be harmed or even destroyed by high concentrations of certain surfactants employed as chemical enhancers.

Transport Mechanism of Drugs

The first stage of pharmacological the drug's passage via mucus is known as absorption from the nasal cavity.[31] Mucus readily allows small particles and uncharged molecules to pass through it. Different transport mechanism of drugs is represented in the Figure 4.[32]

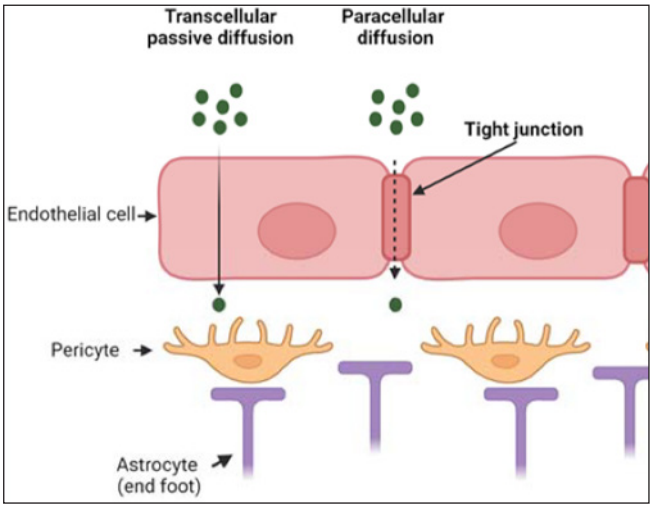

Figure 4.Transport Mechanism of Drugs

Paracellular Pathway

It is the movement of materials across an intercellular gap between cells to cross an epithelium. The paracellular pathway is a passive, sluggish process. Medications having molecular weights of more than 1000 Daltons are known to have poor bioavailability.

Transcellular Pathway

Solutes are transported through cells using transcellular transport. Non-polar materials enter cells through the intercellular pathway.[33] These molecules permeate and dissolve in the non-aqueous lipid matrix that is inserted between the filaments of protein.

Novel Intranasal Drug Delivery System to Target CNS

Microemulsion

There is potential in using microemulsion technology for intranasal delivery. A transparent, stable, isotropic blend of surfactant, water, and oil; often combined with a co-surfactant is called a microemulsion. Because of their enormous potential to include a wide range of medicinal chemicals and serve as drug-delivery vehicles, pharmaceutical experts are becoming interested in these systems.[34] Increased drug solubilisation and bioavailability,

ISSN: 2278-2044
DOI: https://doi org/10.24321/2278.2044.202512

thermodynamic stability, spontaneous production, and simplicity of manufacturing and scaling up are some of its advantages. To prepare a dosage form that pharmaceutical companies will accept, a detailed understanding of the microemulsion's structure, phase behaviour, and thermodynamic stability-promoting elements, The medication release from the formulation must be taken into account, the best microemulsion excipient specifications, and the system's possible uses and limitations.

Nanoparticles

The medicinal material is either confined in the colloidal matrix of nanoparticles, which are colloidal systems with compact structures, or it is coated on the particle surface via conjugation or adsorption.[35] Nanoparticles are mostly composed of lipids, polymers, or a combination of the two, and can be used to regulate and prolong drug release. Solid lipid nanoparticles (SLN), polymeric nanoparticles, nanospheres, nanosuspension, nanoemulsions, nano gels, nano micelles, nanoliposomes, carbon nanotubes, nanofibers, and nanorobots are a few of the nanosystems utilised to develop nano drug delivery systems for the treatment of CNS diseases (LDC). The precise mechanism by which nanoparticles dissolve barriers is unknown. Nonetheless, the given nanoparticles can enter the brain via several endocytotic pathways and cross the blood-brain barrier. Reports state that polymeric albumin or poly (butyl cyanoacrylate) nanoparticles can reach the brain through a process known as small-size mediated endocytosis. Because of the incredibly thin blood-brain barrier, the drug is transported directly from these intact nanoparticles into the brain microenvironment, where it is eventually biodegraded by endocytotic absorption.

Microsphere

Because it allows for prolonged contact with the nasal mucosa, microsphere technology is one of the specialised techniques that is gaining popularity for creating nasal goods enhancing absorption and bioavailability. The nasal mucosa gets dry while the microspheres are there because they absorb moisture. The cells contract reversibly as a result, improving drug absorption and momentarily physically separating the tight (intercellular) junctions. The microspheres used to provide nasal medications can absorb water and create a matrix that makes the spheres inflate and gel, even though they are water-insoluble. Albumin, dextran, starch, and hyaluronic acid are the constituents of microspheres. Starch and dextran-containing microspheres were administered regularly. In several species, the bioavailability of proteins and peptides has been improved by the development of microspheres. Microspheres are another efficient way to give a few low molecular-weight drugs. Microspheres may stay in the nasal cavity for three to five hours, depending on the kind of bioadhesive that was employed in the formulation.[4] Since smaller particles will enter the lungs, for optimal nasal dispersion, microsphere particles must be between 10 and 50 µm in size.

Nasal *In Situ* Gels

Drug delivery systems known as "*in situ* gel formulations" are those that are administered to the body in solution form initially, but then go through a gelation process to solidify into gel. A variety of polymers, including poloxamers, carbopol, PVA, and chitosan, can be used to do this.[5]

Advancements in the Nasal Dosage Forms

Among the most straightforward and practical nasal administration instruments ever created are nasal drops. Prescription nasal drops might not be appropriate drugs due to the lack of dosage accuracy in this method, which is its primary drawback.[36] It has been noted that nasal drops work better than nasal spray at delivering human serum to the nostrils.

Nasal Spray

Nasal sprays can be made using a suspension or a solution. A nasal spray can administer a precise dosage because metered dose pumps and actuators are readily available. These are better than powder sprays since powder irritates mucous membranes.[37]

Nasal Powders

If dosing formulations in suspension and solution are not feasible, for instance, because of the drug's inadequate stability, this dosage form may be created. The nasal powder administration form is favourable due to the formulation's enhanced stability and the absence of preservatives.[5] However, the suitability of the powder formulation depends on the solubility, particle size, aerodynamic properties, and nasal irritancy of the active drug and/ or excipients. A further advantage of this approach is the local administration of medication.

Nasal Inserts

Novel, solid, bioadhesive dosage forms called nasal inserts are designed to deliver medications for long periods of time in the nasal cavity.[38] To prevent the nasal cavity from feeling like a foreign body, the primary idea behind the dosage form is to gather nasal fluid from the mucosa after delivery and gel it there.

Nasal Gel

The nasal gel has gained more attention due to its high viscosity, capacity to improve absorption by targeting the mucosa, ability to reduce anterior formulation leakage, ability to reduce irritation from using soothing/ emollient excipients, and ability to lessen taste impact from swallowing less.[10] Gels are materials that are soft, firm, or semisolid and consist consisting comprises two or more materials, at

ISSN: 2278-2044
DOI: https://doi org/10.24321/2278.2044.202512

least one of which is liquid and present in substantial quantities. Two dynamic mechanical parameters that may be used to describe the semisolid characteristics of gels are the viscous modulus G and the elastic modulus G. The rheological properties of gels rely on the polymer's type, concentration, and physical condition. They might include viscous liquids (such as xanthan gum, hypromellose, methylcellulose, and chitosan) or brittle, highly rigid gels (such as alginate, pectin, and gellan gum).

With their ability to regulate the pace and degree of drug release, bioadhesive polymers have great potential as nasal formulation materials. This has led to reduced drug administration frequency and increased patient compliance. Additionally, by slowing down mucociliary migration, the longer contact time at the absorption site may increase the medicines' bioavailability. The mechanism of mucoadhesion is described by several theories in the nasal cavity, but two main stages—the contact and consolidation stages—are universally acknowledged as the basis of the mechanism.[39] Thus, preparations comprising bioadhesive polymers can spread throughout the nasal epithelium after being injected into the nasal cavity. The polymer chains can spread inside the mucus because of the increased surface contact. Enough contact is made as a result of entanglement. The polymer chains and mucin molecules subsequently create secondary chemical bonds. To create mucoadhesive systems, a variety of biocompatible and biodegradable polymers have been employed. These consist of starch, gellan gum, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl alcohol, chitosan, and carbopol. Mucoadhesive gels have been investigated for use in the nasal delivery of a variety of drugs, including insulin, scopolamine hydrochloride, mometasone furoate, carvedilol, sumatriptan succinate, proteins, and antibiotics like roxithromycin and ciprofloxacin.

Even though the majority of gels display pseudo-plasticity or shear thinning behaviour, it is challenging to apply gel formulations with the right rheological characteristics with a typical nasal spray device.[40] This issue can be solved by using *in situ* gelation, which has also been studied for the nasal delivery of carvedilol, mometasone furoate, and influenza vaccine. In these systems, the formulation's viscosity needs to be both low enough to enable nasal spray device dispensing and high enough to promote adhesion at the application site.

Drug delivery systems known as *in situ* gel-forming polymeric formulations are solutions before intravenous administration, but after intravenous injection, they go through *in situ* gelation to produce gels. Gel formation is dependent on various conditions, including changes in pH, temperature, and the presence of ions, which release the medication in a regulated and sustained manner. A possible substitute for *in situ* gels would be fluid gels. In essence, these fluid gels are structured liquids with a polymer that forms gels. During the gelation process, a shear force is applied to the polymer solution to prepare them. As a result, an ungelled polymer solution contains gelled particles suspended in it. These can be designed so that the gel particles retain their actual gel microstructure while acting as a viscoelastic liquid.[41]

In situ Gel Formulation

The following are some of the several techniques for creating *in situ* gels:

Thermally Triggered System

A mechanism that is activated by heat This method creates the *in situ* gel by modifying the physiological temperature of the body, which causes a polymer to change from solution to gel. As the temperature rises, the biomaterials used to make *in situ* gel change from sol to gel.

pH-Triggered Systems

Another method for creating *in situ* gel is to use pH-sensitive polymers to change the gel's pH in response to physiological signals.[42] When the external pH rises, the hydrogel will swell more if the polymer includes weakly acidic groups; on the other hand, the hydrogel will shrink if the polymer contains weakly basic groups. Osmatic pressure is the driving force for the drug release in these *in situ* gelling systems.

This procedure involves changing the ionic strength to cause the implanted fluid to gel. The osmotic gradient that runs across the gel's surface determines how quickly gelation occurs. When mono- or divalent cations are present, the aqueous polymer solution gels into a transparent substance.[43] Hyaluronic acid, alginates, gellan gum, and other polymers cause gelation.

In Situ Gel System Induced by Chemical Means

- **Ionic cross-linking:** Sodium alginate, pectin, gellan gum, carrageenan and other ions that are sensitive to polysaccharides experience a phase change when K^+, Ca^{2+}, Mg^{2+}, and Na^+ are present.[44] The ion-sensitive polysaccharide class includes these polysaccharides.
- **Enzymatic cross-linking:** *In situ* manufacture using natural enzymes seems to provide certain benefits over chemical and photochemical techniques, despite the fact that it has not been well investigated. An enzymatic process, for example, works well under physiological conditions without requiring potentially harmful materials such as initiators and monomers.
- **Photo-polymerisation:** Biomedical applications have made use of *in situ* photo-polymerisation.

ISSN: 2278-2044
DOI: https://doi org/10.24321/2278.2044.202512

Nasal Drug Delivery System Application

Local Delivery

To cure topical nasal issues organically, the medication is administered through the nose. The most widely used ones are corticosteroids and antihistamines for cold symptoms and nasal decongestants for rhinosinusitis. Comparatively small amounts administered by the nose are effective and have less negative systemic effects.[45]

Systemic Delivery

Intranasal drug administration is a more effective strategy to guarantee systemic availability of medications than oral and intravascular procedures. Numerous planned experiments comparing intranasal medication delivery to oral and parenteral administration have indicated that it looks to enable quick and extended drug absorption. One example of an antiviral drug is acyclovir. Additional examples include hormones like levonorgestrel, progesterone, and insulin; cardiovascular meds like propranolol and carvedilol; analgesics like morphine; and anti-inflammatory pharmaceuticals like indomethacin and ketorolac. Two examples of drugs that are currently on the market to treat migraine and cluster headaches are sumatriptan and zolmitriptan.[46]

Nasal Vaccines

The nasal mucosa's use in immunisation, especially against respiratory illnesses, has been thoroughly researched since it is the first surface that inhaled antigens come into contact with. Because nasal vaccination can raise systemic levels of particular immunoglobulin G and nasal secretory immunoglobulin A, it presents a viable substitute for the traditional parenteral approach. Intranasal vaccinations against influenza A and B viruses, parainfluenza 3 virus, proteasome influenza, and adenovirus-vectored influenza have been shown to be efficacious in human investigations, attenuated respiratory syncytial virus, and native group B meningococcal infection.[478]

CNS Delivery through the Nasal Route

There are several interesting ways to provide drugs to the brain through the intranasal route. The nasal route of drug delivery to the central nervous system may include the olfactory neuroepithelium. Additionally, transmission from the trigeminal nerve system has been recorded from the nasal cavity to the central nervous system. Medication for brain tumours, epilepsy, Alzheimer's disease, pain, and sleep issues have all been shown to reach the central nervous system through the nose.

Conclusion

The development of methods to increase the brain's bioavailability of drugs creates opportunities for the causal treatment of diseases associated with deficits in the brain's neurotransmitters and neurosteroids. Despite a number of disadvantages, intranasal administration seems to be the most promising medication delivery technique for treating CNS conditions including multiple sclerosis and brain damage. In the last ten years, the nasal cavity has become one of the most promising and perhaps versatile drug delivery routes. Its unique ability to delay drug release, circumvent hepatic first-pass metabolism, and deliver drugs straight to the brain is very fascinating in the field of drug delivery. Pharmaceutical companies have intensified research on nasal drug delivery for drugs that are difficult to manage, as well as those affected by first-pass metabolism and hydrophilic drugs. Growing research on nasal drug delivery raises the possibility that it may be used for difficult-to-manage drugs that make drug delivery and manufacturing.

Conflict of Interest: None

Source of Funding: None

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process: None

References

1. Homayun B, Lin X, Choi HJ. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. Pharmaceutics. 2019;11(3):129. [PubMed] [Google Scholar]
2. Wang Z, Xiong G, Tsang WC, Schätzlein AG, Uchegbu IF. Nose-to-brain delivery. J Pharmacol Exp Ther. 2019;370(3):593-601. [PubMed] [Google Scholar]
3. Patel MM, Patel BM. Crossing the blood–brain barrier: recent advances in drug delivery to the brain. CNS Drugs. 2017;31(2):109-33. [PubMed] [Google Scholar]
4. Gänger S, Schindowski K. Tailoring formulations for intranasal nose-to-brain delivery: a review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. Pharmaceutics. 2018;10(3):116. [PubMed] [Google Scholar]
5. Crowe TP, Greenlee MH, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. Life Sci. 2018;195:44-52. [PubMed] [Google Scholar]
6. Selvaraj K, Gowthamarajan K, Karri VV. Nose to brain transport pathways an overview: potential of nanostructured lipid carriers in nose to brain targeting. Artif Cells Nanomed Biotechnol. 2018;46(8):2088-95. [PubMed] [Google Scholar]
7. Galeano C, Qiu Z, Mishra A, Farnsworth SL, Hemmi JJ, Moreira A, Edenhoffer P, Hornsby PJ. The route by which intranasally delivered stem cells enter the central nervous system. Cell Transplant. 2018;27(3):501-14.

ISSN: 2278-2044
DOI: https://doi org/10.24321/2278.2044.202512

[PubMed] [Google Scholar]
8. Gaikwad D, Kurane P, Mali D, Jadhav N. Development of particulate mucoadhesive gel for intranasal delivery. Asian J Pharm Clin Res. 2017;10(5):222. [Google Scholar]
9. Lochhead JJ, Kellohen KL, Ronaldson PT, Davis TP. Distribution of insulin in trigeminal nerve and brain after intranasal administration. Sci Rep. 2019;9(1):2621. [PubMed] [Google Scholar]
10. Ghadiri M, Young PM, Traini D. Strategies to enhance drug absorption via nasal and pulmonary routes. Pharmaceutics. 2019;11(3):113. [PubMed] [Google Scholar]
11. Khan AR, Liu M, Khan WM, Zhai G. Progress in brain targeting drug delivery system by nasal route. J Control Release. 2017;268:364-89. [PubMed] [Google Scholar]
12. Tiago Gião, Tiago Teixeira, Maria Rosário Almeida, Isabel Cardoso. Choroid Plexus in Alzheimer's Disease-The Current State of Knowledge. Biomedicines. 2022;10(2):224. [PubMed] [Google Scholar]
13. Helmbrecht H, Joseph A, McKenna M, Zhang M, Nance E. Governing transport principles for nanotherapeutic application in the brain. Curr Opin Chem Eng. 2020;30(12):112-9. [PubMed] [Google Scholar]
14. Chen TC, da Fonseca CO, Schönthal AH. Intranasal perillyl alcohol for glioma therapy: molecular mechanisms and clinical development. Int J Mol Sci. 2018;19(12):3905. [PubMed] [Google Scholar]
15. Quintana DS, Smerud KT, Andreassen OA, Djupesland PG. Evidence for intranasal oxytocin delivery to the brain: recent advances and future perspectives. Ther Deliv. 2018;9(7):515-25. [PubMed] [Google Scholar]
16. Scherließ R. Nasal formulations for drug administration and characterization of nasal preparations in drug delivery. Ther Deliv. 2020;11(3):183-91. [PubMed] [Google Scholar]
17. Ulusoy S, Muluk NB, Karpischenko S, Passali GC, Negm H, Passali D, Milkov M, Kopacheva-Barsova G, Konstantinidis I, Dilber M, Cingi C. Mechanisms and solutions for nasal drug delivery - a narrative review. Eur Rev Med Pharmacol Sci. 2022;26(2 Suppl):72-81. [PubMed] [Google Scholar]
18. Prajapati M, Mandloi R, Pillai S, Birla N. The review on the nasal drug delivery. Asian J Pharm Res. 2020;10(2):110-6. [Google Scholar]
19. Mali AH, Shaikh AZ. A short review on nasal drug delivery system. Asian J Pharm Technol. 2021;11(4):289-92. [Google Scholar]
20. Bajpai V. *In situ* gel nasal drug delivery system- a review. Int J Pharm Sci. 2014;4(3):577-80. [Google Scholar]
21. Lombardo R, Musumeci T, Carbone C, Pignatello R. Nanotechnologies for intranasal drug delivery: an update of literature. Pharm Dev Technol. Pharm Dev Technol. 2021;26(8):824-845.
22. Vonarburg C, Loetscher M, Spycher MO, Kropf A, Illi M, Salmon S, Roberts S, Steinfuehrer K, Campbell I, Koernig S, Bain J, Edler M, Baumann U, Miescher S, Metzger DW, Schaub A, Kasermann F, Zuercher AW. Topical application of nebulized human IgG, IgA and IgAM in the lungs of rats and non-human primates. Respir Res. 2019;20(1):99. [PubMed] [Google Scholar]
23. Maigler F, Ladel S, Flamm J, Gänger S, Kurpiers B, Kiderlen S, Völk R, Hamp C, Hartung S, Spiegel S, Soleimanizadeh A, Eberle K, Hermann R, Krainer L, Pitzer C, Schindowski K. Selective CNS targeting and distribution with a refined region-specific intranasal delivery technique via the olfactory mucosa. Pharmaceutics. 2021;13(11):1904. [PubMed] [Google Scholar]
24. Ladel S, Flamm J, Zadeh AS, Filzwieser D, Walter JC, Schlossbauer P, Kinscherf R, Lischka K, Luksch H, Schindowski K. Allogenic Fc domain-facilitated uptake of IgG in nasal lamina propria: friend or foe for intranasal CNS delivery? Pharmaceutics. 2018;10(3):107. [PubMed] [Google Scholar]
25. Alberto M, Paiva-Santos AC, Veiga F, Pires PC. Lipid and Polymeric Nanoparticles: Successful Strategies for Nose-to-Brain Drug Delivery in the Treatment of Depression and Anxiety Disorders. Pharmaceutics. 2022;14(12):2742.
26. Higgins TS, Wu AW, Illing EA, Sokoloski KJ, Weaver BA, Anthony BP, Hughes N, Ting JY. Intranasal antiviral drug delivery and coronavirus disease 2019 (COVID-19): a state of the art review. Otolaryngol Head Neck Surg. 2020;163(4):682-94. [PubMed] [Google Scholar]
27. Forbes B, Bommer R, Goole J, Hellfritzsch M, De Kruijf W, Lambert P, Caivano G, Regard A, Schiaretti F, Trenkel M, Vecellio L, Williams G, Sonvico F, Scherließ R. A consensus research agenda for optimising nasal drug delivery. Expert Opin Drug Deliv. 2020;17(2):127-32. [PubMed] [Google Scholar]
28. Clementino AR, Pellegrini G, Banella S, Colombo G, Cantù L, Sonvico F, Del Favero E. Structure and fate of nanoparticles designed for the nasal delivery of poorly soluble drugs. Mol Pharm. 2021;18(8):3132-46. [PubMed] [Google Scholar]
29. Bicker J, Fortuna A, Alves G, Falcão A. Nose-to-brain delivery of natural compounds for the treatment of central nervous system disorders. Curr Pharm Des. 2020;26(5):594-619. [PubMed] [Google Scholar]
30. Egla M, Al Hammid SN. Design zolmitriptan liquisolid orodispersible tablets and their in vitro evaluation. Int J Pharm Pharm Sci. 2017;9(1):297-303. [Google Scholar]
31. Giuliani A, Balducci AG, Zironi E, Colombo G, Bortolotti F, Lorenzini L, Galligioni V, Pagliuca G, Scagliarini A, Calza L, Sonvico F. In vivo nose-to-brain delivery of

ISSN: 2278-2044
DOI: https://doi org/10.24321/2278.2044.202512

the hydrophilic antiviral ribavirin by microparticle agglomerates. Drug Deliv. 2018;25(1):376-87. [PubMed] [Google Scholar]
32. Marcello E, Chiono V. Biomaterials-Enhanced Intranasal Delivery of Drugs as a Direct Route for Brain Targeting. Int J Mol Sci. 2023;24(4):3390. [PubMed] [Google Scholar]
33. Moinuddin S, Razvi SH, Uddin MS, Fazil M, Shahidulla SM, Akmal MM. Nasal drug delivery system: a innovative approach. Pharm Innov J. 2019;8(3):169-77. [Google Scholar]
34. Attri K, Singh M, Sharma K, Srivastav S, Sharma L, Bhalla V. A review on recent trends in nasal drug delivery system. Ann Rom Soc Cell Biol. 2022;26(1):1038-56. [Google Scholar]
35. Mignani S, Shi X, Karpus A, Majoral JP. Non-invasive intranasal administration route directly to the brain using dendrimer nanoplatforms: an opportunity to develop new CNS drugs. Eur J Med Chem. 2021;209:112905. [PubMed] [Google Scholar]
36. Ladel S, Schlossbauer P, Flamm J, Luksch H, Mizaikoff B, Schindowski K. Improved in vitro model for intranasal mucosal drug delivery: primary olfactory and respiratory epithelial cells compared with the permanent nasal cell line RPMI 2650. Pharmaceutics. 2019;11(8):367. [PubMed] [Google Scholar]
37. Savale S, Mahajan H. Nose to brain: a versatile mode of drug delivery system. Asian J Biomater Res. 2017;3(1):16-38. [Google Scholar]
38. Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA, Alexander A. Nose-to-brain drug delivery: an update on clinical challenges and progress towards approval of anti-Alzheimer drugs. J Control Release. 2018;281:139-77. [PubMed] [Google Scholar]
39. Rao M, Agrawal DK, Shirsath C. Thermoreversible mucoadhesive *in situ* nasal gel for treatment of Parkinson's disease. Drug Dev Ind Pharm. 2017;43(1):142-50. [PubMed] [Google Scholar]
40. Vasantha PV, Sherafudeen SP, Rahamathulla M, Mathew ST, Murali S, Alshehri S, Shakeel F, Alam P, Sirhan AY, Iyer BA. Combination of cellulose derivatives and chitosan-based polymers to investigate the effect of permeation enhancers added to *in situ* nasal gels for the controlled release of loratadine and chlorpheniramine. Polymers (Basel). 2023;15(5):1206. [PubMed] [Google Scholar]
41. Mathure D, Ranpise H, Awasthi R, Pawar A. Formulation and characterization of nanostructured lipid carriers of rizatriptan benzoate-loaded *in situ* nasal gel for brain targeting. Assay Drug Dev Technol. 2022;20(5):211-24. [PubMed] [Google Scholar]
42. Giuliano E, Paolino D, Cristiano MC, Fresta M, Cosco D. Rutin-loaded poloxamer 407-based hydrogels for *in situ* administration: stability profiles and rheological properties. Nanomaterials (Basel). 2020;10(6):1069. [PubMed] [Google Scholar]
43. Abdeltawab H, Svirskis D, Sharma M. Formulation strategies to modulate drug release from poloxamer based *in situ* gelling systems. Expert Opin Drug Deliv. 2020;17(4):495-509. [PubMed] [Google Scholar]
44. Jelkmann M, Leichner C, Zaichik S, Laffleur F, Bernkop-Schnürch A. A gellan gum derivative as in-situ gelling cationic polymer for nasal drug delivery. Int J Biol Macromol. 2020;158:1037-46. [PubMed] [Google Scholar]
45. Ramachandran S, Shanmugapriya E, Vigneshwara KT, Tamilselvan M, Sursha V. Novel drug delivery system through nasal (non-invasive). Asian J Pharm Clin Res. 2018;11(4):33-7.
46. Prajapati B, Patel R, Dharamsi A. Intranasal drug delivery system- an overview. Eur J Pharm Med Res. 2017;4(7):277-9.
47. Alnasser S. A review on nasal drug delivery system and its contribution in therapeutic management. Asian J Pharm Clin Res. 2019;12(1):40.

ISSN: 2278-2044
DOI: https://doi org/10.24321/2278.2044.202512