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Fabricating description and importance of nasal drug delivery system

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Abstract
The central nervous system disorders have always been a mystery and remain as a challenge in presence of the blood brain barrier. The presence of BBB restricts the entry of external material including medicines into the brain tissue. The present day's advancement in the drug delivery system is trying to overcome the limited therapeutic effect imposed by the blood brain barrier. In the present scenario the intranasal route has emerged as the promising resolution for the delivery of drug to overcome the barrier. The utilization of lipid based nanoparticles like micro emulsions, nano-structured lipid carriers, liposomes, and solid lipid nanoparticles helps in achieving the enhancement in efficacy of nose to brain delivery. This is being made possible by increasing the drug absorption from the nasal membrane through nano particles. Moreover, in situ gel system have extended the retention time of the administered drug within the nasal cavity for prolonged therapeutic effect. Additionally combining the in situ gel system with the lipid based nano particles results in synergistic effect with overall enhancement of efficacy. The present review work focuses on the importance of nasal drug delivery system in treatment of CNS related disorders.

Keywords: Intranasal, nano particles, efficacy, blood brain barrier, central nervous system

Introduction
Nasal drug delivery offers significant benefits compared to other methods, as it bypasses the hepatic first-pass effect, penetrates the blood-brain barrier, and addresses patient compliance issues associated with parenteral administration [1-2]. While this method is regarded as one of the most effective routes for drug delivery, it does have limitations, including low bioavailability due to metabolism occurring on the mucosal surface. The early 1980s marked the emergence of the nasal route as a promising systemic delivery alternative to traditional drug delivery methods [3]. However, it can sometimes lead to irreversible damage to the nasal mucosa due to the ingredients used in formulations. The nasal passage serves as one of the sensory organs yet is considered as valuable route of drug administration due to high permeability of nasal mucosa and high vascularization in comparison to other routes [4]. Nasal passage is covered entirely by the mucus membrane although the mucociliary clearance poses the significant obstruction in systematic delivery of the drug through nasal cavity [5-6].

The candidates for drug development must exhibit certain fundamental traits to qualify for the nasal drug delivery system. A key requirement is adequate aqueous solubility to ensure the desired dosage can be administered in a volume of 25–150 ml per nostril. Additional criteria for a candidate to be appropriate for nasal delivery include: suitable nasal absorption properties, absence of nasal irritation caused by the drug, no toxic nasal metabolites, a low dosage (under 25 mg per dose), no unpleasant odors or aromas linked to the drug, as well as possessing appropriate stability characteristics and a rapid onset of action [12].

Table 1: Highlights the Advantages and Disadvantages of Nasal Drug Delivery [7-11]

S. No.	Merits	Demerits
1.	Rapid onset of action	Low bioavailability
2.	High rate of absorption	Drug elimination
3.	Self-administration by patients	Loss of drug dosage due to improper usage
4.	Direct nose-to-brain delivery	Restricted dosage
5.	Less drug degradation	The condition of the nasal cavity influences the absorption of medications
6.	High patient compliance	Permanent damage to the nasal mucosa
7.	Non-invasive drug delivery	The volume delivered to the nasal cavity is limited to 25–200 µL
8.	No intricate formulation requirements are necessary	Compounds with high molecular weight cannot be administered via this route (mass cut off ~1 kDa)
9.	Offers lower risk of overdose	Pathological conditions negatively impact this route
10.	Direct delivery into systemic circulation and CNS is achievable	Significant variability between species is noted in this method
11.	Adverse effects are minimized due to the low dosage	Normal defense mechanisms such as mucociliary clearance and ciliary movement influence the permeability of the drug
12.	Improved bioavailability	Irritation of the nasal mucosa caused by drugs like Budesonide and Azilactine
13.	An accessible pathway for the patient over an extended period therapy	The occurrence of systemic toxicity due to absorption enhancers has not yet been confirmed
14.	An alternative to the parenteral route, particularly for proteins and peptides	A limited understanding of mechanisms and underdeveloped models at this point
15.	Drugs that are not suitable for oral administration can be effectively delivered through the nasal route	Enzymatic barriers hinder the permeability of the drug

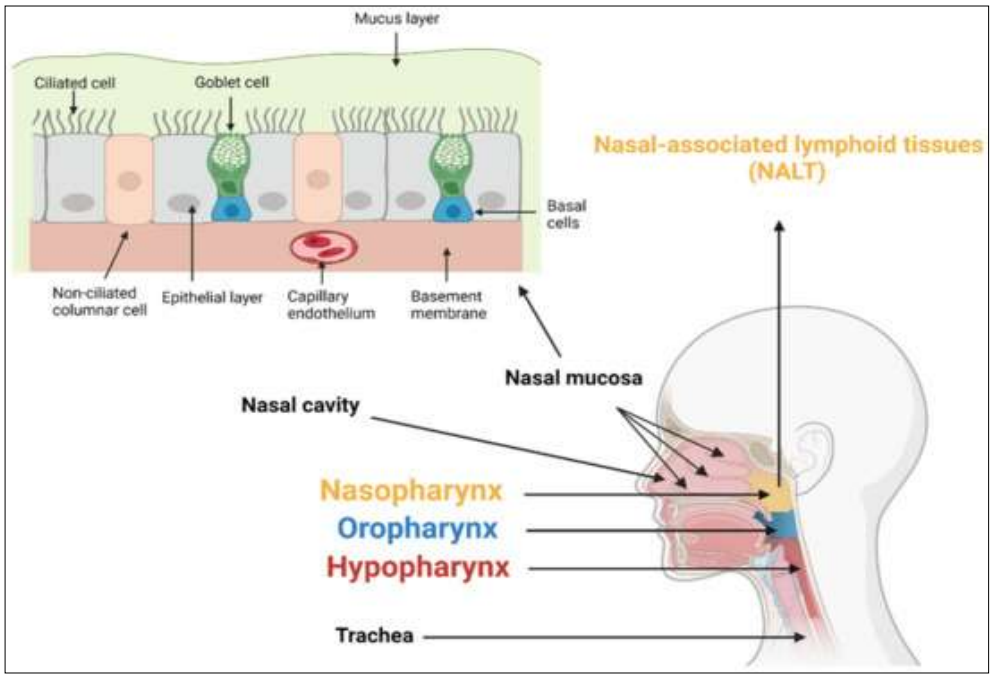

Fig 1: Schematic diagram of the nose, including the main cell types, and characteristic absorption barriers

The structure and function of the nasal passage are critically significant. They determine whether nasal drug delivery can be achieved. Numerous factors can influence the nasal passage and affect effective drug delivery via this route. The nasal cavity extends from the nasal vestibule to the nasopharynx, measuring approximately 12-14 cm in depth. In an adult human, the total surface area of the nasal cavity is around 150 cm^2, with a total volume of about 15 ml [13]. Each of the two nasal cavities can be divided into various regions: the nasal vestibule, inferior turbinate, middle turbinate, superior turbinate, olfactory region, frontal sinus, sphenoidal sinus, and the cribriform plate of the ethmoid bone. Additionally, the nasal cavity houses the nasal associated lymphoid tissue (NALT), primarily located in the nasopharynx. The lining of the nasal cavity consists of a mucus layer and cilia, which play a role in trapping inhaled particles and pathogens. Furthermore, essential functions of the nasal structures include mucociliary clearance, immunological responses, and the metabolism of endogenous substances [14].

Factors affecting nasal drug absorption

Several elements influence the bioavailability of drugs administered through the nasal route, which are detailed as follows [15-24]

I Biological Factors

- Structural characteristics
- Biochemical alterations

II Physiological Factors

- Blood circulation and neuronal control

- Nasal secretions
- Mucociliary clearance and ciliary beating frequency
- Pathological states
- Environmental factors
- Membrane permeability

III Physicochemical Properties of Drugs

• Molecular weight
- Size
- Solubility
- Lipophilicity
- pKa and partition coefficient
- Chemical form of the drug
- Polymorphism
- Chemical state
- Physical state

IV Physicochemical Properties of Formulation

- Physical form of the formulation
- pH
- Osmolarity
- Volume of the solution applied and drug concentration
- Viscosity

The nasal drug delivery system has numerous applications for treating various CNS disorders, including Parkinson's disease, Alzheimer's disease, depression, brain stroke, and epilepsy. Brain-targeted nasal drug delivery offers significant potential for preventing and treating CNS diseases. By delivering drugs through the nasal cavity, they can directly access the brain, enhancing their effectiveness while minimizing side effects. Additionally, this method can improve patients' cognitive abilities, emotional well-being, and overall quality of life. Consequently, brain-targeted nasal drug delivery is poised to become a crucial approach in the prevention and treatment of CNS disorders.

Table 2: Application of brain-targeted nasal drug delivery in CNS diseases [25-41]

S. No.	Disease	Category	Drug Utilized By Nasal Drug Delivery
1.	Epilepsy	Neurological diseases	• Perampanel • Carbamazepine • Midazolam
2.	Parkinson's disease	Movement disorders	• Haloperidol • Rotigotine • Gangliosides • Rasagiline
3.	Alzheimer's disease	Cognitive dysfunction diseases	• Insulin • Oxytocin • Resveratrol
4.	Depression	Mental illness	• Sertraline • Esketamine • Quercetin
5.	Brain stroke	Cerebrovascular diseases	• BDNF • Valsartan • Salvinorin A

There are large numbers of CNS related conditions that are being treated through nasal drug delivery system. However, there is a large possibility to deliver proteins, peptides and non peptides substances thorough this route without any adverse drug effects. The spray solution is the best formulation system that can be used for the administration of the drugs to overcome the conditions like endometriosis, osteoporosis and migraine etc with better patience compliance.

Table 3: Nasal drug products (proteins, peptides and Non peptide) for systemic drug delivery in the market [24]

S. No.	Drug Substance	Product name	Dosage form	Manufacturer	Therapeutic Use	Status
1.	Salmon calcitonin	Karil 200	Solution (spray)	Novartis Pharma	Osteoporosis	Marketed
2.	Buserelin	Profact	Solution (spray)	Aventis Pharma	Buserelin	Marketed
3.	Desmopressin	Minirin	Solution (spray)	Ferring Arzneimitted	Antidiuretic hormone	Marketed
4.	Nafarelin	Synarela	Solution (spray)	Pharmacia	Endometriosis	Marketed
5.	Oxytocin	Syntocinon	Solution (spray)	Novartis Pharma	Lactation induction	Marketed
6.	Protirelin	Antepan	Solution (spray)	Aventis Pharma	Thyroid diagnostics	Marketed
7.	Zolmitriptan	Ascotop	Solution (spray)	Astra Zeneca	Migraine	Marketed
8.	Sumatriptan	Imigran	Solution (spray)	Glaxo SmithKline	Migraine	Marketed
9.	Dihyfroergotamin	Migranal	Solution (spray)	Novartis Pharma	Migraine	Marketed
10.	Estradiol	Aerodiol	Solution (spray)	Servier	Hormone replacement	Marketed

Conclusion

Nose-to-brain drug delivery system is one of the best alternate for the delivery of the drugs that poses the problem of blood brain barrier. This alternate delivery system not only presents the advantages over the conventional method but also increases the patient's compliance. The drugs with poor bioavailability can also be considered as the candidate with this delivery system. Since this is the direct route of drug administration hence the drug degradation can also be prevented from the enzymatic action within the body. The review also suggested that the number of pathological conditions including migraine, endometriosis and hormonal replacement can also be managed and treated through this route.

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