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NOVEL APPROACHES FOR BRAIN TARGETING DRUG DELIVERY SYSTEM THROUGH NASAL ROUTE

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ABSTRACT

The increasing incidence of central nervous system (CNS) disorders such as Alzheimer's disease, Parkinson's disease, stroke, and brain tumors has underscored the urgent need for effective drug delivery strategies that can bypass the blood–brain barrier (BBB). Intranasal drug administration has emerged as a promising non-invasive approach for brain-targeted delivery due to its potential to bypass the BBB. This review explores the major anatomical pathways for nasal-to-brain drug transport—namely, the olfactory nerve, olfactory mucosal epithelium, trigeminal nerve, and systemic circulation. It also discusses key physiological, physicochemical, and formulation-related factors that influence nasal drug absorption and CNS targeting. In addition, strategies to enhance drug delivery through biomaterials such as chitosan, cyclodextrins, penetration enhancers, and new delivery systems (e.g., nanoparticles, liposomes, gels, and microspheres) are detailed. Common experimental techniques for evaluating intranasal drug delivery, including pharmacokinetic, pharmacodynamic, and radiolabeling methods, are reviewed. Despite its potential, challenges such as low targeting efficiency, physiological variability, and interspecies differences limit its clinical application. Continued research is necessary to optimize delivery systems, improve targeting precision, and ensure safety and efficacy in clinical settings. This review highlights literatures regarding pathways and mechanisms of therapeutic agents transporting across nasal mucosa and latest developments on novel DDSs using various formulation strategies to improve the IN drug delivery to brain.

KEYWORDS: Nasal drug delivery, Brain-targeted delivery, Blood–Brain Barrier, Nanoparticles, Intranasal administration.

INTRODUCTION

In recent years, the incidence rate of brain diseases such as Alzheimer's disease, Parkinson's disease, stroke, and brain tumors has continued to increase, which has been hugely detrimental to human health. These changes have led to increased research activity to develop better therapeutic strategies however, there are many obstacles affecting the development of new drugs for the treatment of such diseases, one of which is the existence of the blood–brain barrier (BBB). The BBB is a complex multicellular structure with extremely low permeability, which limits the movement of molecules between the blood and the neural tissues comprising the central nervous system (CNS) to help maintain homeostasis. However, the tight in recent years, the incidence rate of brain diseases such as Alzheimer's disease, Parkinson's disease, stroke, and brain tumors has continued to increase, which has been hugely detrimental to human health. These changes have led to increased research activity to develop better therapeutic strategies; however, there are many obstacles affecting the development of new drugs for the treatment of such diseases, one of which is the existence of the blood–brain barrier (BBB). The BBB is a complex multicellular structure with extremely low permeability, which limits the movement of molecules between the blood and the neural tissues comprising the central nervous system (CNS) to help maintain homeostasis. However, the tight facilitate drug entry into the brain, providing a promising approach to brain-targeted drug delivery.

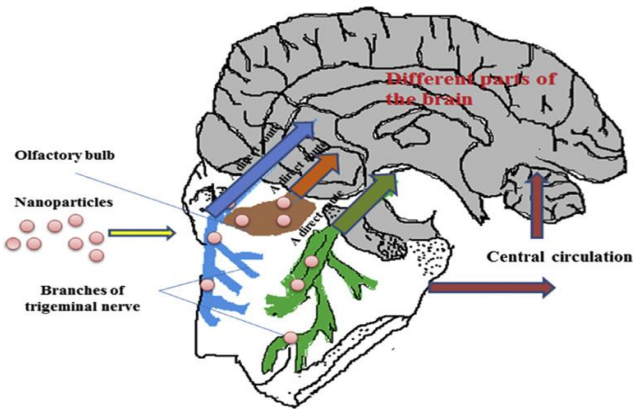

Figure 1: Various Nasal routes to target brain.

The aim of this review article was to summarize what is currently known about the pathways through which drugs can enter the brain through the nose, factors that affect brain-targeted nasal drug delivery, methods to improve brain-targeted nasal drug delivery through the application of related biomaterials, common experimental methods used in intranasal drug delivery research, as well as current limitations to provide a reference for researchers in the field.

THE PATHWAYS THROUGH WHICH DRUGS CAN ENTER THE BRAIN THROUGH THE NOSE

At present, the precise pathways through which drugs are transported to the brain following absorption across the nasal mucosa remain unclear; however, four main approaches have been identified to date.

Olfactory nerve pathway

Some studies have shown that most neurophilic viruses (such as rabies, herpetic stomatitis, and equine encephalomyelitis viruses), steroid hormones, metal ions (such as cadmium and nickel), and proteins enter the brain through the olfactory nerve pathway. After crossing the olfactory mucosa, these substances are absorbed at the axon terminals of olfactory neurons through pinocytosis, endocytosis, or simple diffusion. They subsequently flow through the axonal plasma of neurons and are directly transported through the sieve plates to the olfactory bulb, reaching the

rhinencephalon. The olfactory nerve pathway is considered to be the most important pathway for the entry of drugs into the brain from the nose, and it represents the most direct pathway for bypassing the BBB. However, axonal transport is relatively slow, the rate of which can vary from 0.1~4 mm/d to 20~400 mm/d depending on the properties of the drug being administered. Thus, this pathway is characterized by slow absorption, preventing a drug from entering the brain quickly. At the fastest rate, a drug could enter the brain within 1–2 h, however, at the slower rates, some drugs may not enter the brain for up to 24 h, limiting the clinical applications.

Olfactory mucosal epithelial pathway

The mucosal epithelial pathway (i.e., the nose–brain pathway) is the route through which drugs reach the olfactory mucosal epithelium and enter the CNS directly via cytosolic action or diffusion. Most small-molecule drugs, such as lidocaine, dopamine, 5-fluorouracil, dihydroergotamine, and insulin, are absorbed into the brain via this pathway. This pathway is further divided into two components, including a transcellular transport pathway and a paracellular pathway in the former, drug molecules are transported across mucosal epithelia other than olfactory neuron receptor cells via mechanisms involving carrier transport or cytosolic or passive diffusion into supporting and glandular cells surrounding the olfactory nerve. In the latter pathway, drug molecules enter the intercellular fluid through either the interstitial space of the supporting cells or the peripheral cleft between the supporting cells and the olfactory nerve. If the drug molecules transported to the basement membrane are close to the axons in the lamina propria, they will be transported to the CSF within the cells surrounding the neuron. Simultaneously, drugs in the lamina propria may enter the lymphatic and systemic circulation. If the drug molecules transported to the basement membrane pass through the lamina propria, they will enter the space around the olfactory nerve bundle before being transported into the CSF. This pathway is dependent on the anatomical connections between the olfactory sub mucosa and subarachnoid space. Compared to the rate of absorption via the olfactory nerve pathway, the olfactory mucosal epithelial pathway allows for more rapid drug absorption, facilitating drug entry into brain tissue and the CSF within just a few minutes after nasal administration.

Trigeminal nerve pathway

The ophthalmic and maxillary nerve branches of the trigeminal nerve can extend to epithelial cells in the olfactory and respiratory areas of the nasal cavity, with the opposite end entering the CNS at the pons and terminating at the spinal nucleus of the trigeminal nerve in the brainstem or passing through the ethmoid plate and terminating at the olfactory bulb area. strong radioactivity was observed in the trigeminal nerve, trigeminal branch ganglia, and olfactory bulb following intranasal administration of iodine-125-conjugated insulin-like growth factor 1, with a concentration 10 times higher in the trigeminal nerve than in the olfactory bulb, confirming that, in some cases, the trigeminal nerve may serve as a pathway through which drugs can enter the brain following intranasal administration. However, the transit time along the trigeminal nerve has been reported to be 17–56 h longer than that along the olfactory nerve.

Blood circulation pathway-

Low-molecular-weight lipophilic drugs predominantly enter the brain following absorption into the general circulation through the rich capillary network in the lamina propria of the respiratory region. However, after entering the general circulation, drugs must cross the BBB to reach the CNS; thus, this pathway is a limiting factor in the therapeutic application of many drugs.

Following nasal administration, a drug will eventually reach the CNS through one or more of the pathways, with differences in drug properties, formulations, and routes of administration dictating the dominant pathway of a drug delivery system.

FACTORS AFFECTING BRAIN-TARGETED NASAL DRUG DELIVERY

After a drug is administered via the nose, some of it may enter the CNS directly, whereas some will be absorbed into the general circulation, and some will be removed by the cilia of the nasal mucosa. The amount of drug that can be absorbed through the nasal mucosa is mainly influenced by the physiological characteristics of the nasal cavity, the nature of the drug itself, and factors related to its formulation.

Physiological properties of the nasal cavity

Mechanism of mucociliary clearance

One of the main limitations associated with nasal absorption is the rapid removal of a drug from the nasal cavity by ciliated cells. The cylindrical cilia lining the surface of the nasal mucosa sway at a speed of 5∼6 mm/min in order to move mucus from the nasal cavity to the pharynx and to eliminate substances adhered to the surface of the nasal mucosa. Although this process is a protective mechanism for maintaining optimal respiratory system functionality, it can also shorten the contact time between a drug and the nasal mucosa, directly affecting the efficiency of drug absorption through the nose, as a drug molecule typically remains within the nasal cavity for a period of approximately 20–30 min after administration. To counteract the effects of this clearance mechanism, it is usually possible to extend the drug adhesion time and increase drug absorption by selecting appropriate dosage forms, using bioadhesive materials, or modifying the surface of drug carriers, such as nanoparticles, liposomes, and micro emulsions with specific ligands.

Expression of transport proteins

Efflux mechanisms involving transport proteins expressed in the nasal mucosa, such as multidrug resistance protein 1, breast cancer resistance protein, and P-glycoprotein (P-gp), can limit the absorption of certain drugs. Therefore, inhibiting the synthesis and expression of these proteins can reduce drug clearance. For example, a previous study demonstrated that P-gp plays an important role in drug absorption and efflux in the nasal cavity, and treatment with PSC-833, a specific P-gp inhibitor, increased the amount of quinidine (a P-gp substrate used as a model drug) reaching the brain via the nasal nerves

Role of enzymes

Many enzyme systems catalyze the biological processes occurring within the nasal mucosa; these systems include cytochrome enzyme subunits, epoxidases, polymerases, peptidases, and proteases, all of which can lead to drug degradation in the nasal cavity, producing a “pseudo-first pass effect” that limits the amount of peptide- and protein-based drugs that might otherwise enter the brain. Administration of enzyme inhibitors can reduce the expression or activity of enzymes, thereby increasing drug uptake.

Blood vessel absorption

The abundance of capillaries in the nasal cavity can increase the amount of a drug being absorbed into the bloodstream, resulting in high drug concentrations in the general circulation. However, this also reduces the probability of direct drug entry into the brain and increases the likelihood of side effects. The use of vasoconstrictors at the administration site

can, to some extent, prevent excessive drug diffusion into the bloodstream, thereby increasing brain-targeted drug delivery.

The physical and chemical properties of the drug itself

Drug molecular weight

Under normal circumstances, a higher molecular weight will lower the efficiency of drug absorption. For lipid-soluble drugs, the rate of absorption across the nasal mucosa is nearly 100%; however, these rates are also affected by the molecular weight of a drug, with the absorption efficiency being significantly reduced when the molecular weight exceeds 1 kDa. For macromolecular water-soluble drugs, the concentration of drugs entering the CSF decreases as the relative molecular weight increases. In addition, the absorption efficiency of polar drugs is affected by the molecular weight; for example, when the molecular weight of a polar drug is less than 300 Da, the absorption efficiency is mostly unaffected by the drug's physical and chemical properties, whereas the absorption efficiency is highly affected by the physical and chemical properties of a drug whose molecular weight exceeds 300 Da.

Drug solubility

Before a drug can be absorbed through the nasal mucosa, it must first dissolve in nasal secretions. In terms of composition, water accounts for 90% of the components of nasal secretions, with the remainder comprising small amounts of mucin, proteins, inorganic salts, and lipids, among other factors. Therefore, drugs with high water solubility will also be soluble in nasal secretions. However, for drugs with low water solubility, carriers such as cyclodextrins, micro emulsions and nanoparticle can be selected as drug delivery vectors, allowing the carrier instead of the drug to come into direct contact with the nasal mucosa. The shells of these carriers have good hydrophilicity, which improves their solubility in mucus.

Liposolubility of drugs

The smooth and rapid absorption of drugs across the mucosal layer is dependent on their liposolubility. Usually, drugs with high lipid solubility have good compatibility with the nasal mucosa and are more likely to be absorbed. However, the high fat solubility of a drug can also be detrimental as it can facilitate entry into the general circulation after absorption through the nasal cavity, which is not conducive for drug entry into the brain.

Drug viscosity

In general, drugs with an appropriate viscosity should be more likely to remain in contact with the nasal mucosa for longer periods of time, thereby improving the absorption efficiency. However, a previous study that explored the effect of viscosity on absorption efficiency of metoclopramide hydrochloride drugs reported that although the retention time of a drug in the nasal cavity was prolonged as the viscosity increased, the absorption efficiency decreased. Most new drug carriers, such as microspheres, gels, and nanoparticles, have been developed with an appropriate drug viscosity in mind, improving both the retention time of drugs in the nasal cavity as well as the absorption efficiency.

Preparation-related factors

pH value

Both the pH of a nasal preparation and the composition of the surface of the nasal cavity affect the dissolution, absorption, and penetration of a drug, with the optimal absorption occurring when a drug is in a non-dissipative state. The pH of nasal secretions is approximately 5.5–6.5, and preparations with a pH too far outside this range will irritate

the nasal cavity. Ideally, the pH of the nasal cavity should be maintained at approximately 4.5–6.5 for optimal buffering.

Osmotic pressure

A change in osmotic pressure not only causes the contraction or relaxation of nasal epithelial cells and affects drug absorption, but it may also exacerbate nasal mucosal edema and reduce the beat frequency of ciliated cells in the nasal cavity. Any drugs administered via the nasal cavity should be isotonic with the nasal mucosa (i.e., equivalent to 0.9% sodium chloride solution).

Formulation

Common formulations currently used for the nasal administration of drugs include nasal drops, sprays, powders, gels, microspheres, membranes, emulsions, liposomes, nanoparticles, and micelles. The physical properties of a drug delivery system can affect the dissolution and retention time of drugs in the nasal cavity. Nasal sprays generally result in significantly higher bioavailability of a drug compared with that of drugs administered via nasal drops, which are quickly cleared by nasal cilia. In contrast, drugs administered via nasal sprays are mainly deposited within the front portion of the nasal cavity, with only a small proportion being slowly cleared into the throat, thereby extending the retention time of drugs in the nasal cavity, facilitating absorption, and improving the bioavailability. Powder-based formulations tend to result in stronger and more prolonged contact with the mucosa than solution-based formulations, leading to higher concentration gradients on both sides of the mucosa, thereby increasing drug absorption and brain bioavailability. Many other new dosage forms, such as gel or microsphere preparations, emulsions, liposomes, nanoparticles, and micelles are also conducive to improving the nasal absorption of drugs. In summary, an appropriate dosage form should be selected based on the aforementioned specifications on a case-by-case basis depending on the properties of the drug being administered.

Effects of preservatives

Some commonly used preservatives in nasal preparations include benzalkonium chloride, ethylenediaminetetraacetic acid, ethyl paraben, and thiomersal. Improper selection of a preservative can affect the absorption of drugs across the nasal mucosa. Lipophilic preservatives such as ethylparaben can reversibly accelerate or reduce the frequency of movement of ciliated cells in the nasal cavity, whereas polar preservatives, such as benzalkonium chloride, tend to reduce the movement of cilia in the nasal cavity.

Dosage

Typically, a higher dosage of a drug will lead to greater absorption and improve the efficacy. However, higher drug concentrations may irritate the nasal mucosa. Moreover, the volume of the nasal cavity is limited, and a dosage that is too high can lead to overflow from the nostrils or entry into the pharynx, causing discomfort. According to a previous study, the appropriate nasal administration volume is 0.05–0.15 mL, and the maximum volume should not exceed 0.20 mL.

Administration method

For humans, the method of administration primarily depends on the dosage form. When using nasal drops, for example, the head should be tilted back at an appropriate angle before the medication is administered. Sprays should be directly

administered into the nasal cavity, and a plaster must be applied to the inner wall of the nasal cavity. In experimental animals, medications are usually administered directly.

METHODS TO IMPROVE BRAIN-TARGETED NASAL MUCOSAL DRUG DELIVERY THROUGH THE APPLICATION OF RELATED BIOMATERIALS

Penetration enhancers

Following intranasal drug administration, the actual amount of drug absorbed through the nasal mucosa is very limited; therefore, a key research goal is to identify ways to increase this absorption. One means of achieving this goal is through the use of penetration enhancers, which increase the likelihood that drug molecules will be subsequently transport into the brain.

Pz-peptidase

Pz-peptidase has been shown to promote drug permeability, and the enzyme can instantly and reversibly induce the opening of tight junctions.

Cell-penetrating peptides

Cell-penetrating peptides are short peptides that can penetrate the cell and/or nuclear membrane to guide any connected peptides, proteins, or other bioactive molecules into cells. Although the precise transmembrane mechanism of cellpenetrating peptides is not fully understood, the effects are likely mediated via signal transduction pathways and endocytosis.

Chitosan

The cations present in the amino groups of chitosan can bind to anions in the mucosa, thereby improving the permeability of epithelial cell membranes and promoting the opening of the tight junctions between epithelial cells and enhancing drug absorption. Chitosan functions as a mucosal adhesive and has a good safety profile, which has led to it being extensively investigated in recent years for its potential therapeutic applications.

Cyclodextrins

Cyclodextrins are cyclic compounds composed of D-glucose molecules connected by 1,4-glycosidic bonds; they are watersoluble, non-reducing, molecules that take the form of a white crystalline powder (Rassu et al., 2021). Commonly used α-, β-, and γ-cyclodextrins are composed of six, seven, and eight glucose molecules, respectively (Papakyriakopoulou et al., 2021). The unique spatial structure of cyclodextrins allows them to form inclusion complexes with many substances, especially those that are lipophilic. Thus, cyclodextrins can be used as nasal mucosal absorption enhancers, solubilizers, or stabilizers to promote drug absorption, either directly or indirectly.

Mucosal adhesives

A significant limitation of the nasal route of administration is the rapid clearance of drug molecules mediated by mucosal fibers within the nasal cavity. Thus, the use of mucosal adhesives can inhibit the clearance functions of mucosal cilia, increasing the retention time of drugs at the mucosa and effectively enhancing both drug absorption and the bioavailability of drugs in the brain.

Chitosan

As described in several studies, various types of chitosan and hydroxypropyl methylcellulose can also be used as mucosal adhesives to facilitate nasal drug administration.

Receptor–ligand interactions

To increase the nose-to-brain delivery of nanoscale drugs, selecting appropriate ligands for surface modification of the formulation can increase the affinity between the drug delivery system and the mucosa, leading to enhanced mucosal adsorption. The most commonly used targeting ligands are proteins whose receptors are expressed in the olfactory region, namely lactoferrinor certain glycoproteins. Several lectins, such as wheat germ agglutinin and solanum tuberosum lectin have also been used to promote nose-to-brain drug delivery.

New drug delivery systems

The identification of novel drug delivery systems capable of increasing the absorption of drugs across the nasal mucosa and promoting drug transport to the brain have become a research hotspot in the field of targeted drug delivery in the CNS. Some of these systems can achieve their effects without irritating the nasal mucosa, and many have a good safety profile.

Liposomes

Liposomes are novel dosage forms of targeted drug delivery systems. Liposomes are enclosed bilayer membranes of phospholipids (such as lecithin and cholesterol) that contain hydrophilic cores and possess the characteristics and functions of biofilms. Lipid-soluble compounds can be embedded in phospholipid bilayer membranes, whereas water-soluble compounds can be encapsulated in hydrophilic parts; therefore, liposomes can carry both lipid- and water soluble drugs. Owing to their surface charge, liposomes increase the contact time with the mucosa and improve the bioavailability of drugs while also protecting encapsulated biomolecules from degradation by enzymes in the nasal mucosa. Liposomes cause only slight or no damage to the nasal mucosa, without inducing irritation or ciliary toxicity, and they are suitable for long-term administration

***In situ* gel preparations**

An *in situ* gel, also known as an *in vivo* gel, is a polymer that can undergo a phase change at the drug delivery site into a liquid or semi-solid form. Such preparations can effectively extend the retention time of drugs in the nasal cavity and increase drug concentrations in brain tissue. Depending on the factor that induces the phase change, *in situ* gels can be classified as temperature-, pH-, and ionic-type gels. These gels have a highly hydrophilic three-dimensional network structure, which increases the absorption of drugs across the nasal mucosa by increasing the water permeability. The gels can induce their effects without damaging the mucosal surface because the drugs are transported through the paracellular pathway along with the flow of water. Therefore, in recent decades, researchers have been focusing on optimizing the properties of these gels and improving the understanding of the processes through which they exert their effects.

Microsphere preparations

Microspheres are a new dosage form developed in recent years involving a particle dispersion system formed by drug dispersion and absorption in a polymer matrix. Microspheres are a spherical drug delivery system composed of various materials, including but not limited to, albumin, gelatin, polylactides, and starches. Microspheres act as strong bio-

adhesives and can extend the retention time of drugs in the nasal cavity to 4 hr. In addition, they can protect drugs from enzymatic metabolism, thereby greatly enhancing their bioavailability.

Emulsions

An emulsion is a heterogeneous dispersion system composed of two or more immiscible or partially miscible liquids. The particle size of a microemulsion ranges from 10 to 100 nm, they have a transparent appearance, and they contain surfactants and cosurfactants in a thermodynamically and dynamically stable system . Microemulsions are capable of carrying large amounts of lipophilic and water soluble drugs while simultaneously protecting them from degradation, hydrolysis, and oxidation.

Nanoparticles

Nanoparticles are drug delivery systems with a particle size of 10–100 nm that are generated using polymer materials as carriers to adsorb or encapsulate drugs within the carrier material. Nanoparticles can protect encapsulated drugs from degradation, preventing their unintended removal from the nasal cavity, extending the residence time of drugs in the nasal mucosa, and promoting the direct transport of certain drugs from the nasal cavity to the brain, without increasing drug concentrations within the general circulation; thus, nanoparticles can help facilitate brain targeted drug delivery. Although the precise mechanism remains unknown, the transportation of nanoparticles to the brain may involve receptor-mediated endocytosis into cerebral capillary endothelial cells.

COMMON EXPERIMENTAL METHODS USED IN INTRANASAL DRUG DELIVERY RESEARCH

Currently, there is no suitable *in vitro* method for evaluating brain-targeted drug delivery following nasal administration, and most existing evaluation methods are based on pharmacokinetic or pharmacodynamic techniques.

Cerebellomedullary cistern puncture (single-point puncture method)

The procedure for cerebellomedullary cistern puncture is as follows: after a certain period of drug, administration, the skin on the dorsal side of the head and neck of the mouse is cut open, the foramen magnum is exposed, and a syringe is inserted into the cerebellomedullary cistern to extract the CSF, from which the drug content is quantified. However, due to insufficient CSF supplementation post-extraction, normal intracranial pressure is difficult to maintain, as it is affected by the CSF volume. This method can only be used to determine the CSF concentration of a single mouse at a certain time point after drug administration, and it cannot be used to obtain complete data to characterize the changes in drug concentrations in the CSF over time. It is also difficult to distinguish differences in drug distribution within brain tissue using this method. Because of the need for a large number of animals for experimental purposes, this method has been utilized less frequently than others in brain-targeted drug delivery research.

Brain tissue homogenization method

In the brain tissue homogenization method, the whole brain of an animal is collected post-drug administration according to a predefined experimental timeline, the meninges and blood stains are removed, different brain tissues (such as the olfactory bulb and cerebellum) are separated, and the drug content is measured after weighing, homogenization, and sample pretreatment This method allows researchers to assess the distribution of drugs in brain tissue at specific time points after drug administration; however, to minimize the impact of individual variability in experimental animals, a large sample size is generally required. Despite this limitation, this method remains one of the most widely used in experimental research.

Radionuclide labeling method

The radionuclide labeling method uses isotope labeling to quantify drug content in tissue after administration, making it a suitable technique for studying the brain distribution of peptides or proteins after nasal administration. This method allows for rapid detection with high sensitivity, and it does not require tedious drug extraction steps after tissue homogenization, reducing the risk of experimental errors. However, this method cannot distinguish between raw materials, degradation products, and conjugates, making it impossible to determine the true concentration of a drug from the measured total radioactivity.

Brain microdialysis method

The microdialysis method is a rapidly evolving *in vitro* or *in vivo* brain chemistry sampling technique developed in recent years; it offers good temporal and spatial resolution for determining the concentration of free drugs in the CNS. Compared to traditional research methods, it does not alter the total amount of CSF; thus, it can be performed without affecting the normal physiological function of experimental animals, and it allows for continuous sampling and quantification in a single animal. The technique can also be used to determine the concentration of drugs in different brain tissues as well as changes in the concentration of non-binding drugs in the brain's extracellular fluid over time. This technology has become indispensable in the study of brain-targeting drugs and their active pharmacological effects in the CNS, and it is suitable for *in vivo* biochemical and deep brain region research. However, this method has high instrument requirements and costs, and it is not conducive to large-scale experiments.

Pharmacodynamic evaluation method

When a drug concentration is difficult to measure, its known pharmacological effects can be assessed to indirectly infer the degree of drug absorption into the brain through the nasal mucosa.

CONCLUSION & DISCUSSION

Many researchers have conducted studies on the brain-targeting effects of nasally administered drugs, with aims that have ranged from identifying the mechanism of action to improving drug dosage forms. Low targeting efficiency is currently the biggest and most common problem in brain targeted drug delivery research. The efficiency of such targeted drug delivery systems is usually only several times higher than that of clinically administered drugs or conventional non-targeted drug delivery systems. Brain targeting studies mainly focus on ways to improve drug delivery to the brain, with fewer studies focusing on how drugs are distributed after they enter the brain. The use of excipients, receptors, or carriers to enhance drug delivery to the brain can inadvertently affect the metabolism and distribution of endogenous substances, and long-term use of certain medications may cause serious toxic side effects. The physiological condition of the nasal cavity has a significant impact on the absorption of drugs. Nevertheless, nasal administration of drugs in order to bypass the BBB and facilitate direct entry of a drug into the CSF or brain tissue is still a safe, convenient, and non-destructive method of targeted drug delivery to the CNS. To optimize the clinical utility of brain targeted nasal drug administration strategies, it will be necessary to further increase the volume of drugs that can be transported through the nose into the brain, to reduce the significant variability in drug absorption that is caused by physiological changes in the nasal cavity, and to reduce the irritation and long-term toxicity of nasal preparations.

REFERENCES

1 Agrawal, M. Saraf, S. Saraf, S., Dubey S. K. Puri, A. Gupta. Stimuli-responsive In situ gelling system for nose-to-brain drug delivery. 235–265.

2 Antunes, J. L., Amado, J., Veiga, F., Paiva-Santos, A. C., and Pires, P. C. Nanosystems, drug molecule functionalization and intranasal delivery: An update on the most promising strategies for increasing the therapeutic efficacy of antidepressant and anxiolytic drugs. *Pharmaceutics*, 2023; 15: 998.

3 Prashant Purohit and Mayank Goyal. Artificial Intelligence in Pharmaceutical Sector: an Overview of Innovation. Indo American Journal of Pharmaceutical Research. 2024; 14(03).

4 Sanju, S.K. Singh, Prashant Purohit,Tejaram and Kashi Ram , Preparation and Characterization of Isoniazid Loaded Nanoparticles Using Natural Polymers.Int J Pharm Sci, 2024; 15(2): 31-39.

5 Rapid intranasal delivery of chloramphenicol acetyltransferase in the active form to different brain regions as a model for enzyme therapy in the CNS. *J. Neurosci* 129–134.

6 Prashant Purohit and Himisha Gaur, Lipid Based Nano Particles in Cancer Therapy, Indo American Journal of Pharmaceutical Research, 2023; 4: 225-29.

7 Prashant Purohit and Sahil, A review on wound healing activity of medicinal plants, international journal of pharmaceutics & drug analysis, 2018; 6(7): 545 – 547.

8 Babu, S. R., Shekara, H. H., Sahoo, A. K., Harsha Vardhan, P. V., Thiruppathi, N., and Venkatesh, M. P. Intranasal nanoparticulate delivery systems for neurodegenerative disorders, 2023: 571–594.

9 Prashant Purohit and Harendra Singh Rathore, Isabgol: A Herbal Remedy, World Journal of Pharmaceutical Research, Volume 8, Issue 7, 579-585.

10 Bonaccorso, A., Gigliobianco, M. R., Lombardo, R., Pellitteri, R., Di Martino, P., Mancuso, A., et al. Nanonized carbamazepine for nose-to-brain delivery: Pharmaceutical formulation development, 2023: 248–263.

11 Prashant Purohit, Mahesh Kumar Kataria. Formulation and Evaluation of Polyherbal Ointment Using Carica Papaya and Leptadenia Pyrotechnica International Journal of Current Pharmaceutical Review and Research, 2024; 16(5): 22-27.

12 Bors, L. A., Bajza, Á, Mándoki, M., Tasi, B. J., Cserey, G., Imre, T., et al. Modulation of nose-to-brain delivery of a P-glycoprotein (MDR1) substrate model drug (quinidine) in rats. *Brain Res. Bull*, 2020; 160: 65–73.

13 Boyuklieva, R., Zagorchev, P., and Pilicheva, B. Computational, in vitro, and in vivo models for nose-to-brain drug delivery studies. *Biomedicines*, 2023; 11: 2198.