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# Nose-to-brain drug delivery: a short review of the available systems and their applications

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## ABSTRACT

The brain is a crucial organ that controls most bodily functions; however, its protection by the blood-brain barrier (BBB) makes drug delivery to the brain difficult. The BBB prevents most drugs from entering the brain, which is a challenge for treating neurological diseases such as Parkinson disease, Alzheimer disease, multiple sclerosis, and stroke. The nasal-to-brain delivery route is a promising, non-invasive method to bypass the BBB, offering a direct connection between the nasal cavity and the central nervous system. This short review is focusing on ways through which drugs can reach the brain *via* the olfactory nerve, and the strategies to improve drug delivery through the intranasal route. In addition, it discusses the advantages and limitations of this type of drug administration and the recent formulations and applications of intranasal drug delivery with examples. Intranasal drug delivery holds great promise for treating neurological diseases and other conditions such as pain and cancer, and also provides a mean for reusing drugs that otherwise fail to reach the brain through the BBB. However, further developments in terms of the used formulations and the overcoming of challenges relating to absorption and mucosal irritation are essential for its widespread use in clinical settings.

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## 1. Introduction

The brain, a highly complex and vital organ, processes sensory information and controls body functions[1]. The blood-brain barrier (BBB) is a unique microvascular system in the brain that controls the movement of ions, molecules, and cells between the blood and the brain. The BBB restricts the passage of toxins and pathogens, but is also a major barrier to the delivery of therapeutic drugs, with

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98% of small molecules and almost all macromolecules being unable to do so[2]. There are many neurological diseases that require treatment where drugs must reach the brain, such as neuroinfections, Parkinson disease, Alzheimer disease, multiple sclerosis, age-related neurodegenerative diseases, and cerebral ischaemia. The nasal-to-brain route offers a non-invasive method to bypass the BBB, leveraging the direct anatomical link between the nasal cavity and the central nervous system (CNS). This makes nasal formulations a promising strategy for targeted brain drug delivery. Indeed, it is well known that the nasal cavity and the CNS are anatomically directly linked, suggesting the development of nasal formulations for brain targeting[3].

The aim of this short review is to discuss how drugs can reach the brain *via* the olfactory nerve, and the strategies to improve drug delivery through the intranasal route. In addition, it discusses the advantages and limitations of this type of drug administration as well as the recent formulations and applications of intranasal drug delivery systems.

## 2. Pathways for the achievement of nose-to-brain drug delivery

The nasal cavity is divided by the nasal septum into two halves, each containing three zones: the nasal vestibule, the respiratory zone, and the olfactory zone. The nasal vestibule is the nose's entrance, while the respiratory zone covers most of the nasal surface. The olfactory zone, located on the nasal cavity's roof about 7 cm from the nostrils, contains olfactory nerves that bypass the BBB, providing direct access to the CNS. One route is systemic absorption from the respiratory zone, whereby drugs are taken into the systemic circulation and then pass through the BBB to the brain (especially lipophilic drugs). The other route is through the olfactory and trigeminal pathways, where drugs are transported directly from the nasal cavity to the CNS (cerebrospinal fluid and brain tissue)[4]. The mechanisms by which drugs that pass through the olfactory membrane reach the CNS are different. The first mechanism involves the drug migrating directly to the primary neurons in the olfactory epithelium, being transported to the olfactory bulb *via* an intracellular axonal transport, and then being distributed to more distant brain tissues. A second mechanism is through the penetration of drugs into olfactory epithelial cells by transcellular or paracellular mechanisms and, subsequently, through uptake by the CNS[5].

## 3. Strategies to improve drug delivery to the brain

Two main approaches can be used in order to bypass the BBB: invasive and non-invasive. Invasive techniques involve direct injection of the drug into the brain parenchyma or the cerebrospinal fluid or the therapeutic opening of the BBB. The direct injection or the implantation of drugs into the brain parenchyma has been studied in order to treat neurological and mental disorders as well as stroke. However, a direct injection can be less efficient because of limited diffusion between the cerebrospinal and the extracellular fluids. In addition, there can be potential risks of brain tissue damage and significant fluctuations in intracranial pressure as a result of such invasive techniques[6]. Non-invasive methods utilize endogenous cellular mechanisms in order to facilitate the transport of drugs into the CNS through transcellular pathways. Non-invasive strategies include the nose-to-brain route of administration, the inhibition of efflux transporters, the development of prodrugs and chemical drug delivery systems, and the application of nanocarriers[7]. The intranasal drug delivery approach offers more advantages over the other methods.

## 4. Advantages and limitations of the intranasal drug delivery approach

Some intranasal drug delivery systems can bypass the BBB, offering direct drug delivery to the brain with several advantages, such as a large surface area, the ease of self-administration, the avoidance of hepatic first-pass metabolism, the utilization of a highly vascular mucosa, and increased absorption[8]. However, challenges include the limited drug absorption

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**Table 1.** Different formulations for nose-to-brain drug delivery, with specific examples and advantages.

| Formulation strategy | Description | Preclinical applications | Advantages |
|---|---|---|---|
| Solution | drug dissolved in an aqueous solution and administered *via* nasal delivery devices | insulin delivery to the brain; oxytocin delivered with a $C_{max}$ of 0.003% of a 10-g dose | simple and effective for small molecules; allows direct brain targeting |
| *In situ* gelling systems | systems that transition from fluid to gel upon exposure to environmental stimuli (e.g., temperature, pH) | amantadine, levodopa, and ropinirole have been delivered *via* intranasal *in situ* gelling systems | high compatibility with a wide range of drugs; controlled release |
| Nanoparticles | colloidal solid particles ranging from 1 to 1000 nm that enhance mucosal penetration | nanoparticles used for immune delivery *via* the nasal route | small size enables transport through tight junctions in the mucosa, thereby enhancing delivery efficiency |
| Lipid-based nanoparticles | colloidal systems composed of lipids, oils, surfactants, and additives like nanoemulsions and liposomes | used for efficient nose-to-brain drug delivery | improved stability and enhanced brain targeting for a variety of drugs, including soluble and insoluble ones |

and penetration, a variability in absorption due to the nasal anatomy and mucosal differences, and a short duration of action requiring frequent dosing. Additionally, nasal irritation, dryness, and mucosal damage may occur, thereby affecting absorption and patient comfort. These limitations must be addressed in order to optimize therapeutic efficacy and patient tolerance[9].

## 5. Recent formulations and applications

Generally, the most frequently used formulation for the administration of drug molecules through the nose to the brain is the solution. The drug is usually dissolved in an aqueous solution and administered through the nose. The solution is usually given through a nasal delivery device. One of the first studies on peptide delivery to the brain has attempted the delivery of insulin through the nose to the brain. Oxytocin has also been delivered to the brain *via* the nose in solution form[4].

*In situ* gelling systems are undergoing a left-to-gel transition at the site of administration. They are fluid prior to administration and with the help of environmental stimuli (such as temperature, pH, ionic shift, magnetic field or other biological backgrounds) undergo a left-to-gel transition. Therefore, they are highly compatible with a wide range of drugs, including soluble and insoluble ones as well as low and high molecular weight ones.

Nanoparticles are colloidal solid particles that offer advantages over other delivery techniques due to their small size. Furthermore, only the smallest nanoparticles can pass through the mucosa by extracellular transport through tight junctions. As a result, nanoparticles are considered the most suitable technology for nasal antigen delivery.

Finally, lipid-based nanoparticles are colloidal systems composed of lipids, oils, surfactants, and other additives (including nanoemulsions, liposomes, and solid lipid nanoparticles). They have attracted great interest as a promising approach for nasal-to-brain drug delivery[10]. Table 1 provides an overview of different formulations assessed for nose-to-brain drug delivery, with specific examples and advantages.

## 6. Conclusion

The nose-to-brain drug delivery holds significant

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potential for treating neurological diseases by bypassing the BBB. However ongoing research and development are needed in order to optimize formulation strategies, improve absorption efficiency, and address challenges such as mucosal irritation. With continued innovation, this method could become a valuable tool in the treatment of brain-related conditions.

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**Conflicts of interest**

None exist.

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