DOI: https://doi.org/10.31351/vol35iss3pp113-128

Targeted Intranasal Delivery of Antiretrovirals for NeuroAIDS: Opportunities, Barriers, and Formulation Strategies

Salam Shanta Taher*,[1] and Khalid KadhemAl-kinani

[1]Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

***Corresponding author**

Received 2/11/2025 , Accepted 1/5/2026, Published 28/9/2026

Abstract

NeuroAIDS refers to the spectrum of neuropsychiatric complications observed in approximately 30–50% of Human immunodeficiency virus (HIV)/Acquired immunodeficiency syndrome (AIDS) patients. Although the advent of antiretroviral therapy has reduced the severity of AIDS, mild cognitive deficits persist in nearly half of treated patients, highlighting limitations in central nervous system (CNS) drug delivery. These limitations are attributed to poor blood-brain barrier (BBB) permeability, P-glycoprotein efflux, low solubility, first-pass metabolism, and short half-lives of many antiretroviral (ART) drugs. Nose-to- brain drug delivery emerged as a promising alternatives, by passing the BBB via olfactory and trigeminal pathways. This route offers direct CNS access while minimizing systemic exposure. Factors such as drug molecular weight, lipophilicity, pH, osmolality, viscosity, particle size, and surface charge significantly influence nasal drug absorption and brain targeting. Approaches to optimize nose-to-brain delivery include the use of prodrugs, permeation enhancers, mucoadhesive agents, enzyme inhibitors, and P-glycoprotein inhibitors. Despite encouraging preclinical data, challenges remain, including mucociliary clearance, enzymatic degradation, and species-specific anatomical variations that hinder translational research. A rational formulation design that considers physiological and physiochemical barriers is essential for clinical success. Nanocarriers including nanovesicles, solid lipid nanoparticles, and nanoemulsions offer several advantages: they protect drugs from enzymatic degradation, improve solubility and stability, enable controlled release, and enhance mucoadhesion and uptake across the nasal mucosa. Overall, intranasal delivery system, particularly those employing nanocarriers and functional excipients, offer a novel and efficient approach to manage NeuroAIDS by enhancing ART bioavailability in CNS and improving drug access to HIV reservoirs in the brain.

Keywords: Antiretroviral therapy (ART), Intranasal delivery, Nanocarrier, NeuroAIDS, Nose-to-brain delivery.

Introduction

Approximately 30-50% of individuals diagnosed with AIDS develop neuropsychiatric complications collectively referred to as NeuroAIDS. In certain instances, these complications manifest as impaired cognitive and motor functions, as well as alterations in behavior and mood. These clinical manifestations are broadly categorized under the term HIV-associated Neurocognitive Disorder (HAND) [(1)]. According to the Frascati criteria ,HAND is roughly categorized into three stages : asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV- associated dementia (HAD). Although asymptomatic neurocognitive impairment (ANI) does not present with overt symptoms. It remains a significant concern due to its potential to progress into more severe forms of HIV-associated neurocognitive disorder (HAND).Mild cognitive impairments are observed in approximately 50 % of patients receiving antiretroviral therapy (ART), though only a small proportion of these individuals advance to more severe HAND subtypes [(2)]. The progression or onset of HAND may be further aggravated by aging and commonly associated comorbidities, such as substance abuse. A 2014 study also indicated that the patients diagnosed with ANI were at a greater risk of developing mild neurocognitive disorder (MND) or HIV- associated dementia (HAD), compared to HIV-positive individuals without cognitive decline[(3)]. Despite the widespread implementation of combination antiretroviral therapy (cART) over the past two decades, the overall prevalence of HAND has remained relatively stable;however , the severity of neurocognitive impairment has notably decreased.Even with effective ART, milder forms of HAND can persist in some individuals, suggesting mechanisms beyond viral replication, such as chronic inflammation or comorbidities[(4,5)].

In addition, certain ART drugs, such as efavirenz, may cause neuropsychiatric side effects or exacerbate cognitive issues [6] .

Search methodology

An extensive literature search was done to give the relevant studies to be used in this review. The following electronic databases were used: PubMed, Scopus, Web of Science, and Google Scholar. The search strategy used a mix of the following keywords: intranasal drug delivery, nose-to-brain delivery, nanocarriers, antiretroviral drugs. Articles published between 2010 and 2025 were included to make sure that the latest developments were covered. Inclusion criteria included original research articles, review papers, preclinical /clinical studies that were centered on nasal delivery systems to the brain. The exclusion criteria were the publication in languages other than English, the research which was not related to nose-to-brain delivery, or the research lacked enough methodological description or pharmacokinetic data. This systematic search strategy enabled a systematic review of the existing strategies and technologies in intranasal nanocarriers -mediated brain drug delivery.

Pathophysiological Mechanisms Underlying NeuroAIDS

HIV may invade the brain of the infected individuals at an early stage through a "Trojan horse" mechanism, by overcoming the blood-brain barrier (BBB) by infecting lymphocytes and monocytes [7]. A number of studies have also shown that free forms of the virus can also traverse the BBB, thus accessing the central nervous system (CNS) and infecting the macrophages and microglia. Significant neurodegenerative alterations are primarily observed in the basal ganglia, brainstem, and deep white matter of the CNS. The monocyte and macrophages activated by HIV entry release cytokines such as TNF-α and IL-1β, along with chemokines. These substances, in conjunction with HIV-encoded proteins (including gp120, Vpr, and TAT),exert cytotoxic effects on neurons, astrocytes, and Schwan cells. Consequently, this lead to a decrease in the viability of neural cells, manifesting as retraction of neural processes [8,9]. HIV-associated neurocognitive disorders persist as a common complication of HIV infection, affecting approximately half of the HIV -diagnosed patients. During the early stages of infection, the central nervous system is potentially infiltrated by HIV-infected CD4+ T cells and monocytes, serving as primary mediators of viral entry into the CNS [10].

Role of Conventional Anti-HIV Drugs for NeuroAIDS

Most antiretroviral (ARV) drugs used to treat HIV are given orally in the form of tablets, capsules, or liquids. The administration of either a single antiretroviral (ARV) drug or a combination of multiple ARVs forms the foundation of highly active antiretroviral therapy (HAART).HAART has been extensively utilized to suppress the progression of AIDS, significantly improving survival rates among individuals diagnosed with the disease. The primary challenges associated with orally administered highly active antiretroviral therapy (HAART) include poor patient adherence due to complex dosing regimen [11]. Additionally, the continuous mutation rate of HIV contributes to the emergence of multidrug resistance (MDR), reducing the effectiveness of treatment. The tight junction and selective permeability of the BBB further restrict the penetration of ARV drugs into the CNS, limiting therapeutic access to HIV reservoirs within the brain [12]. As summarized in Table 1, a significant proportion of anti-HIV drugs exhibit low aqueous solubility, extensive hepatic first-pass metabolism, and predictable gastrointestinal degradation, posing additional barriers to successful drug delivery to the CNS [13] . Furthermore, certain ARV agents, such as indinavir and ritonavir, serve as substrates for P-glycoprotein (P-gp) efflux transporters, which actively remove these drugs from CNS compartments, thereby preventing the attainment of effective therapeutic concentrations in the brain [14].Additionally, the short half-lives of drugs such as zidovudine (AZT) and saquinavir (SQV), along with decreased residence time, can lead to sub-therapeutic drug levels in the affected area [15]. ARVs that are highly bound to plasma proteins (e.g., albumin) may have reduced free drug concentrations available to cross the BBB, as only the unbound fraction can pass into the CNS. A significant number of ARV medications such as nevirapine, ritonavir, lopinavir, nelfinavir, and efavirenz are highly binding to plasma protein such as alpha-1-acid glycoprotein and albumin [16,17]. This is the reason why these ARVs might fail to attain satisfactory therapeutic levels in the brain regions. The combination of these factors complicates the achievement of adequate ARV levels in the CNS, which is especially significant in the management of HIV-associated neurocognitive disorders, as well as eradication of HIV reservoirs in the brain.

Table 1. Physicochemical Properties and CNS Penetration of common Antiretroviral Drugs [18-20]

Drug	MW (g/mol)	logP	Aqueous solubility (mg/ml)	CNS notes
Zidovudine (AZT)	267.24	0.05	10	Detectable CSF; modest brain tissue levels; CSF/plasma
Dolutegravir (DTG)	419.4	2.2	0.095	High plasma protein binding; low CSF:plasma ratios; limited free CNS exposure
Efavirenz (EFV)	315.68	4.6	<0.001)	Low CSF but brain accumulation; associated neuropsychiatric AEs
Lamivudine (3TC)	230.26	-1.4	~70	Detectable CSF; good penetration relative to many ARVs but low brain tissue accumulation vs. target cells
Lopinavir (LPV)	628.8	1.92	4.69	Poor CNS penetration; high protein binding and P-gp efflux limit brain exposure
Atazanavir (ATV)	704.9	4.11	0.003	Poor brain penetration; highly lipophilic protease inhibitor

Nose to Brain Delivery for Management of NeuroAIDS

Intranasal drug delivery is an exciting method of administration that can circumvent the blood brain barrier enabling medications to reach brain tissues directly, providing a reliable alternative to oral and parenteral delivery routes. The nasal mucosa has been extensively investigated as an appropriate site for drug administration, providing numerous benefits over the oral route, including a large blood supply, lack of hepatic first-pass metabolism, and convenient administration [21,22]. It was shown that delivery of efavirenz by Intranasal administration offers the potential to bypass first pass metabolism, allowing direct transport of the drug from nose to brain via olfactory and trigeminal pathways. This targeted delivery can increase CNS bioavailability while minimizing systemic exposure, thereby reducing the risk of neuropsychiatric adverse effects at doses significantly lower than oral dosing. Intranasal nano formulations further enhance drug bioavailability to the CNS by safeguarding the drug from chemical and enzymatic degradation. A diverse range of therapeutic agents can be delivered intranasally for systemic or CNS effects. The development of advanced drug delivery strategies for the treatment of life-threatening HIV infections holds the potential to protect the brain from NeuroAIDS and improve the overall socio-economic well-being of HIV patients [23].

To understand the nose-to-brain drug delivery route, it is essential to explore the key pathways that facilitate drug transport from the nasal cavity to the brain (Figure 1) . The primary pathways involved in nose-to-brain targeting include

A-Systemic pathway (indirect pathway)

The nasal respiratory epithelium covers up to 90% of the nasal cavity in humans and is highly vascularized, hence well suited for the systemic absorption of drugs. While this route may be affected by the blood-brain barrier (BBB), certain nano formulations could improve CNS penetration. Shah et al. successfully developed solid lipid nanoparticles (SLNs) loaded with Zidovudine and assessed their potential for brain-targeted delivery. The area under the curve and mean residence time of zidovudine -SLNs were found to be 1.27-fold and 1.83-fold higher, respectively, compared to the Zidovudine solution, suggesting enhanced ability of the SLNs to cross the blood-brain barrier [24].

B-Lymphatic pathway

Drugs could also be transported from lymphatic channels originating from the submucosal region of the olfactory area. These extracellular routes are associated with olfactory nerves that extend from the lamina propria of the olfactory epithelium to the olfactory bulb in the brain. Furthermore, the elimination of a drug can occur from the olfactory submucosa through olfactory blood or lymphatic vessels, ultimately reaching the deep cervical lymph nodes located in the neck. Furubayashi et al. (2021) showed that intranasally administered drugs are absorbed into nasal lymphatic capillaries and transported to cervical lymph nodes [25].

Neuronal pathway

The neuronal pathway involves drug transport along the olfactory and trigeminal (CN nerves that innervate the olfactory epithelium in the nasal cavity, where molecules enter through the nasal mucosa, travel via axonal transport, and reach the olfactory bulb, brainstem, or other CNS regions. Thorne et al proved that the insulin-like growth factor-I (IGF-I) given intranasally readily reached the brain through the trigeminal neuronal pathway. Comparatively, the intra-neuronal transport mechanism, which is based on axonal

movement, is by far slower and can take hours to days before the drug can reach various parts of the brain [26].

Extraneuronal pathway

Non-Neuronal transport for nose-to-brain drug delivery involves extracellular mechanisms that bypass neuronal axonal transport, primarily utilizing perivascular, perineural, and lymphatic pathways to facilitate drug movement into the central nervous system (CNS). The perivascular pathway enables drug diffusion through spaces surrounding blood vessels, allowing molecules to reach cerebrospinal fluid (CSF) and brain parenchyma. The perineural pathway involves transport along the extracellular spaces surrounding the olfactory and trigeminal nerves, enabling drug movement without direct intracellular uptake. By this pathway, the active compound can reach brain directly within just a few minutes [27].

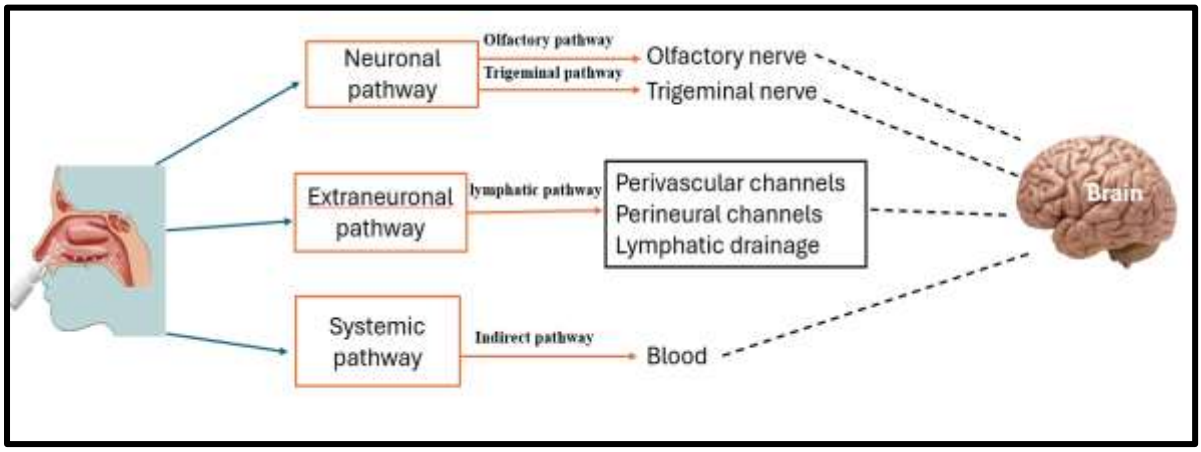

Figure 1. Schematic representation of the pathways involved in nose-to-brain drug delivery

Factors Affecting Nose to Brain Delivery

1- Physiological factors

a- Mucociliary Clearance:

The nasal mucosa contains an integrated system of cilia and mucus, which constitutes the mucociliary clearance (MCC) mechanism. It considered the first line of defense mechanism that prevent harmful particles from entering the nose. The average rate of nasal mucociliary clearance rate is ranging between 10 and 20 minutes. Facilitating the rapid elimination of nasally administered drugs (liquid dosage forms). Consequently, this rapid elimination decreases the residence time of medications in nasal cavity, thereby limiting their therapeutic effectiveness [28,29].

b-Enzymatic degradation

The nasal cavity contains a range of metabolic enzymes such as cytochrome P450, proteases, and esterases that can break down drug molecules before they are absorbed into the bloodstream. This enzymatic activity can greatly reduce the availability of certain drugs, especially peptides and proteins, since they are particularly vulnerable to degradation[30]. At the same time, these enzymes may play an even more important role when drugs are intended for brain delivery. This is because the olfactory region lacks effective mucociliary clearance, and drugs tend to permeate more slowly from this area into the brain.

P-glycoprotein efflux transporters

It should be noted that P-glycoprotein (P-gp) is expressed regionally in the nose, where it is expressed more in the olfactory mucosa. Research by Kandimalla and Donovan revealed that P-gp is concentrated in the epithelial cells, the nasal glands and in the vascular endothelium of the bovine olfactory glands and the nasal respiratory mucosae [31]. Further, P-gp is quite important in limiting the nose-to-brain delivery of a number of drugs including quinidine, which has an impact on drug bioavailability and location in the CNS system [32]. These results emphasize the functional importance of P-gp in regulating drug permeability across the nasal epithelium.

The physical and chemical properties of the drug

The absorption rate across the nasal epithelium is influenced by both the molecular weight and lipophilicity of the drug. Generally, the small compounds with molecular weights not exceeding 300 Dalton can easily penetrate the nasal epithelium and are readily absorbed, irrespective of lipophilic nature. Lipophilic compounds are passively diffused through nasal epithelium when their molecular weights between 300 and 1000 Dalton. The low molecular weight and high lipophilicity of some medications make them easily permeable through nasal epithelium, which increases absorption, and the increased bioavailability of the drug in the brain after intranasal delivery. The absorption efficiency

however, drops drastically when the molecular weights go above 1000 Da. Hydrophilic drugs (smaller than 1000 Da) can penetrate cerebral spinal fluid more quickly than lipophilic drugs because they are not as susceptible to being transported by neurons and supporting cells of the olfactory epithelium after nasal delivery. Conversely, polar macromolecules (above 1000 Da), including proteins and peptides, exhibit low bioavailability, and are mainly absorbed by endocytosis[33].

Solubility

Solubility is an important physiochemical property that significantly affects nasal drug absorption. As nasal secretions are more watery in nature, a drug must first dissolve in nasal secretions before it can be absorbed through the mucosa. Highly water-soluble drugs dissolve easily but may face challenges penetrating the lipophilic epithelial membrane, while poorly soluble drugs may struggle to dissolve, reducing their bioavailability. The balance between aqueous solubility and lipophilicity is essential for effective absorption. However, for drugs with low water solubility, carriers such as cyclodextrins[34] ,microemulsions[35], and nanostructured lipid carriers[36] can be utilized as drug delivery system to enhance solubility and ensure optimum nasal absorption.

Considering these physiochemical constraints, several characteristics define an ideal drug candidate for nose-to-brain delivery

1-Molecular weight ≤ 1000 Da [37].

2-Moderate lipophilicity (Log P 1-3) to ensure optimal permeability [38].

3-Adequate aqueous solubility for dissolution in nasal secretions.

4-Low effective dose, typically ≤ 25 mg per administration, due to the limited nasal cavity volume(~ 150–200 µL per nostril) [39].

5-Non irritating nature of the drug and formulation constituents (excipient, preservative, absorption enhancer)

These characteristics not only determine absorption efficiency but also serve as essential selection criteria for identifying the optimum requirement for nose to brain delivery.

Formulation Factors

pH

Physiological pH of nasal mucosa is estimated as 4.5-6.5, and it is imperative that nasal preparations are adjusted to be near this level to minimize mucosal irritation, and enhance drug absorption [40]. The change in this physiological pH can lead to the discomfort and destruction of the mucous membrane and loss of therapeutic effect. The pH of the formulation also influences drug permeation across the nasal epithelium as the ionization can influence the ionization state of the drug. Therefore, pH optimization is a key aspect of nasal formulation development, which directly affects the efficacy of drugs, their compliance, and overall stability of products [41]

Osmolality

Nasal formulations should be designed to maintain an osmolality in the range of approximately 290–500 mOsm/kg in order to achieve isotonicity and ensure compatibility with the nasal mucosa. Hypertonic and hypotonic preparations may disrupt normal ciliary activity, which may decrease the effectiveness of drug uptake. Glycerin, sodium chloride and glucose may be added to the nasal preparations to achieve isotonicity. Properly adjusted tonicity ensures effective drug delivery while minimizing adverse effects on the nasal mucosa [42] .

Viscosity

Viscosity is an important formulation parameter in nasal formulations that affects drug retention, mucociliary clearance and general drug absorption. The viscosity of the formulation increases the time of contact between the drug and the nasal mucosa, which may result in an increase in permeation and absorption. Unfortunately, highly viscous formulations could interfere with ciliary beating or mucociliary clearance and thus alter permeability of drugs [43].By carefully optimizing viscosity, nasal drug formulations can achieve a balance between prolonged retention and efficient clearance, ensuring effective drug delivery and patient compliance [44].

Particle size

Particles that are in the nanometer size range (typically below 100 nm) are especially advantageous for nose-to-brain delivery due to their ability to bypass the blood-brain barrier through the olfactory and trigeminal pathways whereas moderately larger particles (approximately 100–500 nm) are more efficiently taken up into the lymphatic system and transported to cervical lymph nodes via extraneuronal pathways. [45,46]. These fine particles are also more likely to be taken up by olfactory sensory neurons, which transport them directly to the central nervous system, thus enhancing brain bioavailability. It has been reported that polystyrene particles with a diameter of 100 nm, coated with chitosan or polysorbate 80, exhibited greater accessibility to the olfactory mucosa compared to larger- sized particles (200 nm) [47]. Ahmad et al. developed nanoemulsions (NE) of varying sizes, labeled with different fluorescent markers, and investigated their brain biodistribution following intranasal administration. The study found that NEs with a particle size less than 100 nm demonstrated an extended residence time in the nasal epithelium and a slower rate of

mucociliary clearance in comparison to larger nanoparticles (200, 500, and 900 nm) [48]. Thus, controlling the particle size is critical in optimizing nose-to-brain drug delivery, ensuring efficient drug targeting, prolonging retention in the nasal cavity, and maximizing therapeutic efficacy in the brain.

Surface charge of nanocarriers

The net negative charge of the mucosa of the nose is attributed to the sialic acid residues of mucins. Consequently, more electrostatically positive (cationic) nanoparticles have a greater affinity to the mucosal surface, resulting in stronger adhesion, longer retention, and increased drug absorption [49]. Cationic polysaccharide polymers such as chitosan have been widely applied to coat different nanocarriers, improving their mucoadhesive properties and facilitating transport of drug across the nasal epithelium [50]. Several studies have demonstrated that nanocarriers can reach brain regions following intranasal administration, regardless of their surface charge. A. Bonaccorso et al. investigated the effect of surface charge on the nose-to-brain delivery of nanoparticles. Fluorescent imaging of both positively (chitosan) and negatively charged nanoparticles (PLGA nanoparticles) demonstrated their transport into different brain regions, with a residence time of up to 48 hours following intranasal administration [51]. Another study by Takumi et al. studied the influence of surface charge on the localization of nanocarriers in different brain regions. The findings revealed that positively charged liposomes exhibited greater distribution in the olfactory bulb and forebrain, whereas negatively charged liposomes were more predominantly distributed in the hindbrain and bulbospinal tract [52].

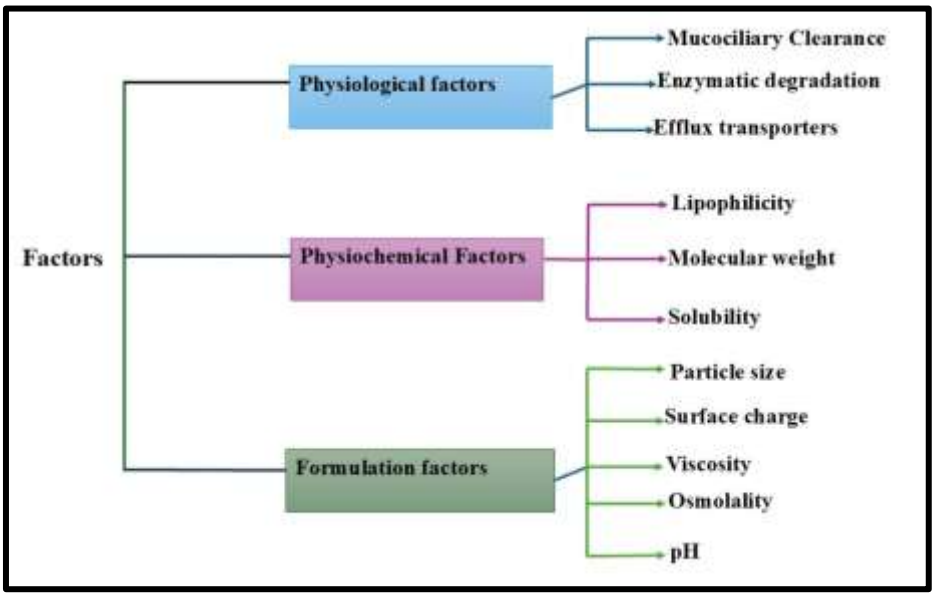

Figure 2. Key factors influencing nose-to-brain drug delivery.

Challenges Associated with Nose to Brain Delivery

1-There are several challenges associated with nasal drug delivery, including physiological factors such as mucociliary clearance and enzymatic degradation; physicochemical properties such as extreme pH, low solubility, and large molecular weight; and formulation-related factors such as low viscosity or hypotonic/hypertonic solutions. These factors must be carefully considered when optimizing nasal formulations for effective brain targeting [33,53].

2- Safety is an important factor in the design and development of effective nasal drug delivery systems. It is important to evaluate not only the safety profile of the active pharmaceutical ingredient (API) but also that of the excipients included in the formulation, as some may introduce potential risks. For example, benzalkonium chloride, although widely used as a preservative, has been reported to impair ciliary function, which may lead to toxicity in a dose and time dependent manner [39,54]. Likewise, while penetration enhancers can improve drug absorption, they may compromise the integrity of the nasal epithelium, potentially resulting in undesirable adverse effects. In addition, some excipients such as lectins have been linked to cytotoxicity and the induction of oxidative stress in mammalian cells. To address these concerns, a range of naturally derived compounds including bile salts, medium chain fatty acids, phospholipids, poloxamers, and saponins have been explored as alternative permeation enhancers due to their relatively favorable safety profiles. Furthermore, the use of excipients

classified as Generally Recognized As Safe (GRAS) has been proposed as a strategy to enhance mucosal permeability while minimizing epithelial damage.These approaches highlight the ongoing effort to achieve an optimal balance between formulation efficacy and biocompatibility. However, they also emphasize the importance of conducting thorough toxicological assessments, particularly for intranasal nanoparticle-based drug delivery systems, to ensure both safety and long-term tolerability [55].

3-Anatomical and Physiological Variations of the Nasal Cavity Across Animal Models

Anatomical variations of the nasal cavity across animal models significantly influence drug absorption, transport pathways, and the overall efficiency of nose to brain delivery. These interspecies differences present notable challenges when attempting to extrapolate preclinical findings to humans, particularly in the development of intranasal formulations for clinical application [56]. Differences in nasal cavity size, olfactory surface area, and overall nasal geometry can affect both the volume of formulation that can be administered and the efficiency of drug deposition. Rodent models have provided comprehensive understandings into the brain to blood distribution of antiretroviral drugs (ARVs) following intranasal administration. However, anatomical differences between rodents and humans limit direct translational applicability. For example, rats possess relatively large olfactory regions but can accommodate only small dosing volumes, necessitating highly concentrated formulations. In contrast, humans have smaller olfactory regions but allow for the administration of larger volumes, resulting in distinct deposition and absorption patterns. Despite the anatomical differences between rodents, such as rats and mice, and humans (Table 2), these animals are widely employed in in vivo studies owing to several key advantages. The primary reasons for their widespread use in research include their cost effectiveness, ease of handling, and the extensive body of scientific data available on their biology and physiology. Rabbits and monkeys have olfactory regions that are similar to those in humans. However, their high cost and may restrict their broader application in research. The volume that can be delivered per nostril also varies depending on the animal species [57].

Table 2. Comparative anatomical differences in the nasal cavity between humans and animal models

Species	Olfactory surface area	Volume of administration	Implications for Drug Delivery
Human	10 cm^2	~ 200 µl	Moderate nasal volume enables practical dosing; most clinically relevant reference for intranasal delivery.
Rat	30–40 cm^2	40-50 µl	Limited dosing volume necessitates highly concentrated formulations; widely used for mechanistic and proof-of-concept studies despite translational limitations.
Monkey	8–10 cm^2	~ 58 µL	Anatomical features and olfactory region distribution closer to humans; suitable for translational preclinical evaluation.
Dog	150 cm^2	~ 207 µl	Large olfactory surface and dosing capacity allow higher drug administration; less representative of human anatomy but useful for safety/toxicology studies.
Rabbit	10–15 cm^2	~ 58 µL	Small olfactory surface but moderate volume; suitable for preliminary screening, though limited comparability to human intranasal physiology.

Strategies for effective nose to brain targeting

Several strategies have been developed to overcome the challenges associated with nose-to-brain drug delivery, including the use of prodrugs, mucoadhesive and in situ gels, use of permeation enhancers and application of nanocarriers

Figure 3. Strategies for brain targeting

Prodrug

A prodrug is a chemically modified inactive form of a drug that is converted into its active form within the body. For nose-to-brain delivery, prodrugs are designed to enhance solubility, stability, permeability, and targeting efficiency for improved transport across the nasal mucosa. Curcumin, known for its antioxidant and anticancer properties, has been formulated as an ester-based prodrug and administered via the nasal route for targeted brain delivery. Due to its extensive liver metabolism, and its high lipophilicity, the systemic bioavailability of curcumin is significantly limited, with less than 0.1% of the administered dose reaching the brain. However, upon reaching the olfactory region, the designed prodrug undergoes enzymatic hydrolysis mediated by local esterases (carboxylesterases) to its active parent compound, which can readily diffuse into brain tissue, enhancing its therapeutic effectiveness [(58)]. Zidovudine (AZT), a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI), is commonly used in the treatment of HIV. However, antiretroviral drugs like AZT often fail to achieve therapeutic concentrations in the central nervous system (CNS), primarily due to their role as substrates for active efflux transporters (AETs). These transporters are expressed on the membranes of lymphocytes, macrophages, and the cells forming the blood-brain barrier (BBB). To overcome this limitation, AZT can be conjugated with ursodeoxycholic acid (UDCA) to form a prodrug, U-AZT. This modification allows the prodrug to bypass the efflux transporter systems, enabling it to more effectively permeate and accumulate in murine macrophages, exhibiting an uptake efficiency that is twenty times greater than that of AZT [(59)].

Permeation enhancer

Permeation enhancers have been investigated to enhance the absorption of high molecular weight drugs , particularly peptides and proteins, as well as small molecules with poor permeability across biological barriers such as the BBB.The suggested mechanisms involve increasing membrane fluidity and tight junction permeability, creation of temporary aqueous pores, and reducing both viscosity and enzymatic activity in the nasal cavity. Permeation enhancers used in intranasal (IN) drug delivery such as cyclodextrins, emulsifiers, plant derived compound (saponins), sodium deoxycholate, Ethanol and fatty acids [(60)]. Lauroylcholine chloride (LCC), a cationic surfactant, facilitates the efficient delivery of domperidone from the olfactory region to the brain in rats, likely via direct nose-to-brain transport rather than through systemic circulation [(61)].

Mucoadhesive agents

Mucoadhesive agents, such as chitosan, poloxamer, carbopol, and hyaluronic acid, have been utilized to enhance nose-to-brain drug delivery [(62-65)]. These agents interact with the nasal mucus, thereby extending the drug's residence time within the nasal cavity and promoting greater absorption. Furthermore, mucoadhesive can improve mucosal permeability by facilitating the fluidization of the mucosal membrane. Trimethyl chitosan complexes successfully enhanced the nose-to-brain delivery of insulin in rats [(66)]. A group of researchers successfully developed a nose-to-brain delivery system using an HA–FGL conjugate. Fluorescence images of dissected brains showed the accumulation of the FGL compound in the rat brain even 6 hours after intranasal administration [(67)].

Enzyme inhibitors for nose to brain delivery

Inhibiting enzymatic activity within the nasal cavity using enzyme inhibitors can decrease nasal metabolism, thereby extend drug stability and enhance absorption, ultimately leading to improved bioavailability. Various enzyme inhibitors commonly employed for this purpose include α-aminoboronic acid derivatives, boroleucine, fluvoxamine, and phospholipids [(30)].

P-glycoprotein inhibitors

To enhance nose-to-brain drug delivery, inhibition of P-glycoprotein (P-gp) has been proposed as a strategy to overcome the efflux mechanism, thereby facilitating greater drug absorption and retention within the brain. P-gp inhibitors function by binding to the transporter and preventing the active extrusion of drugs, which increases permeability and enhances central nervous system (CNS) drug concentrations. This approach has been widely used for the delivery of therapeutic agents in the management of neurological disorders such as Alzheimer's disease, Parkinson's disease, brain tumors and neuroAIDS. Commonly studied P-gp inhibitors include medicinal agents such as verapamil, cyclosporine A, quinidine, tariquidar, and elacridar [(68)], while excipients and surfactants such as polysorbates, Cremophor EL, and Labrasol have also been used for similar purposes [(66)]. Despite these promising outcomes, systemic inhibition of P-gp poses significant safety concerns. The coadministration of verapamil has been associated with relevant drug drug interactions, particularly with antiretroviral therapies (ARVs), which may alter pharmacokinetics and increase the risk of adverse effects. To reduce the outcome of these risks, nanocarrier based systems have been developed to enable localized P-gp modulation at the nasal epithelium or the blood brain barrier, thereby minimizing systemic exposure and reducing the

likelihood of interactions. It was shown that peptide functionalized nanoparticles were capable of delivering small interfering RNA (siRNA) to the brain, effectively silencing P-gp expression [(69)]. Collectively, these findings emphasize the importance of balancing efficacy with safety when employing P-gp inhibition strategies for nose to brain drug delivery.

Nanocarriers for Effective Nose to Brain Drug Delivery

Despite progress in the development of nasal drug delivery systems, the targeted delivery of drugs with poor physiochemical and biopharmaceutical properties to the brain is still challenging. These include high enzymatic degradation, being a substrate for efflux pumps, low solubility and poor permeability. Hence, an appropriate carrier is required to enhance the drug delivery to the brain regions while maintaining the nasal epithelium structure and function. Nanocarrier systems have recently emerged as a potential strategy to enhance nose to brain delivery of neurotherapeutics. Nanocarrier-based systems, with a diameter in 10-1000 nm, have several advantages. These systems can prevent chemical and enzymatic degradation of the drugs they encapsulate, improving drug stability and efficacy. They also enhance the water solubility of poorly soluble drugs and prolong their residence time in the nasal cavity, which may enhance drug absorption and bioavailability. An additional advantage of nanocarriers is sustained drug release, which can help maintain a desired level of drug release for an extended time. Furthermore, the targeting ability to specific brain regions by the surface modification of nanocarriers with particular ligands helps in reducing drug leakage to non targeted regions and the systemic side effects. Different types of nanocarriers have been widely investigated for nose to brain delivery such as Lipid based nanocarriers (SLNs and NLCs), Nanosuspension, Dendrimers and Nanoemulsions [(70-72)].

Nanovesicle

Nanovesicles, such as liposomes, transferosome, solusome, spanlastic and ethosome, are excellent carriers for nose to brain delivery. Solusomes are nanovesicular systems composed of non-ionic surfactant and cholesterol, designed to improve drug stability and enhance mucosal permeation. Spanlastics are elastic nanovesicles formulated using nonionic surfactants and edge activators, which impart flexibility to the vesicle bilayers, allowing improved nasal absorption and drug targeting to the brain **[(73.74)]**. A liposome is a spherical vesicle composed of one or more phospholipids bilayers that enclose aqueous core. A study conducted by Raju Saka et al. investigated the potential of liposomal formulations for nasal delivery of Imatinib Mesylate to the brain. The researchers developed Imatinib Mesylate loaded liposomes with a particle size of less than 150 nm, ensuring efficient transport.These liposomes exhibited a sustained drug release profile lasting up to 96 hours. Furthermore, in vivo experiments demonstrated a significant enhancement in brain drug deposition from the liposomal formulation compared to the pure drug solution, as evidenced by the higher area under the curve (AUC) values **[(75)]**. The addition of mucoadhesive agent such as xanthan gum to liposomal formulations offers several advantages by enhancing mucoadhesion, drug retention, and controlled release, thereby improving brain drug targeting **[(76)]**.

Transferosomes are an advanced derivative of liposomes, unlike conventional liposomes, transferosomes are ultra-deformable vesicles that can squeeze through narrow biological barriers, including the skin, nasal mucosa, and blood-brain barrier (BBB). Ofloxacin drug was encapsulated in transferosomes and assessed for its ability to target the brain. The transfersomal formulations were prepared using a thin film hydration technique. Pharmacokinetic results revealed that after 30 minutes of drug administration, the **brain-to-blood ratios** of Ofloxacin were **0.305** for the intravenous solution, **0.579** for the intranasal solution, and **1.858** for the intranasal ofloxacin loaded transferosome loaded in an **in situ gel**. The significantly higher brain uptake observed with the transfersomal formulation suggests its potential for effective brain targeting and therapeutic application in the treatment of meningitis **[(77)]**.One of the derivatives of liposomes is ethosome , a novel nanovesicles containing a high content of ethanol and phospholipid. The ethosome based formulation has shown significantly greater penetration and release rates through the nasal cavity compared to liposomes. Group of researchers were developed nanoethosome formulations for delivery of eletriptan hydrobromide to the brain. The researchers developed an eletriptan incorporated ethosome containing ethanol, soya lecithin, and cholesterol. The in vitro drug release from the optimized ethosomal formulation was nearly 100% after 24 hours of initiating the study. Histopathological examination of the nasal mucosa verified the safety of the ethosomal formulation. The eletriptan-loaded ethosomal gel has potential as a more efficient brain-targeting when administered via the intranasal route **[(78)]**.

Nanoemulsion

Nanoemulsion is a thermodynamically stable and optically isotropic liquid system consisting of water, oil, and an amphiphilic

surfactant, often supplemented by a co-surfactant to enhance its properties. The o/w (oil-in-water) type nanoemulsions are particularly well-suited for brain-targeted drug delivery systems due to their small size, lipophilicity, and ability to efficiently cross the blood-brain barrier (BBB). Patel and colleagues developed an o/w nanoemulsion using Capmul as oil to facilitate the brain delivery of the antiepileptic drug (topiramate). A 2:1 ratio of surfactant (Tween 20) and co surfactant (Carbitol) were used to prepare topiramate loaded nanoemulsion. The resulting nanoemulsion exhibited a mean droplet size of approximately 4.73 nm and an optimal polydispersity index value of less than 0.3. Pharmacokinetic studies in Wistar albino rats revealed improved bioavailability and significant brain uptake of the encapsulated drug compared to the oral nanoemulsion formulation [79,80].

Anroop B. Nairal. developed nanoemulsion system for brain delivery of dolutegravir. The formulated nanoemulsion incorporating dolutegravir exhibited a mean droplet diameter of 103 nm and demonstrated a sustained release profile. Intranasal administration of the selected formulation resulted in greater Cmax (~six-fold) and AUC (~five-fold), in the brain regions compared to intravenous administration. These results suggest that the in situ gel nanoemulsion of dolutegravir holds potential as an effective strategy for NeuroAIDS management [81].

Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) consist of a solid lipid core surrounded by a surfactant layer, which act as a barrier between lipid core and the surrounding aqueous medium. The unique structural organization of SLNs help shields the encapsulated drug molecules from metabolic activity of enzymes within the nasal mucosa while also enabling a more sustained and controlled release profile. SLNs have emerged as a promising drug delivery system for nose to brain due to their ability to circumvent blood brain barrier (BBB). SLNs have gained increasing attention in management brain tumor. Doxorubicin, a hydrophilic anticancer drug, is unable to penetrate the blood-brain barrier (BBB) and is associated with significant systemic toxicity when administered by conventional route. These limitations can pose considerable therapeutic challenges in achieving therapeutic level in the brain. A study demonstrated the successful incorporation of doxorubicin into solid lipid nanoparticles using lipid (stearic acid), surfactant (Epikuron 200), and cosurfactant (taurocholate sodium). Following intravenous administration in rats, the SLN-modified doxorubicin exhibited reduced drug accumulation in the liver, heart, and kidneys, while achieving a higher concentration in the brain tissue. This enhanced brain targeting was attributed to the ability of SLNs to evade the reticuloendothelial system (RES), in contrast to free drug [82]. Numerous investigations have been carried out to assess the efficacy of SLNs in the management of neurological disorder. Haloperidol is an antipsychotic medication commonly utilized for the management of psychiatric disorders such as schizophrenia. A major challenge associated with its oral administration is extensive first-pass metabolism and high plasma protein binding, both of which significantly reduce its bioavailability, thereby limiting amount of the drug that reaches the brain. However, the formulation of haloperidol into SLNs stabilized with tween 80 has demonstrated improved drug accumulation in brain regions compared to the unformulated drug [83,84]. The surface of solid lipid nanoparticles can be functionalized with polyethylene drug (PEG). The PEGylation reduces opsonization and prolongs circulation time, facilitating efficient drug delivery across the blood -brain barrier. Arya Bazargani et al. developed PEGylated SLNs for the targeted delivery of Atazanavir and Elvitegravir to the brain as a therapeutic approach for NuroAIDS [85]. While SLNs offer high biocompatibility and protection for labile molecules, they are limited by drug loading capacity and the potential of drug expulsion during storage. In contrast, nanostructured lipid carriers (NLCs), a second generation lipid based system, combine solid and liquid lipids, thereby improving encapsulation efficiency and reducing drug leakage. NLCs also allow for more controlled release kinetics compared to conventional SLNs. These results underscore the potential of lipid based nanocarriers (SLNs, NLCs) as a promising nanocarrier system for enhancing administration of anti-HIV drugs in management of NeuroAIDS.

Conclusion

Intranasal drug delivery has emerged as a novel noninvasive approach to treat neurological diseases and could also be useful to improve the treatment of neuroAIDS, due to persistent HIV reservoirs in the brain that have not been effectively targeted with traditional strategies. By bypassing the blood brain barrier and employing advanced formulation strategies such as nanoparticles, mucoadhesive systems, and prodrug approaches,intranasal administration offers the potential to enhance drug delivery to the central nervous system. Despite these advantages, the successful clinical translation of intranasal therapies depends on several critical considerations. These include ensuring formulation safety, optimizing the physicochemical properties of the drug, and accounting for interspecies

anatomical and physiological differences observed during preclinical studies. In addition, challenges such as enzymatic degradation within the nasal mucosa, variability in drug absorption, and regulatory complexities associated with the approval of intranasal antiretroviral therapies must be carefully addressed. Overall, a balanced and systematic evaluation of these factors is essential to support the development of safe, effective, and clinically viable intranasal treatment strategies for NeuroAIDS.

Authors' Declaration

We confirm that the Figures and Tables in the manuscript are part of the present study.

Conflict of Interest

The authors state that they have no conflicts of interest in the publication of this manuscript.

Funding

None

Authors' Contributions Study

Salam Shanta Taher performed the literature search, drafted the manuscript, and prepared figures and tables. Khalid Al-Kinani contributed to literature review, critically revised the manuscript, and assisted with editing.

References

1. Sarma A, Das MK. Nose to brain delivery of antiretroviral drugs in the treatment of neuroAIDS. Mol Biomed. 2020;1(1):15. doi: 10.1186/s43556-020-00019-8
2. Wei J, Hou J, Su B, Jiang T, Guo C, Wang W, et al. The Prevalence of Frascati-Criteria-Based HIV-Associated Neurocognitive Disorder (HAND) in HIV-Infected Adults: A Systematic Review and Meta-Analysis. Front Neurol. 2020;11:581346. doi: 10.3389/fneur.2020.581346
3. Grant I, Franklin DR, Deutsch R, Woods SP, Vaida F, Ellis RJ, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. Neurology. 2014 Jun 10;82(23):2055–62. doi: 10.1212/WNL.0000000000000492
4. Gill, A.J., Kolson, D.L. Chronic Inflammation and the Role for Cofactors (Hepatitis C, Drug Abuse, Antiretroviral Drug Toxicity, Aging) in HAND Persistence. Curr HIV/AIDS Rep 11, 325–335 (2014). https://doi.org/10.1007/s11904-014-0210-3
5. Cysique LA, Brew BJ. Neuropsychological functioning and antiretroviral treatment in HIV/AIDS: a review. Neuropsychol Rev. 2009 Jun;19(2):169–85.
6. Dheda M. Efavirenz and neuropsychiatric effects. South Afr J HIV Med. 2017;18(1):741 . https://hdl.handle.net/10520/EJC-7358159c5
7. Ash MK, Al-Harthi L, Schneider JR. HIV in the Brain: Identifying Viral Reservoirs and Addressing the Challenges of an HIV Cure. Vaccines (Basel). 2021 Aug 5;9(8):867. https://doi.org/10.3390/vaccines9080867
8. Rani A, Ergün S, Karnati S, Jha HC. Understanding the link between neurotropic viruses, BBB permeability, and MS pathogenesis. J Neurovirol. 2024 Feb;30(1):22–38. doi: 10.1007/s13365-023-01190-8
9. Michalicová A, Bhide K, Bhide M, Kováč A. How viruses infiltrate the central nervous system. Acta Virol. 2017;61(4):393-400. doi: 10.4149/av_2017_401
10. Subra C, Trautmann L. Role of T Lymphocytes in HIV Neuropathogenesis. Curr HIV/AIDS Rep. 2019 Jun;16(3):236–43. doi: 10.1007/s11904-019-00445-6
11. Iacob SA, Iacob DG, Jugulete G. Improving the Adherence to Antiretroviral Therapy, a Difficult but Essential Task for a Successful HIV Treatment-Clinical Points of View and Practical Considerations. Front Pharmacol. 2017;8:831. doi: 10.3389/fphar.2017.00831
12. Blassel L, Zhukova A, Villabona-Arenas CJ, Atkins KE, Hué S, Gascuel O. Drug resistance mutations in HIV: new bioinformatics approaches and challenges. Curr Opin Virol. 2021 Dec;51:56-64. doi: 10.1016/j.coviro.2021.09.009
13. Nicol MR, McRae M. Treating viruses in the brain: Perspectives from NeuroAIDS. Neurosci Lett. 2021 Mar 23;748:135691. doi: 10.1016/j.neulet.2021.135691
14. Kumar S, Maurya V, Dandu H, Bhatt M, Saxena S. Global perspective of novel therapeutic strategies for the management of NeuroAIDS: novel drug delivery methods for NeuroAIDS. Biomol Concepts. 2018;9(1):33-42. https://doi.org/10.1515/bmc-2018-0005
15. Schenfeld EM, Ribone SR, Quevedo MA. Stability and plasmatic protein binding of novel zidovudine prodrugs: Targeting site ii of human serum albumin. Eur J Pharm Sci. 2018 Mar 30;115:109-118. doi: 10.1016/j.ejps.2018.01.024
16. Boffito M, Back DJ, Blaschke TF, Rowland M, Bertz RJ, Gerber JG, Miller V. Protein binding in antiretroviral therapies. AIDS Res Hum Retroviruses. 2003 Sep;19(9):825-35. doi: 10.1089/088922203769232629
17. Illamola SM, Hirt D, Tréluyer JM, Urien S, Benaboud S. Challenges regarding analysis of unbound fraction of highly bound protein antiretroviral drugs in several biological matrices: lack of harmonisation and guidelines.

Drug Discov Today. 2015 Apr;20(4):466-74. doi: 10.1016/j.drudis.2014.11.010

18. Butar-Butar ME, Wathoni N, Ratih H, Wardhana YW. Solid dispersion technology for improving the solubility of antiviral drugs. Pharm Sci Res. 2023;10(1):3.doi: 10.7454/psr.v10i1.1292

19. Khan SA, Rehman S, Nabi B, Iqubal A, Nehal N, Fahmy UA, Kotta S, Baboota S, Md S, Ali J. Boosting the Brain Delivery of Atazanavir through Nanostructured Lipid Carrier-Based Approach for Mitigating NeuroAIDS. Pharmaceutics. 2020 Nov 6;12(11):1059. doi: 10.3390/pharmaceutics12111059.

20. Belgamwar AV, Khan SA, Yeole PG. Intranasal dolutegravir sodium loaded nanoparticles of hydroxypropyl-beta-cyclodextrin for brain delivery in Neuro-AIDS. J Drug Deliv Sci Technol. 2019 Aug 1;52:1008–20.https://doi.org/10.1016/j.jddst.2019.06.014.

21. Keller LA, Merkel O, Popp A. Intranasal drug delivery: opportunities and toxicologic challenges during drug development. Drug Deliv Transl Res. 2022 Apr;12(4):735–57. doi: 10.1007/s13346-020-00891-5

22. Wu X, Zang R, Qiu Y, Zhang Y, Peng J, Cheng Z, et al. Intranasal Drug Delivery Technology in the Treatment of Central Nervous System Diseases: Challenges, Advances, and Future Research Directions. Pharmaceutics. 2025 Jun 13;17(6):775. doi: 10.3390/pharmaceutics17060775

23. Huang Q, Chen Y, Zhang W, Xia X, Li H, Qin M, Gao H. Nanotechnology for enhanced nose-to-brain drug delivery in treating neurological diseases. J Control Release. 2024 Feb;366:519-534.https://doi.org/10.1016/j.jconrel.2023.12.054

24. Purvin S, Vuddanda PR, Singh SK, Jain A, Singh S. Pharmacokinetic and tissue distribution study of solid lipid nanoparticles of zidovudine in rats. J Nanotechnol. 2014;2014:1–7. http://dx.doi.org/10.1155/2014/854018

25. Furubayashi T, Inoue D, Kimura S, Tanaka A, Sakane T. Evaluation of the pharmacokinetics of intranasal drug delivery for targeting cervical lymph nodes in rats. Pharmaceutics. 2021;13(9):1363. doi:10.3390/pharmaceutics13091363

26. Thorne RG, Pronk GJ, Padmanabhan V, Frey WH. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. Neuroscience. 2004 Jan;127(2):481–96. doi: 10.1016/j.neuroscience.2004.05.029

27. Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. Life Sciences. 2018 Feb;195:44–52. DOI: 10.1016/j.lfs.2017.12.025

28. Grassin-Delyle S, Buenestado A, Naline E, Faisy C, Blouquit-Laye S, Couderc LJ, Le Guen M, Fischler M, Devillier P. Intranasal drug delivery: an efficient and non-invasive route for systemic administration: focus on opioids. Pharmacol Ther. 2012 Jun;134(3):366-79. doi: 10.1016/j.pharmthera.2012.03.003

29. Agu RU. Challenges in Nasal Drug absorption: How Far have We come? Ther Deliv. 2016 Jul;7(7):495–510. doi: 10.4155/tde-2016-0022

30. Sarkar MA. Drug metabolism in the nasal mucosa. Pharm Res. 1992 Jan;9(1):1–9 . doi: 10.1023/a:1018911206646

31. Kandimalla KK, Donovan MD. Localization and differential activity of P-glycoprotein in the bovine olfactory and nasal respiratory mucosae. Pharm Res. 2005 Jul;22(7):1121-8. https://doi.org/10.1007/s11095-005-5420-3

32. Bors LA, Bajza Á, Mándoki M, Tasi BJ, Cserey G, Imre T, Szabó P, Erdő F. Modulation of nose-to-brain delivery of a P-glycoprotein (MDR1) substrate model drug (quinidine) in rats. Brain Res Bull. 2020 Jul;160:65-73. https://doi.org/10.1016/j.brainresbull.2020.04.012

33. Huang Q, Chen X, Yu S, Gong G, Shu H. Research progress in brain-targeted nasal drug delivery. Front Aging Neurosci. 2024 Jan 17;15:1341295. doi: 10.3389/fnagi.2023.1341295

34. Saitani, E.-M.; Pippa, N.; Perinelli, D.R.; Forys, A.; Papakyriakopoulou, P.; Lagopati, N.; Bonacucina, G.; Trzebicka, B.; Gazouli, M.; Pispas, S.; et al. Fabricating Polymer/Surfactant/Cyclodextrin Hybrid Particles for Possible Nose-to-Brain Delivery of Ropinirole Hydrochloride: In Vitro and Ex Vivo Evaluation. Int. J. Mol. Sci. **2024**, *25*, 1162. https://doi.org/10.3390/ijms25021162

35. Saba Abdulhadi Jaber, Nawal Ayash Rajab. Preparation and In vitro/Ex vivo Evaluation of Nanoemulsion-Based in Situ Gel for Intranasal Delivery of Lasmiditan. IJPS. 2024 Sep 15;33(3):128–41. https://doi.org/10.31351/vol33iss3pp128-141

36. Tamer MA, Kassab HJ. Optimizing Intranasal Amisulpride Loaded Nanostructured Lipid Carriers: Formulation, Development, and Characterization Parameters. PNT. 2025 Apr;13(2):287–302. https://doi.org/10.2174/0122117385301604240226111533

37. Illum L. Nasal drug delivery--possibilities, problems and solutions. J Control Release. 2003 Feb 21;87(1–3):187–98. doi: 10.1016/s0168-3659(02)00363-2

38. Raghav M, Gupta V, Awasthi R, Singh A, Kulkarni GT. Nose-to-brain drug delivery: challenges and progress towards brain targeting in the treatment of neurological disorders. J Drug Deliv Sci Technol. 2023 Sep;86:104756.https://doi.org/10.1016/j.jddst.2023.104756

39. Papakyriakopoulou P, Valsami G. The nasal route for nose-to-brain drug delivery: advanced nasal formulations for CNS disorders. Expert Opin Drug Deliv. 2025 Jun;22(6):823-839. doi: 10.1080/17425247.2025.2489553

40. Salade L, Wauthoz N, Goole J, Amighi K. How to characterize a nasal product. The state of the art of in vitro and ex vivo specific methods. Int J Pharm. 2019 Apr;561:47–65. doi: 10.1016/j.ijpharm.2019.02.026

41. Scherließ R. Nasal formulations for drug administration and characterization of nasal preparations in drug delivery. Ther Deliv. 2020 Mar;11(3):183-191. doi: 10.4155/tde-2019-0086

42. Koo J, Lim C, Oh KT. Recent Advances in Intranasal Administration for Brain-Targeting Delivery: A Comprehensive Review of Lipid-Based Nanoparticles and Stimuli-Responsive Gel Formulations. Int J Nanomedicine. 2024 Feb 23;19:1767-1807. doi: 10.2147/IJN.S439181

43. Ugwoke MI, Agu RU, Jorissen M, Augustijns P, Sciot R, Verbeke N, Kinget R. Toxicological investigations of the effects carboxymethylcellulose on ciliary beat frequency of human nasal epithelial cells in primary suspension culture and in vivo on rabbit nasal mucosa. Int J Pharm. 2000 Sep 15;205(1-2):43-51. doi: 10.1016/s0378-5173(00)00484-1

44. Wei S, Zhai Z, Kong X, Wu C, Zhu B, Zhao Z, Zhang X. The review of nasal drug delivery system: The strategies to enhance the efficiency of intranasal drug delivery by improving drug absorption. Int J Pharm. 2025 May 15;676:125584. https://doi.org/10.1016/j.ijpharm.2025.125584

45. Alkufi HK, Kassab HJ. Nanospanlastic in situ Gel for Nose to Brain Delivery of Nimodipine: In vitro Optimization and in vivo Pharmacokinetic Study. Al-Rafidain J Med Sci. 2025 Feb 18;8(1):97–105. doi**:** https://doi.org/10.54133/ajms.v8i1.1687

46. Taher SS, Kadhem Al-Kinani K. In vivo Brain Pharmacokinetics of Dolutegravir Sodium-Loaded Nanostructured Lipid Carrier in situ Gel: Comparative Study with an Intravenous Drug Solution. Al-Rafidain J Med Sci. 2025 Feb 22;8(1):115–25. https://doi.org/10.54133/ajms.v8i1.1692

47. Mistry A, Stolnik S, Illum L. Nose-to-Brain Delivery: Investigation of the Transport of Nanoparticles with Different Surface Characteristics and Sizes in Excised Porcine Olfactory Epithelium. Mol Pharm. 2015 Aug 3;12(8):2755-66. doi: 10.1021/acs.molpharmaceut.5b00088

48. Ahmad E, Feng Y, Qi J, Fan W, Ma Y, He H, Xia F, Dong X, Zhao W, Lu Y, Wu W. Evidence of nose-to-brain delivery of nanoemulsions: cargoes but not vehicles. Nanoscale. 2017 Jan 19;9(3):1174-1183. doi: 10.1039/c6nr07581a

49. Chen Y, Zhang C, Huang Y, Ma Y, Song Q, Chen H, Jiang G, Gao X. Intranasal drug delivery: The interaction between nanoparticles and the nose-to-brain pathway. Adv Drug Deliv Rev. 2024 Apr;207:115196. doi: 10.1016/j.addr.2024.115196

50. Quiñones JP, Peniche H, Peniche C. Chitosan Based Self-Assembled Nanoparticles in Drug Delivery. Polymers. 2018 Feb 26;10(3):235. https://doi.org/10.3390/polym10030235

51. Bonaccorso A, Musumeci T, Serapide MF, Pellitteri R, Uchegbu IF, Puglisi G. Nose to brain delivery in rats: Effect of surface charge of rhodamine B labeled nanocarriers on brain subregion localization. Colloids Surf B Biointerfaces. 2017 Jun 1;154:297-306. doi: 10.1016/j.colsurfb.2017.03.035

52. Kurano T, Kanazawa T, Ooba A, Masuyama Y, Maruhana N, Yamada M, Iioka S, Ibaraki H, Kosuge Y, Kondo H, Suzuki T. Nose-to-brain/spinal cord delivery kinetics of liposomes with different surface properties. J Control Release. 2022 Apr;344:225-234. doi: 10.1016/j.jconrel.2022.03.017

53. Qiu Y, Huang S, Peng L, Yang L, Zhang G, Liu T, Yan F, Peng X. The Nasal-Brain Drug Delivery Route: Mechanisms and Applications to Central Nervous System Diseases. MedComm (2020). 2025 Jun 6;6(6):e70213.doi: 10.1002/mco2.70213

54. Mickenhagen A, Siefer O, Neugebauer P, Stennert E. Der Einfluss verschiedener alpha-Sympathomimetika und Benzalkoniumchlorid auf die Zilienschlagfrequenz humaner Flimmerzellen in vitro (The influence of different alpha-sympathomimetic drugs and benzalkoniumchlorid on the ciliary beat frequency of in vitro cultured human nasal mucosa cells). Laryngorhinootologie. 2008 Jan;87(1):30-8. German. doi: 10.1055/s-2007-966891

55. Gorelik E. Cytotoxic effects of lectins. Methods Mol Med. 1998;9:453–9 .doi: 10.1385/0-89603-396-1:453

56. Chamanza R, Wright JA. A Review of the Comparative Anatomy, Histology, Physiology and Pathology of the Nasal Cavity of Rats, Mice, Dogs and Non-human Primates. Relevance to Inhalation Toxicology and Human Health Risk Assessment. J Comp Pathol. 2015 Nov;153(4):287-314.doi: 10.1016/j.jcpa.2015.08.009

57. Al-Tamimi D, Al-Kinani K, Taher S, Hussein A. Effect of food on the pharmacokinetics of fluoxetine in healthy male adult volunteers. Iraqi J Pharm Sci (Internet). 2023 Feb 18 (cited 2025 Aug 11);31(Suppl):153-61. Available from: https://bijps.uobaghdad.edu.iq/index.php/bijps/article/view/1927

58. Jeong SH, Jang JH, Lee YB. Drug delivery to the brain via the nasal route of administration: exploration of key targets and major consideration factors. J Pharm Investig. 2023;53(1):119-152. doi: 10.1007/s40005-022-00589-5

59. Dalpiaz A, Fogagnolo M, Ferraro L, Capuzzo A, Pavan B, Rassu G, Salis A, Giunchedi P, Gavini E. Nasal chitosan microparticles target a zidovudine prodrug to brain HIV sanctuaries. Antiviral Res. 2015 Nov;123:146-57.doi: 10.1016/j.antiviral.2015.09.013

60. Ghadiri M, Young PM, Traini D. Strategies to Enhance Drug Absorption via Nasal and Pulmonary Routes. Pharmaceutics. 2019 Mar 11;11(3):113. . DOI: 10.3390/pharmaceutics11030113

61. Fukakusa S, Suzuki C, Sasaki K, Sonoda Y, Hatano Y, Haruta S, Magata Y. Brain drug delivery from the nasal olfactory region is enhanced using lauroylcholine chloride: An estimation using in vivo PET imaging. Nucl Med Biol. 2024 Nov-Dec;138-139:108968.doi: 10.1016/j.nucmedbio.2024.108968

62. Hamzah ML, Kassab HJ. Formulation and Characterization of Intranasal Drug Delivery of Frovatriptan-Loaded Binary Ethosomes Gel for Brain Targeting. Nanotechnol Sci Appl. 2024 Jan 16;17:1-19. doi: 10.2147/NSA.S442951

63. Taher SS, Al-Kinani KK. Formulation and characterization of dolutegravir sodium-loaded nanostructured lipid carrier in situ gel for targeted brain delivery via intranasal route. OpenNano. 2025;100270. doi:10.1016/j.onano.2025.100270.

64. Alabdly A, J. Kassab H. Formulation Variables Effect on Gelation Temperature of Nefopam Hydrochloride intranasal in Situ Gel (Conference Paper) #. IJPS. 2023 Feb 16;31(Suppl.):32–44. https://doi.org/10.31351/vol31issSuppl.pp32-44

65. Alkufi HK, Kassab HJ. Formulation and Evaluation of Sustained Release Sumatriptan Mucoadhesive Intranasal in-Situ Gel. IJPS. 2019 Dec 22;28(2):95–104. https://doi.org/10.31351/vol28iss2pp95-104

66. Jintapattanakit A, Peungvicha P, Sailasuta A, Kissel T, Junyaprasert VB. Nasal absorption and local tissue reaction of insulin nanocomplexes of trimethyl chitosan derivatives in rats. J Pharm Pharmacol. 2010 May;62(5):583–91. doi: 10.1211/jpp.62.05.0004

67. Kim YS, Sung DK, Kim H, Kong WH, Kim YE, Hahn SK. Nose-to-brain delivery of hyaluronate - FG loop peptide conjugate for non-invasive hypoxic-ischemic encephalopathy therapy. J Control Release. 2019 Aug 10;307:76-89. doi: 10.1016/j.jconrel.2019.06.021

68. öscher W, Gericke B. Novel Intrinsic Mechanisms of Active Drug Extrusion at the Blood-Brain Barrier: Potential Targets for Enhancing Drug Delivery to the Brain? Pharmaceutics. 2020 Oct 14;12(10):966. DOI: 10.3390/pharmaceutics12100966

69. Gomes MJ, Kennedy PJ, Martins S, Sarmento B. Delivery of siRNA silencing P-gp in peptide-functionalized nanoparticles causes efflux modulation at the blood-brain barrier. Nanomedicine (Lond). 2017 Jun;12(12):1385-1399. doi: 10.2217/nnm-2017-0023

70. Emad NA, Ahmed B, Alhalmi A, Alzobaidi N, Al-Kubati SS. Recent progress in nanocarriers for direct nose to brain drug delivery. J Drug Deliv Sci Technol. 2021 Aug;64:102642. https://doi.org/10.1016/j.jddst.2021.102642

71. Taher SS, Al-Kinani KK. Current nanotechnological strategies for delivery of anti-retroviral drugs: overview and future prospects. Curr Drug Ther. 2024 Oct 29;20. Available from:https://www.eurekaselect.com/235841/article.**doi:** 10.2174/0115748855331460241017100207

72. Alwan ZS, Rajab NA. Preparation and characterization of febuxostat as nanosuspension. Iraqi J Pharm Sci. 2025 Feb 15;33(4 Suppl 1):261–270. https://doi.org/10.31351/vol33iss(4SI)pp261-270

73. Ramadhan SH, Al-Kinani KK. Statistical Optimization and Characterization of Nimodipine Transferosomes. Al-Rafidain J Med Sci. 2024 Sep 14;7(1(Special)):S77-83. https://doi.org/10.54133/ajms.v7i1(Special).1015

74. Salman A. H., Alkufi H. K., Taher S. S., Al-mahmood S., Haiss M. A.: Response surface optimization and in vitro study of nasal solusomes nanovesicles for the bioavailability improvement and brain targetting of sumatriptan. Ep. Klin. Farmakol. kai Farmakokinet. 2024;42(Suppl 1):107–117. DOI: 10.61873/RNYL6796

75. Saka R, Chella N, Khan W. Development of Imatinib Mesylate-Loaded Liposomes for Nose to Brain Delivery: In Vitro and In Vivo Evaluation. AAPS PharmSciTech. 2021 Jun 28;22(5):192. doi: 10.1208/s12249-021-02072-0

76. Samudre S, Tekade A, Thorve K, Jamodkar A, Parashar G, Chaudhari N. Xanthan Gum Coated Mucoadhesive Liposomes for Efficient Nose to Brain Delivery of Curcumin. DDL. 2016 Apr 1;5(3):201–7. doi: 10.2174/2210303106666160120215857

77. Eid HM, Elkomy MH, El Menshawe SF, Salem HF. Transfersomal nanovesicles for nose-to-brain delivery of ofloxacin for better management of bacterial meningitis: formulation, optimization by Box-Behnken design, characterization and in vivo pharmacokinetic study. J Drug Deliv Sci Technol. 2019 Dec;54:101304.https://doi.org/10.1016/j.jddst.2019.101304

78. Shelke S, Shahi S, Jadhav K, Dhamecha D, Tiwari R, Patil H. Thermoreversible nanoethosomal gel for the intranasal delivery of Eletriptan hydrobromide. J Mater Sci: Mater Med. 2016 Jun;27(6):103. doi: 10.1007/s10856-016-5713-6

79. Patel RJ, Parikh RH. Intranasal delivery of topiramate nanoemulsion: Pharmacodynamic, pharmacokinetic and brain uptake studies. Int J Pharm. 2020 Jul 30;585:119486. doi: 10.1016/j.ijpharm.2020.119486

80. Kondapuram P, Sahoo SK. A review of merely polymeric nanoparticles in recent drug delivery system. Asian J Pharm Clin Res. 2022 Apr;15(4):4-12. doi:10.22159/ajpcr.2022.v15i4.43239.

81. Nair AB, Chaudhary S, Jacob S, Patel D, Shinu P, Shah H, Chaudhary A, Aldhubiab B, Almuqbil RM, Alnaim AS, Alqattan F, Shah J. Intranasal Administration of Dolutegravir-Loaded Nanoemulsion-Based In Situ Gel for Enhanced Bioavailability and Direct Brain Targeting. Gels. 2023 Feb 3;9(2):130 . doi: 10.3390/gels9020130

82. Satapathy MK, Yen TL, Jan JS, Tang RD, Wang JY, Taliyan R, Yang CH. Solid Lipid Nanoparticles (SLNs): An Advanced Drug Delivery System Targeting Brain through BBB. Pharmaceutics. 2021 Jul 31;13(8):1183. doi: 10.3390/pharmaceutics13081183

83. Raj R, Kolay A, Havelikar U. A review on solid lipid nanoparticles. Int J Curr Pharm Res. 2023 Sep;15(5):10-16. doi:10.22159/ijcpr.2023v15i5.3051.

84. Yasir M, Chauhan I, Zafar A, Verma M, Alruwaili NK, Noorulla KM, et al. Glyceryl behenate-based solid lipid nanoparticles as a carrier of haloperidol for nose to brain delivery: formulation development, in-vitro, and in-vivo evaluation. Braz J Pharm Sci. 2022;58:e20254. http://dx.doi.org/10.1590/s2175-97902022e20254

85. Bazargani A, Hejazi M, Fernandez M, Cordeiro A, Tsala Ebode J, Lewinski N, da Rocha S, Golshahi L. PEGylated solid lipid nanoparticles for the intranasal delivery of combination antiretroviral therapy composed of Atazanavir and Elvitegravir to treat NeuroAIDS. Int J Pharm. 2025 Feb 10;670:125166. doi: 10.1016/j.ijpharm.2025.125166

التوصيل الأنفي الموجّه لمضادات الفيروسات الراجعة في علاج الاعتلال العصبي المرتبط بفيروس نقص المناعة البشرية (NeuroAIDS): الفرص، الحواجز، واستراتيجيات التصميم الدوائي

سلام شنتة طاهر*[1] و خالد كاظم الكناني[1]

[1] قسم الصيدلانيات، كلية الصيدلة، جامعة بغداد، بغداد، العراق

الخلاصة

يشير مصطلح الاعتلال العصبي المرتبط بفيروس نقص المناعة البشرية (NeuroAIDS) إلى مجموعة من المضاعفات العصبية والنفسية التي تُلاحظ لدى نحو ٣٠–٥٠٪ من مرضى فيروس نقص المناعة البشرية/الإيدز. وعلى الرغم من أن ظهور العلاج المضاد للفيروسات الراجعة (ART) قد قلّل من شدة الإيدز، فإن العجز الإدراكي الخفيف ما يزال مستمرًا لدى ما يقرب من نصف المرضى الذين يتلقون العلاج، مما يسلّط الضوء على القيود المفروضة على توصيل الأدوية إلى الجهاز العصبي المركزي . تُعزى هذه القيود إلى ضعف نفاذية الأدوية عبر الحاجز الدموي الدماغي(BBB) ، ونشاط ناقلات الجليكوبروتين (P-glycoprotein) التي تُخرج الدواء من الخلايا، وانخفاض الذوبانية، والتمثيل الغذائي الكبدي الأولي، وقصر عمر النصف للعديد من أدوية العلاج المضاد للفيروسات.

لقد برز التوصيل الدوائي عبر الأنف إلى الدماغ كبديل واعد، إذ يتجاوز الحاجز الدموي الدماغي عبر المسارات الشمّية والعصب ثلاثي التوائم، مما يتيح وصول الدواء مباشرة إلى الجهاز العصبي المركزي مع تقليل التعرض الجهازي.تؤثر عدة عوامل على امتصاص الدواء من الأنف واستهدافه للدماغ، منها :الوزن الجزيئي، والدهون (الليبوفيلية)، ودرجة الحموضة(pH) ، والضغط الأسموزي، واللزوجة، وحجم الجسيمات، والشحنة السطحية .وتشمل الاستراتيجيات المستخدمة لتحسين التوصيل عبر الأنف إلى الدماغ :المركّبات الطليعية(prodrugs) ، والمُعزّزات

النفاذية، والعوامل اللاصقة للمخاط(mucoadhesive agents) ، ومثبطات الإنزيمات، ومثبطات بروتين.P-glycoprotein وعلى الرغم من النتائج المشجعة في الدراسات قبل السريرية، ما تزال هناك تحديات قائمة، مثل :إزالة المخاط الهدبية(mucociliary clearance) ، والتحلل الإنزيمي، والاختلافات التشريحية بين الأنواع التي تعيق ترجمة النتائج إلى البشر. لذا، فإن تصميم التركيبات الدوائية بطريقة عقلانية تراعي الحواجز الفسيولوجية والفيزوكيميائية يُعدّ أمرًا حاسمًا للنجاح السريري.تُعد الأنظمة النانوية الحاملة للأدوية —مثل الحويصلات النانوية (nanovesicles)، والجسيمات الصلبة الشحمية(SLNs) ، والمستحلبات الدقيقة(microemulsions) من أكثر الاستراتيجيات الواعدة، لما توفره من مزايا عديدة، تشمل :حماية الدواء من التحلل الإنزيمي، وتحسين الذوبانية والثبات، وإتاحة الإطلاق المتحكم فيه، وتعزيز الالتصاق بالمخاط وزيادة الامتصاص عبر الغشاء الأنفي.وباختصار، فإن أنظمة التوصيل عبر الأنف، وخاصة تلك التي تستخدم الحوامل النانوية والمواد المساعدة الفعالة، تمثل نهجًا مبتكرًا وفعّالًا في إدارة الاعتلال العصبي المرتبط بفيروس نقص المناعة البشرية، من خلال زيادة التوافر الحيوي للعلاج المضاد للفيروسات في الجهاز العصبي المركزي وتحسين وصول الدواء إلى مخازن الفيروس في الدماغ

الكلمات المفتاحية: العلاج بمضادات الفيروسات القهقرية(ART) ، الإعطاء عبر الأنف، النواقل النانوية، الإيدز العصبي(NeuroAIDS) ، التوصيل من الأنف إلى الدماغ.