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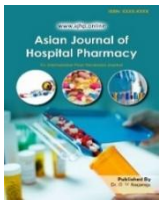

# REVIEW ON THE MEDICATION TRABSOIRT MECHANISM FROM NOSE TO BRAIN

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**Abstract**

This review focuses on the nose-to-brain drug delivery system, a promising approach for treating central nervous system (CNS) disorders by bypassing the blood-brain barrier (BBB). The BBB prevents many therapeutic agents from reaching the brain, complicating treatments for diseases like Alzheimer's, Parkinson's, and other neurological disorders. By utilizing the nasal route, drugs can directly access the brain through the olfactory and trigeminal nerve pathways, ensuring more effective delivery while minimizing systemic side effects. The review discusses various drug delivery systems, such as liposomes, solid lipid nanoparticles, dendrimers, and polymeric nanoparticles, which enhance drug solubility, targeting, and bioavailability. These systems are particularly suitable for nose-to-brain delivery, with nanotechnology playing a crucial role in overcoming biological barriers and ensuring sustained or controlled drug release. Despite these advancements, challenges like toxicity, scalability, and regulatory concerns remain. Preclinical models, including in silico, in vitro, ex vivo, and in vivo studies, are vital to understanding how drugs interact with the nasal mucosa and are transported to the brain. These models help optimize formulations and improve drug absorption and brain targeting. Looking ahead, advancements in delivery devices and formulations will be crucial for improving the efficiency and reliability of nasal drug delivery. Innovations such as stimuli-responsive nanocarriers, mucoadhesive formulations, and nasal in situ gels show promise in enhancing drug retention and controlled release. In conclusion, while nose-to-brain drug delivery offers great potential for treating CNS disorders, addressing challenges related to formulation, device development, and regulatory approval will be key to realizing its full of clinical potential.

***Keywords:*** In situ gel, neural pathways, nose to brain drug delivery, olfactory neural pathway, trigeminal neural pathway, vascular pathway



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## Introduction

Nose to brain drug delivery system is an interesting approach to deliver a drug directly in the brain through the nose. Intranasal drug delivery is very beneficial because it avoids first-pass metabolism and achieves a greater concentration of drugs in the central nervous system (CNS) at a low dose.[1] The brain is one of the most intricate and important organs in the body; it processes information received from the sense organs and controls the majority of the body's functions. Movements, both voluntary and involuntary, the release of hormones, the storing of memories, and the operations of many other organs are all under its command. Because it plays such an important part in the functioning of the human body, the brain is guarded both on the outside and the inside. Cerebrospinal fluid (CSF), the CSF- blood barrier, and the blood-brain barrier (BBB) all work together to provide an additional layer of defence for the brain, in addition to the protection provided by the skull's multiple layers of membranes that prevent injury from the outside environment. These barriers contribute to the homeostasis of the brain and help prevent any ill consequences, including damage to the tissue, infections, endotoxins, and other potentially dangerous substances [2]. These debilitating neurological conditions can be treated with a variety of various medicinal medicines that have been developed by researchers. However, the primary purpose of these medications is to slow down the progression of sickness; they are not capable of entirely reversing the condition [3]. The presence of the blood-brain barrier (BBB), which prevents more than 98% of neuroherapeutic compounds from entering the central nervous system (CNS) [4]

## Anatomy and Physiology Nose

The human nasal region is split into two sides by a septum and has a total capacity of 16 to 19 mL and around 180 cm2. Each hole has a capacity of around 7.5 mL and a surface area (SA) of more than 75 cm2. After the drug delivery in the nasal cavity, the solute may pass through one or more distinct areas, such as vestibular, respiratory, and olfactory (Fig 01). In addition to the bordered by a ciliated pseudostratified columnar epithelium called respiratory epithel The low viscosity periciliary layer grows 3 -5 m thick and includes the motile cilia (2-4 m long), and the underlying viscous gel layer, which broadens 2 -4 m in thickness, is present on the respiratory epithelium [5].

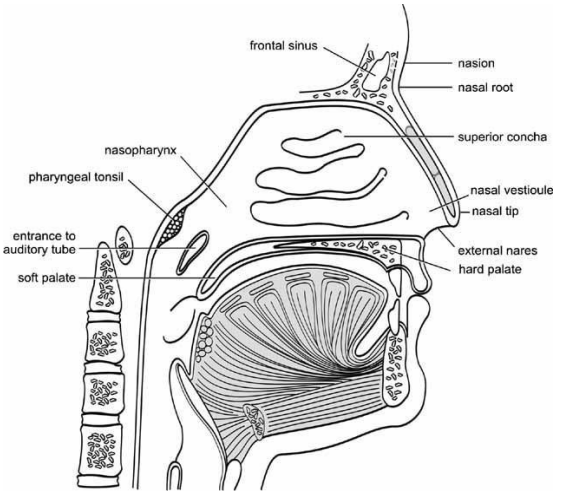



Fig 01: Anatomy of nasal cavity

## Different Pathways from Delivery System

### Olfactory Region (Major Pathway)

Olfactory neural pathways, drug material is travelled from the olfactory region in the nasal cavity to CSF or brain parenchyma, It is also transverse to the nasal olfactory epithelium. In this pathway, the arachnoid membrane surrounding the subarachnoid space having three different pathways across the olfactory epithelium, first is transcellular pathways especially across the Sustentacular cells were receptor mediated endocytosis, fluid phase endocytosis or the passive diffusion for the lipophilic drugs is mediated rapidly and at a high rate. Drugs with a molecular weight in the range between 300 - 1000 Dalton shows good bioavailability without absorption enhancer. [6]

### Trigeminal pathway (Major pathway)

The drug enters the olfactory bulb via the olfactory epithelium in the trigeminal pathway, innervated by the trigeminal nerve, the largest cranial nerve. The trigeminal nerve leads to ganglion to CNS. The nerve enters the cerebrum through the anterior lacerated foramen close to the pons and cribriform plate close to the olfactory bulbs [7].

### Vascular Pathway

Pharmaceutical or Therapeutic agents is transported in nose to brain through the blood vessels supplying the nasal cavity to systemic circulation following the nasal administration. The olfactory mucosa was received blood from the anterior and posterior ethmoidal artery (smallest artery of ocular cavity), where the respiratory mucosa is received the blood from the sphenopalatine artery The relative density of the blood vessels is greater in the respiratory mucosa than the olfactory mucosa, making the former an ideal region for adsorption of drug into the systemic circulation.olfactory mucosa, and receives blood from the anterior and posterior ethmoidal arteries, which are the smallest arteries in the ocular cavity. [8]

## Types of Formulation Used Nasal

### Nanoparticles

To address the very low drug transfer levels seen with conventional solution nasal formulations, drug delivery experiments have been conducted with nanoparticulate formulations (nano emulsions, lipids, or polymer particles).. Others found that nano emulsion particles of 100 nm penetrated the olfactory bulb and could be found in the brain to a small extent while particles of 900 nm did not penetrate the brain at all. The nano emulsion cargo was distributed throughout the brain with the 100 nm emulsion droplets [9].

For Example, Lorazepam nanopartical.

### Lipid Nanoparticle

They are solid structures called lipid nanoparticles, which offer a cool alternative to other types of nanoparticles—like polymeric ones, nanogels, & nanoemulsions. The size of these lipid nanoparticles is super tiny too! They can be anywhere from 1 to 1000 nanometers in size[27].Since the surface of these solid lipid nanoparticles is made from safe lipids and surfactants, people generally say they're okay for our bodies. Common lipids include thingslike triglycerides, monoglycerides, diglycerides, fatty acids, & waxes [10].

### Liposomes

One of the most popular lipid-based NPs for drug delivery applications is liposomes. A liposome normally consists of one or more phospholipid bilayers, frequently combined with additional lipids like phosphatidylcholine or cholesterol. The size and surface charge of liposome membranes can be changed by utilizing different kinds of lipids. For example, hydrophilic (located inside the aqueous core) or hydrophobic (located inside the lipid membrane) active substances can both be included in neutral or slightly negatively charged liposomes. On the other hand, negatively charged nucleic acid and positively charged liposomes can create multiplexes [11].

## Nanoemulsions

Three phases make up the micelles that comprise nanoemulsions: an oily phase, an emulsifier, and an aqueous phase. There are three distinct types of nanoemulsions: bi- continuous (inter-dispersed water and oil domain), water in oil (sometimes called "reversed" micelles), and oil in water.[12] Particularly for lipophilic medications, nanoemulsions can increase the drug's stability and bioavailability while increasing drug absorption through a larger surface area from nano-sized droplets [13].

### Ligand Based Approach

A suitable ligand-based approach utilizes crossing the BBB without causing injury, which can carry and circulate medicines or possibly hereditary material into Aluminium cross linked gel, monomer gels, Inorganic gels. the lesioned brain. In the ligand-based approach, specific ligands are employed to enhance the targeting of therapeutic agents to the brain. Ligands are molecules that have a high affinity and selectivity for a particular receptor or protein.

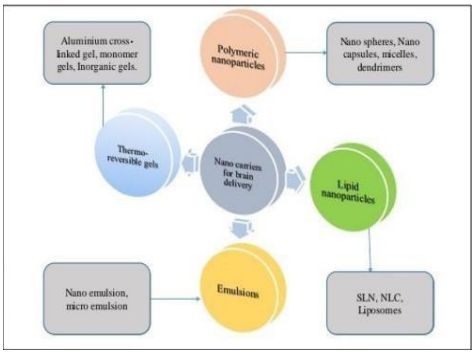



Fig 02: Type of nanocarriuers

## Polymers and Nanocarriers Used For the Nasal Drug Delivery System

### Carbopol

It is a polymer made of polyacrylic acid which forms gel at nasal pH level when pKa surpassed which is approximately 5.5. These polymers convert itself into a soul-to-gel when they are exposed to a pH of 4.0–6.0 due to their pKa of 6.0. It get expand in water up to 1000 times their original volume and by 10 times their original diameter. The polymer expands when the pH of the solution rises since it is a pH-sensitive polymer. Triethanolamine, sodium hydroxide, or potassium hydroxides are used to counteract the gelling effect.

### Chitosan

Chitosan, a cationic polymer that is pH-dependent, is an amine-polysaccharide. Chitosan transforms into a pH-sensitive gel when it is combined with poly salts which have a single anionic head for ex-glucose phosphate salts.

### Pectin

The amount of galacturonic acid is the primary component of pectin that has been methoxylated. The degree of methoxylation impacts how well pectin works. Low methoxylated pectin in aqueous solution converted in to gel when the carboxyl groups on the backbone of the pectin make contact with Ca2+, an “egg box” structure is produced.

### Thermo Sensitive Polymers Used in Situ Gelling System

Thermo-sensitive polymers react to little external changes in their environment and go through significant and unanticipated physical and chemical changes. They undergo considerable and unwanted physicochemical changes in response to environmental changes. This system becomes gels when the temperature changes, continuing the medication release.. Gels with a positive thermosensitive sign (+): This type of method has higher critical solution temperature and becomes hydrogel when the upper critical solution temperature is lowered. Gels with negative thermosensitive sign: These are a system that has a lower critical solution temperature (LCST) and contract when heated over the LCST [14].

### Poloxamer

It is a tri-block copolymer soluble in water.[37] Studies of dynamic light scattering and ultrasonic velocity on the poloxamer 407 solutions reveal that aqueous poloxamer solutions convert into a gel as a result of inherent changes in micellar properties [15].

### Ethyl (Hydroxyethyl) Cellulose (HEC)

The hydrophilic and hydrophobic unit structure in the polymer backbone of HEC is distributed erratically. HEC is a non-ionic amphiphilic polysaccharide [39].

### Ion-Activated In Situ Gel

These types of in situ gel cause gelation due to the phase transition in the presence of ions. An anionic polysaccharide (gellan gum) undergoes a phase change when monovalent and divalent cations (Ca2 +, Mg2 +, K+, and Na+) are present in the nasal discharge [16].

### Gellan Gum

Before being used commercially, an anionic exocellular polysaccharide known as gellan gum goes through complete de-esterification during alkali treatment. The gelation process of gellan gum includes two steps [17].

### Ionic Crosslinking

Polymers may transit into another phase when certain ions are present. Ion-sensitive polysaccharides are a category of polysaccharides.

For example, Gellan gum, a commercially available anionic polysaccharide also known as Gelrite® which solidifies in the presence of monovalent and divalent cations (Ca2 +, Mg2 +, K+, and Na+).

## Method of Formulation

### Cold Method

This process involves mixing the drug with a sufficient volume of double-distilled water and cooling it down to 4°C overnight. The in situ gelling polymer is gradually added and continuously agitated. After that, the prepared dispersion solution is refrigerated until a solution becomes clear. Due to the precipitation reaction polypropylene oxide chain in the poloxamer diminishes at high temperatures which leads to precipitation [18].

### Hot Method

The hot method is used for the polymers such as pectin or gellan gum. The sol-gel transformation occurs on the cooling of the gellan gum solution due to the presence of K+ or Ca2+ ions. Similarly, in the case of pectin, it requires a higher temperature for de-methoxylation, which promotes the solubility or dissolution of the pectin

For example, Gellan gum, a commercially available anionic polysaccharide also known as Gelrite® which solidifies in the presence of monovalent and divalent cations (Ca2 +, Mg2 +, K+, and Na+)

## Evaluation Parameters of Intra Nasal Solutions

Tab 01: Evaluation Parameters Intra Nasal Solutions

| Sr. No | Parameter | Instrument/Equipment |
|---|---|---|
| 1. | Appearance, Colour, Clarity | Visual Detection |
| 2. | In-vitro Diffusion Studies | Nasal Diffusion Cell, |
| 3. | Drug Content | U.V. Spectrophotometer. |
| 4. | In-Vivo Nasal Absorption Studies | Rat, Rabbit, Monkey & Dog Model |
| 5. | Rheological Property | Brook-Field Viscometer |
| 6. | Gelation Temperature | Thermometer |
| 7. | Flammability and Combustibility<br>a) Flash Point<br>b) Flash Projection | a) Open cup tag apparatus<br>b) Product Spray on flame |

## Marketed Formulation of Nasal Drug

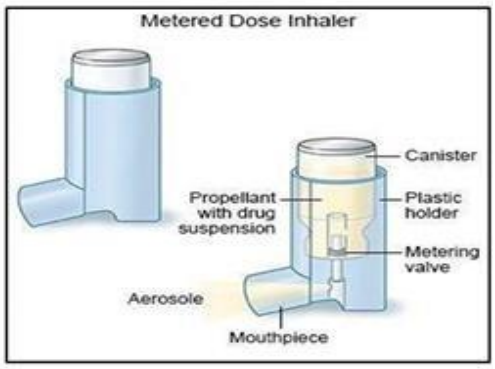
### Nasal Drug Delivery Devices

### A) Metered-dose pump sprays

- Marketed nasal formulation such as suspension, emulsion, solution are directly delivered to intranasal pathway by using metered dose pump sprays
- Disease Condition: nasal hypersensitivity and other nasal disorders, topical decongestants, antihistamine [19].

Fig 03: Metered Dose Inhaler8.Future Prospects

Drug delivery methods that are currently accessible are




not widely accepted or complied. Improved solubility or stability, enhanced bioavailability, and biological half-life are the present needs of industry.[46] Targeted delivery methods that take advantage of the drug's capacity for variation to boost efficacy and decrease negative effects

1. Biotechnology and advanced technologies are being used in new macromolecule delivery methods
2. Consolidated or enhanced nasal drug formulations
3. Integrated device development for effective therapeutic drug delivery [20].

## Conclusion

Recent advancements in drug delivery have improved brain-targeted therapies by utilizing the permeability of brain injuries and novel techniques like MEUS and TMS. Traditional methods, including viral vectors and nanoparticles, remain essential, while innovative approaches enhance diagnostics and treatment. Understanding the brain's leaky barrier has enabled the application of nanoparticles originally designed for tumor targeting via the EPR effect to brain diseases. Gliomas, with their heterogeneous permeability, may require combined strategies to penetrate both permeable and normal regions effectively. Another crucial research area is the impact of aging on brain dysfunctions.

## Author Contributions

All authors are contributed equally

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None

## Declaration of Competing Interest

The Authors have no Conflicts of Interest to Declare.

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