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Nose-to-Brain Drug Delivery

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Definition

Nose-to-brain drug delivery is an innovative approach that leverages the unique anatomical pathways connecting the nasal cavity to the brain, including the olfactory and trigeminal nerve routes. This method bypasses the blood–brain barrier, enabling direct and efficient transport of therapeutic agents to the central nervous system. It offers significant advantages, such as rapid drug action, reduced systemic side effects, and improved patient compliance through non-invasive administration. This entry summarizes factors affecting the nose-to-brain delivery of drugs and the recent development of nanoparticle-based nose-to-brain delivery.

Keywords: nose-to-brain; blood–brain barrier; bioavailability; drug delivery; nanoparticle; polymeric nanoparticles; SLNs; NLCs; emulsions; liposomes

1. Introduction

Nose-to-brain drug delivery is an approach to directly deliver therapeutic agents from the nasal cavity to the brain, bypassing the blood–brain barrier (BBB) [1,2]. The BBB is a highly selective structure that prevents most drugs from reaching the brain when administered through conventional routes, such as oral or parenteral methods [3,4]. The anatomical connection between the nasal cavity and the brain, primarily through the olfactory and trigeminal nerve pathways, offers a unique route for drug delivery that avoids the challenges posed by the BBB [5–7]. This approach has emerged as a promising non-invasive technique for treating various central nervous system (CNS) disorders, including Alzheimer's disease, Parkinson's disease, brain tumors, epilepsy, and psychiatric conditions [8–10].

Intranasal (IN) administration has several advantages over traditional drug delivery routes. It bypasses the gastrointestinal tract and liver metabolism, eliminating the risk of drug degradation during first-pass metabolism, improving bioavailability [11,12]. Furthermore, IN delivery allows for rapid drug absorption and onset of action, making it particularly beneficial in conditions requiring immediate therapeutic effects [10,13]. The localized administration also minimizes systemic side effects, as the drug is directed specifically to the brain. Additionally, the ease of self-administration makes IN delivery a patient-friendly option, enhancing compliance and accessibility for chronic or acute treatments [14,15].

The underlying mechanism of nose-to-brain delivery involves the olfactory and trigeminal nerve pathways [16]. The olfactory nerve, located in the upper nasal cavity, provides a direct connection to the brain's olfactory bulb, allowing drugs to bypass the systemic

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Academic Editor: Jose L. Arias

Received: 24 April 2025
Revised: 14 June 2025
Accepted: 27 June 2025
Published: 30 June 2025

Citation: Nguyen, L.T.-T.; Duong, V.-A. Nose-to-Brain Drug Delivery. *Encyclopedia* **2025**, *5*, 91. https://doi.org/10.3390/encyclopedia5030091

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circulation and enter the CNS directly [17,18]. Similarly, the trigeminal nerve, which innervates the nasal mucosa, also facilitates drug transport to various brain regions [19]. These pathways enable therapeutic agents to reach the brain quickly and effectively, bypassing the restrictive barriers that would otherwise impede drug delivery [20]. They are considered direct nose-to-brain delivery pathways. The lymphatic pathway is an emerging route in nose-to-brain drug delivery, offering an alternative to direct neuronal transport via the olfactory and trigeminal nerves. Drugs administered intranasally can enter the nasal lymphatic vessels and reach the CNS through cerebrospinal fluid exchange or perivascular spaces [21]. This route may be especially useful for delivering large molecules or biologics that are otherwise restricted by the BBB. By reducing systemic exposure and enabling more targeted CNS delivery, the lymphatic pathway holds promise for enhancing the efficacy and safety of IN therapeutics [22]. Besides these routes, IN-administered drugs can reach the brain via indirect pathways. A part of the drug administered intranasally is distributed in the respiratory region and absorbed by respiratory epithelia to the systemic circulation. It can also be distributed to the lungs and gastrointestinal tract and then absorbed into the blood stream [23,24]. From the blood, the drug can cross the BBB to enter the brain. However, BBB has many efflux pumps to prevent drugs from entering the brain [6,25,26]. Figure 1 presents direct and indirect routes for nose-to-brain delivery.

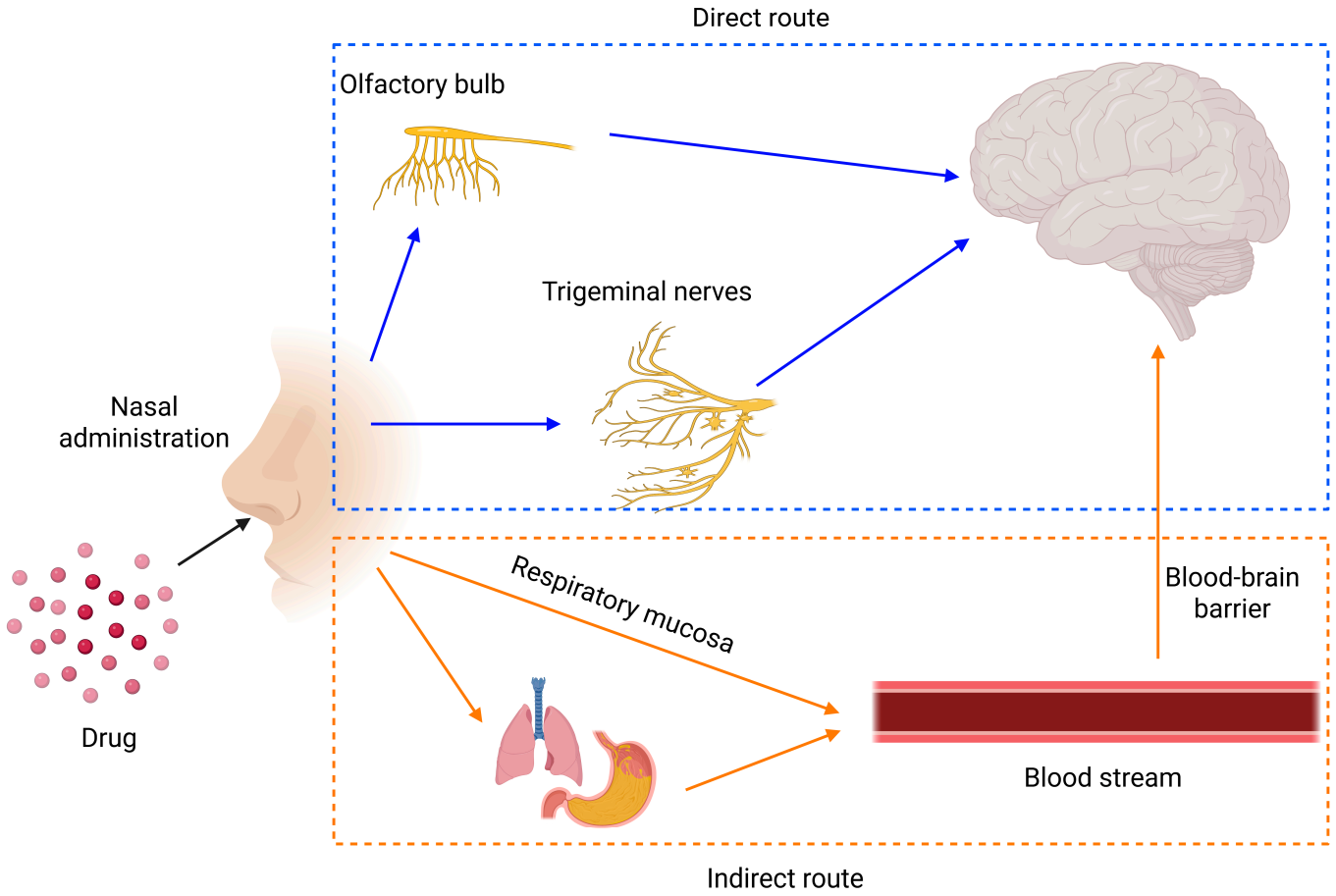


Figure 1. Direct and indirect routes of nose-to-brain delivery. Created in BioRender.

Despite its advantages, nose-to-brain delivery poses certain challenges that must be addressed during formulation development [27]. The nasal cavity's limited surface area and small volume capacity restrict the amount of drug that can be delivered at a time [28]. Additionally, the mucociliary clearance mechanism rapidly removes foreign substances, limiting the residence time of formulations in the nasal cavity [29–31]. The enzymatic

degradation of drugs and variability in absorption due to individual nasal conditions also present significant obstacles [32]. To overcome these limitations, researchers have developed different nanoparticle (NP)-based drug delivery systems, such as liposomes [33], nanoemulsions [34], solid lipid nanoparticles (SLNs) [35,36], nanostructured-lipid carriers [37], polymeric NPs [38,39], and micelles [40], to improve drug solubility, stability, and retention in the nasal cavity [32,41,42].

In this entry, the authors summarize the key factors influencing the efficiency and effectiveness of nose-to-brain drug delivery. Additionally, the authors highlight the recent advancements in nanotechnology-based delivery systems that have been developed to overcome current challenges in nose-to-brain delivery, thereby providing a deeper understanding of how these advanced drug delivery systems are paving the way for more effective treatments of central nervous system disorders through the intranasal route.

2. Factors Affecting Nose-to-Brain Delivery of Drugs

2.1. Properties of Drugs

2.1.1. Molecular Weight

The molecular weight of a drug plays a pivotal role in determining its permeability across the nasal mucosa, which is a key consideration for nose-to-brain drug delivery. Compounds with molecular weights below approximately 1000 Da are generally able to diffuse through the tight junctions of the nasal epithelial cells, facilitating more efficient absorption into the CNS [43–45]. In contrast, high-molecular-weight drugs, such as peptides, proteins, and biologics, often encounter significant barriers due to their size, which limits their ability to cross the nasal epithelium. This reduced permeability can compromise their therapeutic effectiveness when administered intranasally. To overcome this challenge, advanced formulation strategies such as the use of permeation enhancers, carrier systems (e.g., emulsions, liposomes, and NPs), or mucoadhesive agents are often employed to improve the transport of larger molecules across the nasal barrier.

2.1.2. Lipophilicity

Lipophilicity of a drug plays a critical role in its nasal absorption profile. Lipophilic drugs, which have an affinity for lipid-rich environments, can readily cross the nasal mucosa through transcellular diffusion, where they dissolve into and pass through the lipid bilayers of cell membranes [43,46]. This property enhances their penetration rate, making them ideal candidates for nose-to-brain delivery systems. On the other hand, highly hydrophilic drugs, which prefer aqueous environments, face challenges in permeating the lipid-rich nasal membrane, resulting in lower absorption rates [20,47]. To overcome this, formulation strategies such as incorporating lipophilic excipients or encapsulation in lipid-based NPs can enhance the delivery of hydrophilic drugs.

2.1.3. Solubility

The solubility of a drug in the aqueous environment of the nasal cavity is a key factor influencing its bioavailability. Drugs with poor solubility in nasal secretions may fail to dissolve adequately, leading to suboptimal concentrations at the absorption site and reduced therapeutic effectiveness [45,48]. Poorly water-soluble drugs may require solubilizing agents or specialized delivery systems to enhance dissolution in the nasal environment. Improving solubility through formulation techniques, such as using co-solvents or surfactants, can significantly boost the drug's availability for absorption, ensuring that sufficient quantities reach the target site, whether the systemic circulation or the CNS.

2.1.4. Stability

The chemical and physical stability of a drug within a nasal formulation is vital to ensure its therapeutic potency during delivery. Drugs that are prone to degradation, due to enzymatic activity, pH changes, or oxidative processes in the nasal environment, may lose their efficacy before reaching the target site [17,47]. For instance, peptide-based drugs like insulin are susceptible to enzymatic breakdown in the nasal cavity, necessitating protective strategies such as enzyme inhibitors or stabilizing excipients. Stable formulations, achieved through encapsulation in protective matrices, ensure that the active pharmaceutical ingredient remains intact and functional throughout the delivery process, maximizing therapeutic outcomes [45,49].

2.1.5. pH

The pH of a nasal formulation significantly affects both drug stability and absorption efficiency. The nasal mucosa maintains a physiological pH range of approximately 4.5 to 6.5, which is slightly acidic [50,51]. Formulations should be designed to align with this range to minimize irritation to the sensitive nasal tissues and optimize drug absorption. Deviations from this pH range can lead to drug instability (e.g., hydrolysis of certain compounds) or mucosal irritation, potentially causing discomfort or tissue damage. For example, a formulation with a pH significantly below 4.5 may cause stinging or inflammation, while a highly alkaline pH could disrupt the mucosal barrier. Buffering agents are often incorporated to maintain pH compatibility, ensuring both patient comfort and effective drug delivery.

2.2. Formulation Properties

2.2.1. Particle Size

The size of particles in nasal formulations, particularly NPs, is a critical factor in determining their ability to penetrate the nasal epithelium. NPs smaller than 200 nm can effectively permeate lipid membranes or pass through tight junctions in the nasal mucosa, facilitating efficient drug delivery to the brain [32,52,53]. In contrast, larger particles may become trapped in the anterior nasal cavity or cleared by mucociliary mechanisms, reducing their effectiveness for nose-to-brain delivery. When larger particles reach the mucosal surface, they must release the drug for absorption via passive diffusion, which can be slower and less efficient [54,55]. Polymeric NPs, SLNs, NPCs, and liposomes are often engineered to optimize particle size, ensuring better penetration and targeted delivery.

2.2.2. Permeation Enhancers

Permeation enhancers are specialized additives incorporated into nasal formulations to improve drug absorption by temporarily increasing the permeability of the nasal mucosa. Common enhancers, such as polysorbate 80, dodecyl maltoside, tetradecyl maltoside, methyl-β-cyclodextrin, and chitosan, work by disrupting tight junctions or altering the mucosal structure to facilitate drug passage [56,57]. For example, chitosan can open tight junctions by interacting with negatively charged mucosal surfaces, enhancing paracellular transport. However, the use of these enhancers requires careful consideration, as excessive disruption of the mucosal barrier can lead to irritation, inflammation, or long-term damage [58,59]. Balancing efficacy and safety is critical, often requiring rigorous testing to ensure that enhancers improve absorption without compromising mucosal integrity.

2.2.3. Formulation Viscosity

The viscosity of a nasal formulation influences its retention time and distribution within the nasal cavity, directly impacting drug absorption. Formulations with higher vis-

cosity, often achieved by incorporating polymers like carboxymethylcellulose or carbopol, can prolong contact with the nasal mucosa, enhancing drug absorption by allowing more time for diffusion [46,60]. However, excessively viscous formulations may impede drug release or cause discomfort during administration, potentially reducing patient compliance. For example, gel-based formulations may provide extended mucosal contact but could feel sticky or obstructive. Striking a balance in viscosity is essential to optimize both therapeutic efficacy and user experience, ensuring that the formulation is neither too runny nor too thick [61].

2.2.4. Delivery Device

The choice of delivery device, such as nasal sprays, pumps, or nebulizers, significantly affects the deposition and distribution of the drug within the nasal cavity. Devices that produce fine, uniform droplets ensure better coverage of the nasal mucosa, particularly the olfactory region, which is critical for nose-to-brain delivery [61,62]. Advanced devices, such as precision olfactory delivery systems, can target specific nasal regions to maximize absorption. Poorly designed devices may result in uneven distribution or deposition in non-target areas, reducing efficacy. For instance, a coarse spray may deposit primarily in the anterior nasal cavity, limiting access to deeper absorptive sites. Device optimization is, therefore, crucial for effective nasal drug delivery.

2.2.5. Osmolarity

The osmolarity of a nasal formulation influences mucosal hydration and drug absorption efficiency. Formulations that are isotonic with nasal secretions (approximately 280–310 mOsm/kg) are generally well tolerated, minimizing irritation and maintaining normal mucosal function [62,63]. Hypertonic formulations may dehydrate the mucosa, causing discomfort or reduced absorption, while hypotonic solutions can lead to excessive hydration, potentially diluting the drug and hindering uptake [64,65]. In addition, a hypertonic saline-based formulation might cause a burning sensation, deterring patient use. Careful adjustment of osmolarity, often through the addition of salts or sugars, ensures compatibility with the nasal environment and enhances both comfort and absorption.

2.3. Nasal Cavity Conditions

2.3.1. Nasal Mucosa Condition

The condition of the nasal mucosa is a critical factor in determining the success of drug absorption. A healthy, intact mucosa provides an optimal surface for drug uptake, allowing efficient diffusion or transport to the CNS [62,66]. However, conditions such as chronic rhinitis, sinusitis, or nasal trauma can compromise mucosal integrity, leading to inflammation, altered permeability, or reduced drug absorption. For example, inflamed mucosa may exhibit increased mucus production, which can trap or dilute the drug, lowering bioavailability. Mucociliary clearance, a natural defense mechanism that removes foreign particles and pathogens, further complicates drug delivery by reducing residence time in the nasal cavity [67]. To counter this, mucoadhesive agents like chitosan or hydroxypropyl methylcellulose are often included in formulations to extend contact time with the mucosa, enhancing absorption [62,65]. Additionally, environmental factors like humidity can affect mucus viscosity, with low humidity causing thickened mucus that hinders drug penetration, while high humidity may alter drug solubility or stability [20]. Excessive mucus production, common in allergies or infections, can further impede delivery by obstructing the formulation or reducing device efficacy. Formulations must therefore be designed to adapt to varying mucosal conditions, incorporating strategies like mucolytics to manage excess mucus [59,68].

2.3.2. Nasal Temperature

The temperature within the nasal cavity can influence the performance of nasal formulations by affecting drug solubility, viscosity, and absorption [62,66]. Variations in nasal temperature, typically ranging from 32–34 °C, can alter the physical properties of a formulation. For instance, colder temperatures may increase the viscosity of a gel-based formulation, slowing drug release, while warmer conditions could enhance solubility but risk drug degradation. External factors, such as ambient temperature or humidity, can further modulate nasal temperature, impacting mucosal conditions and absorption efficiency. For example, cold, dry environments may cause mucosal drying, reducing drug dissolution. Advanced delivery systems account for these variations by incorporating thermoresponsive polymers that maintain optimal viscosity and release profiles across a range of temperatures, ensuring consistent drug delivery under diverse conditions.

2.3.3. Nasal Blood Flow

Nasal blood flow affects drug absorption and its subsequent transport to the brain or systemic circulation. Increased blood flow, often induced by vasodilation, can enhance drug uptake by providing a larger vascular surface area for absorption, while vasoconstriction may reduce absorption by limiting blood supply to the mucosa [59]. Physiological factors, such as exercise or stress, or pharmacological agents like vasoconstrictors (e.g., phenylephrine) or vasodilators, can modulate nasal blood flow, impacting delivery efficiency.

3. Conventional Formulations for Nose-to-Brain Delivery

Several products have been developed and approved for therapeutic indications that benefit from nose-to-brain delivery, leveraging the nasal cavity's anatomical and physiological connections to the CNS. Table 1 summarizes the formulations have been approved, with clinical indications aligning with the nose-to-brain pathway [69]. These include treatments for neurologic and psychiatric conditions such as migraine, depression, epilepsy, and opioid overdose. For example, sumatriptan nasal sprays (Imitrex®, OnzetraXsail®, and Tosymra®) were approved for acute migraine attacks, with the advantage of rapid onset of action. Another notable example is naloxone nasal spray (Narcan®), used to reverse opioid overdose. Esketamine nasal spray (Spravato®) was approved for depression. The nose-to-brain delivery allows for rapid brain entry and fast-acting antidepressant effects, making it a significant advancement in treatment. Diazepam nasal spray (Valtoco®) provides a non-invasive therapy in the treatment of seizure clusters.

In addition, numerous clinical trials have been conducted to investigate the potential of nose-to-brain drug delivery for various CNS disorders. For epilepsy, diazepam (NRL-1) successfully completed a Phase 3 trial (NCT02721069). For migraine, several drugs have been evaluated, such as dihydroergotamine delivered via a Precision Olfactory Delivery (POD) device (NCT03874832—Phase 1 and NCT03557333—Phase 3), lidocaine (NCT03806595—Phase 1), zolmitriptan (NCT03275922—Phase 3), and zavegepant (NCT04571060—Phase 3). For depression, esketamine has been extensively studied for major depressive disorder in two Phase 3 studies (NCT04338321 and NCT03039192), and a Phase 2 study in combination with midazolam (NCT03185819). For schizophrenia and bipolar disorder, intranasal olanzapine delivered via a POD device completed a Phase 1 safety study (NCT03624322). These trials collectively underscore the rapid development and potential of nose-to-brain delivery for rapid and targeted treatment of various CNS diseases [2].

Table 1. Representative FDA-approved nose-to-brain formulations.

Active Ingredient	Brand Name	Company	Approval Year	Dosage Form	Indication
Butorphanol tartrate	Stadol NS	Bristol-Myers Squibb	1991 (discontinued in 2004)	Nasal spray	Pain
Diazepam	Valtoco®	Neurelis	2020	Nasal spray	Epilepsy
Dihydroergotamine mesylate	Migranal®	Bausch Health US	1997	Nasal spray	Migraine
Dihydroergotamine mesylate	Trudhesa®	Impel	2021	POD® system	Migraine
Esketamine hydrochloride	Spravato®	Janssen	2019	Nasal spray	Depression
Midazolam	Nayzilam®	Ucb Inc.	2019	Nasal spray	Epilepsy
Naloxone hydrochloride	Narcan®	Emergent Operations Ireland	2015	Nasal spray	Opioid overdose
Naloxone hydrochloride	Kloxxado®	Hikma	2021	Nasal spray	Opioid overdose
Naloxone hydrochloride	Naloxone hydrochloride	Amphastar pharms	2023	Nasal spray	Opioid overdose
Sumatriptan	Imitrex®	GlaxoSmithKline	1997	Nasal spray	Migraine
Sumatriptan	OnzetraXsail®	Currax	2016	Xsail® system	Migraine
Sumatriptan	Tosymra®	Upsher Smith Laboratories	2019	Nasal spray	Migraine
Varenicline	Tyrvaya®	Oyster Point Pharma	2021	Nasal spray	Dry Eye Disease
Zavegepant	Zavzpret®	Pfizer	2023	Nasal spray	Migraine
Zolmitriptan	Zomig®	Amneal	2003	Nasal spray	Migraine

4. Advanced Nanoparticles for Nose-to-Brain Delivery

4.1. Advantages of Nanoparticles for Nose-to-Brain Delivery

NPs can significantly enhance nose-to-brain drug delivery, offering a promising strategy for treating neurological disorders. They have different components, structures, and properties. Polymeric NPs are usually prepared from biodegradable and biocompatible polymers like poly(lactic-co-glycolic acid) (PLGA) [70] and chitosan (CS) [71]. They are highly versatile, enabling precise surface modifications for targeted delivery and controlled or sustained drug release [72]. Polymeric NPs protect sensitive therapeutics from degradation, prolong circulation time, and degrade safely in the body. Liposomes are spherical vesicles with one or more phospholipid bilayers, which can encapsulate hydrophilic drugs in their aqueous core and lipophilic drugs within their lipid bilayers [73]. They provide biocompatibility, non-toxicity, and enhanced drug protection. SLNs are produced from solid lipids stable at body temperature, whereas NLCs combine solid and liquid lipids for superior drug loading and stability [74–76]. They offer high entrapment efficiency, particularly for hydrophobic drugs, and are produced via methods like high-pressure homogenization or solvent emulsification [77,78]. Nanoemulsions are formed by blending immiscible liquids (e.g., oil and water) with surfactants to create droplets typically under 100 nm, facilitating controlled release, enhanced stability, and targeted delivery for diverse drugs [79].

Encapsulation of drugs in NPs can improve their solubility and permeability across the nasal mucosa [55,80]. For example, dexamethasone showed 14-fold higher solubility and an increased permeability in vitro after encapsulation in micelles [81]. Duloxetine

incorporated in PLGA-CS NPs exhibited four-fold higher ex vivo permeation than the free drug solution [82]. Encapsulation of paliperidone in NLCs increased the drug permeation three times [83]. The NPs with small size and adequate lipophilicity can readily penetrate the intercellular gaps between olfactory cells, particularly lipid-based NPs such as liposomes, nanoemulsions, SLNs, and NLCs [84–86]. NPs smaller than 100 nm can reduce mucociliary clearance and enhance nerve-mediated drug transport to the brain [87,88]. Some surfactants, such as Tween 80, Tween 20, and sodium lauryl sulfate, are usually used to prepare NPs to maintain their dispersibility and stability. These surfactants disrupt tight junctions between epithelial cells, improving drug permeability [89]. Additionally, NPs can protect drugs from degradation due to environmental factors such as pH, enzymes, and oxidation, increasing the drug stability and efficacy [90].

The encapsulation of drugs into NPs can prevent them from rapid mucociliary clearance, thereby increasing their retention in the nasal cavity and enhancing drug absorption [91]. Embedding these NPs into gels or modifying their surfaces with suitable materials can increase retention time [92]. Mucoadhesive polymers such as chitosan, hyaluronic acid, cellulose derivatives, and poloxamers can adhere to the nasal mucosa through physical or chemical interactions, including hydrogen bonding, van der Waals forces, or ionic interactions with mucin glycoproteins [93]. Therefore, modifying NPs with these polymers can prolong the contact of NPs with the mucosal surface and increase the opportunity for drugs to traverse the olfactory and trigeminal nerve pathways, facilitating direct transport to the brain. Coating NPs with some polymers, such as chitosan, can make them positively charged NPs, which effectively adhere to negatively charged mucosa [94,95]. Hydrogels can adhere to the nasal mucosa and prolong the residence time of NPs in the nasal cavity [96]. Hydrogels can be engineered as in situ gelling systems, which transition from a liquid to a gel state in response to stimuli like temperature, pH, or ionic changes in the nasal cavity. For instance, thermoresponsive hydrogels based on poloxamers gel at body temperature, ensuring that the formulation remains localized [96].

4.2. Recent Advanced Nanoparticles for Nose-to-Brain Delivery

4.2.1. Micelles

Different NP-based formulations have been developed and characterized for nose-to-brain delivery. For example, rotigotine micelles were produced from methoxy-poly(ethyleneglycol)-block-poly(lactic-co-glycolic acid) and then loaded into a poloxamer gel for intranasal administration. In rats, the gel showed better rotigotine distribution than the control (IV free drug), with 2.76-, 1.70-, 1.66-, and 1.84-fold higher drug levels in the olfactory bulb, cerebrum, cerebellum, and striatum, respectively [97]. Similarly, clozapine micelles were prepared from three polymers (Tetronic® 904, 701, and Synperonic® PE/F127). This is a drug used to treat schizophrenia, but its oral administration has low brain distribution due to the poor solubility and dissolution rate, drug degradation, and hepatic first-pass metabolism. The ex vivo nasal permeation study showed that the flux of micelles was five-fold higher than that of the clozapine suspension. The formulation did not cause histological irritation. The IN micelles exhibited higher brain distribution in mice than the IV micelles. The successful nose-to-brain delivery was confirmed by the drug targeting efficiency (DTE) of 397% and direct transport percentage (DTP) of 74.8%. This DTP value indicates that following IN administration, 74.8% of clozapine distributed to the brain was from the direct nose-to-brain route, and the remaining 25.2% was from the bloodstream after the drug crossed the BBB. In addition, the IN micelles showed a faster onset than the IV micelles as evidenced by shorter Tmax in the brain (30 vs. 120 min) [98].

4.2.2. Polymeric Nanoparticles

Vinpocetine is a drug used to improve memory, cognitive function, and cerebrovascular disorders. Vinpocetine CS NPs were prepared and then loaded into an in situ gel of Poloxamer 407 and Poloxamer 188. The pharmacokinetic study showed that the vinpocetine CS NPs gel had higher C_{max} (2.2-fold) and AUC (1.7-fold) in the rat brain than oral commercial vinpocetine tablets [99]. This indicates the improved brain availability of the drug in the CS NPs gel formulation administered via the IN route. Similarly, piribedil lecithin-CS NPs were prepared and loaded into a thermo-responsive in situ gel. Following IN administration of the gel to rats, the AUC in the brain increased 6.4-fold compared with the free drug suspension. The DTP was 56% for the gel, indicating the direct nose-to-brain delivery [100]. About 44% of the drug distributed to the brain was from the systemic circulation, suggesting the importance of the indirect pathway.

4.2.3. Lipid-Based Nanoparticles

Nanoemulsions of aripiprazole were prepared from Capmul PG-8 Tween 80 and Transcutol HP and then loaded into Carbopol 971 gel. In the pharmacokinetic study in rats, the C_{max} and AUC in the brain of the IN nanoemulgel were higher than those of the IV aripiprazole solution. The direct nose-to-brain delivery was demonstrated by a DTP of 90%. The nanoemulgel showed improved behaviors as evaluated in the paw test and locomotor test [34]. In another study, imatinib was encapsulated into liposomes prepared from egg phosphatidylcholine, cholesterol, and cardiolipin. The AUC in the rat brain was increased seven-fold in the IN liposomes compared to the oral and IN imatinib solutions, suggesting that the IN liposomes could substantially enhance the drug distribution to the brain [101].

Asiatic acid-loaded SLNs were previously prepared from rice bran wax, Tween 80, and soybean lecithin. In a pharmacokinetic study, the IN SLNs showed enhanced brain distribution in mice compared with the IV SLNs [102]. In a pharmacodynamic study in rats using a Morris water maze and novel object recognition tests, IN SLNs improved learning and memory abilities. In Alzheimer's disease rats (induced by $A\beta_{1\text{-}42}$), the IN SLNs exhibited potential in treating early stages of the disease, as demonstrated by the reduced tau hyperphosphorylation, glial activation, and lipid peroxidation [103]. Sumatriptan-loaded NLCs were prepared from stearic acid, cholesterol, triolein, and Brij 35. Following IN administration in rats, the optimized sumatriptan-loaded NLCs exhibited direct nose-to-brain delivery with DTP of 61% and DTE of 258% [104]. The indirect route was responsible for 39% of the drug distributed to the brain, suggesting the significance of this route in nose-to-brain delivery.

A previous study explored cationic and anionic polymeric lipid NPs (PLNs) loaded with rivastigmine-docosahexaenoic acid ion-pair complex. The cationic PLNs were prepared from PLGA, stearyl amine, Miglyol 812, and Span 80, which had a zeta potential of 36.4 mV. The anionic PLNs were prepared from PLGA, glyceryl monostearate, and PEG-32-stearate, which showed a zeta potential of −39.3 mV. Both PLNs were incorporated into hydrogels composed of Poloxamer 407 and Poloxamer 188. Compared to a free rivastigmine gel, the PLN-loaded hydrogels demonstrated significantly enhanced ex vivo nasal permeation, by 4.07- and 3.18-fold for the cationic and anionic PLN gels, respectively. Additionally, mucociliary residence time in rat nasal tissue was prolonged by 3.18-fold for cationic and 2-fold for anionic PLN gels relative to the control. Pharmacokinetic studies in rats showed increased brain exposure after IN administration of both PLN gels, with the cationic and anionic PLN gels elevating C_{max} by 2.37- and 1.99-fold, mean residence time (MRT) by 9.26- and 5.63-fold, and brain AUC by 7.67- and 5.18-fold, respectively, when compared to the IN free drug gel. DTE followed the trend: free RIV gel (281.3%) < anionic PLN gel (672.3%) < cationic PLN gel (792.5%). Similarly, DTP values were 64.4%, 85.1%, and

87.4%, respectively. These findings underscore the brain-targeting capability of intranasally administered PLN-based hydrogels over the free drug formulation [105].

These examples highlight the development and evaluation of different NPs for the nose-to-brain delivery of various drugs. They demonstrate that micelles, polymeric NPs, nanoemulsions, liposomes, SLNs, NLCs, and PLNs can successfully deliver different drugs to the brain via direct and indirect nose-to-brain pathways.

4.3. Industrial and Translational Limitations

Despite the promising potential of NPs for nose-to-brain drug delivery, several industrial and translational limitations remain significant hurdles for clinical and commercial success. One of the main cost-related barriers stems from the complexity of the NP design and synthesis. Many NPs (SLNs, NLCs, liposomes, polymeric NPs) require multi-step fabrication processes that involve precise control over parameters like size, charge, encapsulation efficiency, and drug loading [106]. These processes often rely on high-purity reagents, specialized equipment, and stringent aseptic conditions, all of which contribute to elevated production costs. Furthermore, when surface modifications are needed to enhance mucoadhesion, targeting, or penetration through the nasal epithelium, such as with PEGylation or ligand conjugation, the associated costs can increase substantially due to the added materials and quality control requirements [107].

Beyond cost, large-scale production presents a significant challenge. Some NP synthesis methods, such as solvent evaporation, nanoprecipitation, or emulsification, are optimized for laboratory or pilot scale and may not effectively translate to industrial-scale manufacturing. Ensuring uniformity in particle size, morphology, and drug encapsulation becomes increasingly challenging during scale-up, which can compromise the batch-to-batch consistency that is critical for regulatory approval. Reproducibility and stability are especially vital for intranasal formulations, as variations in particle characteristics can affect mucosal penetration, residence time, and ultimately, brain targeting efficiency [100].

Additionally, formulation stability during storage and distribution presents another industrial hurdle. NPs are prone to aggregation, degradation, or loss of functional integrity over time, particularly in liquid suspensions. Although strategies such as lyophilization (freeze-drying) or incorporating stabilizers may mitigate these issues, they also add extra steps and costs to the production workflow. Furthermore, for IN delivery, the formulation must also maintain suitable viscosity, pH, and osmolarity to ensure nasal tolerability and efficacy, which adds further complexity to large-scale formulation development [3,101].

5. Conclusions

Nose-to-brain drug delivery offers a promising non-invasive approach for targeting CNS disorders by bypassing the BBB. Several IN formulations, such as sumatriptan, naloxone, diazepam, and esketamine nasal sprays, have already received FDA approval for various CNS disorders (migraine, epilepsy, depression, and opioid overdose). These clinically successful products demonstrate the therapeutic relevance and practicality of the IN route. Building on this foundation, NP-based systems, including micelles, polymeric NPs, nanoemulsions, liposomes, SLNs, and NLCs, have shown significant potential to enhance brain targeting, improve drug solubility and permeability, and prolong nasal residence time. Preclinical studies have demonstrated enhanced brain bioavailability and direct nose-to-brain transport efficiency when drugs are encapsulated in NPs. Despite these advances, challenges remaining for industrial translation, such as high production costs, difficulties in scaling up manufacturing processes, and stability concerns, are key barriers to clinical implementation. Furthermore, formulation parameters must be carefully optimized to ensure mucosal compatibility and minimize variability in drug delivery. Addressing

these limitations through innovation in formulation science and manufacturing technology will be essential to fully realize the potential of NP-based nose-to-brain drug delivery for future CNS therapies.

Author Contributions: Conceptualization, L.T.-T.N. and V.-A.D.; writing—original draft preparation, L.T.-T.N.; writing—review and editing, V.-A.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Prabakaran, A.; Agrawal, M.; Dethe, M.R.; Ahmed, H.; Yadav, A.; Gupta, U.; Alexander, A. Nose-to-brain drug delivery for the treatment of Alzheimer's disease: Current advancements and challenges. *Expert Opin. Drug Deliv.* **2022**, *19*, 87–102. [CrossRef]
2. Koo, J.; Lim, C.; Oh, K.T. Recent Advances in Intranasal Administration for Brain-Targeting Delivery: A Comprehensive Review of Lipid-Based Nanoparticles and Stimuli-Responsive Gel Formulations. *Int. J. Nanomed.* **2024**, *19*, 1767–1807. [CrossRef]
3. Du, L.; Chen, L.; Liu, F.; Wang, W.; Huang, H. Nose-to-brain drug delivery for the treatment of CNS disease: New development and strategies. *Int. Rev. Neurobiol.* **2023**, *171*, 255–297. [CrossRef] [PubMed]
4. 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**, *366*, 519–534. [CrossRef] [PubMed]
5. Hong, S.-S.; Oh, K.T.; Choi, H.-G.; Lim, S.-J. Liposomal Formulations for Nose-to-Brain Delivery: Recent Advances and Future Perspectives. *Pharmaceutics* **2019**, *11*, 540. [CrossRef]
6. Nguyen, T.-T.-L.; Maeng, H.-J. Pharmacokinetics and Pharmacodynamics of Intranasal Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Nose-to-Brain Delivery. *Pharmaceutics* **2022**, *14*, 572. [CrossRef]
7. Achar, A.; Myers, R.; Ghosh, C. Drug Delivery Challenges in Brain Disorders across the Blood—Brain Barrier: Novel Methods and Future Considerations for Improved Therapy. *Biomedicines* **2021**, *9*, 1834. [CrossRef]
8. Gao, H. Progress and perspectives on targeting nanoparticles for brain drug delivery. *Acta Pharm. Sin. B* **2016**, *6*, 268–286. [CrossRef]
9. Agrawal, M.; Saraf, S.; Saraf, S.; Antimisiaris, S.G.; Chougule, M.B.; Shoyele, S.A.; Alexander, A. Nose-to-brain drug delivery: An update on clinical challenges and progress towards approval of anti-Alzheimer drugs. *J. Control. Release* **2018**, *281*, 139–177. [CrossRef]
10. Xu, K.; Duan, S.; Wang, W.; Ouyang, Q.; Qin, F.; Guo, P.; Hou, J.; He, Z.; Wei, W.; Qin, M. Nose-to-brain delivery of nanotherapeutics: Transport mechanisms and applications. *WIREs Nanomed. Nanobiotechnol.* **2024**, *16*, e1956. [CrossRef]
11. Chakraborty, S.; Karmakar, V.; Chatterjee, K.; Chatterjee, A.; Dwivedi, M.; Gorain, B. Chitosan nanoparticle-mediated nose-to-brain delivery of naringenin: Attenuating memory decline in experimental animals via behavioural assessment and modulation of biochemical parameters. *Int. J. Biol. Macromol.* **2025**, *286*, 138336. [CrossRef] [PubMed]
12. Hameed, H.; Faheem, S.; Younas, K.; Jamshaid, M.; Ereej, N.; Hameed, A.; Munir, R.; Khokhar, R. A comprehensive review on lipid-based nanoparticles via nose to brain targeting as a novel approach. *J. Microencapsul.* **2024**, *41*, 681–714. [CrossRef] [PubMed]
13. Liu, Y.; Tan, Y.; Cheng, G.; Ni, Y.; Xie, A.; Zhu, X.; Yin, C.; Zhang, Y.; Chen, T. Customized Intranasal Hydrogel Delivering Methylene Blue Ameliorates Cognitive Dysfunction against Alzheimer's Disease. *Adv. Mater.* **2024**, *36*, e2307081. [CrossRef]
14. Teng, Z.; Meng, L.-Y.; Yang, J.-K.; He, Z.; Chen, X.-G.; Liu, Y. Bridging nanoplatform and vaccine delivery, a landscape of strategy to enhance nasal immunity. *J. Control. Release* **2022**, *351*, 456–475. [CrossRef]
15. Duong, V.-A.; Nguyen, T.-T.-L.; Maeng, H.-J. Recent Advances in Intranasal Liposomes for Drug, Gene, and Vaccine Delivery. *Pharmaceutics* **2023**, *15*, 207. [CrossRef]
16. Deshmukh, V.; Pathan, N.S.; Haldar, N.; Nalawade, S.; Narwade, M.; Gajbhiye, K.R.; Gajbhiye, V. Exploring intranasal drug delivery via nanocarriers: A promising glioblastoma therapy. *Colloids Surf. B Biointerfaces* **2024**, *245*, 114285. [CrossRef] [PubMed]
17. Keller, L.A.; Merkel, O.; Popp, A. Intranasal drug delivery: Opportunities and toxicologic challenges during drug development. *Drug Deliv. Transl. Res.* **2022**, *12*, 735–757. [CrossRef]

18. 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**, *207*, 115196. [CrossRef]
19. Musumeci, T.; Bonaccorso, A.; Puglisi, G. Epilepsy Disease and Nose-to-Brain Delivery of Polymeric Nanoparticles: An Overview. *Pharmaceutics* **2019**, *11*, 118. [CrossRef]
20. Jin, Z.; Han, Y.; Zhang, D.; Li, Z.; Jing, Y.; Hu, B.; Sun, S. Application of Intranasal Administration in the Delivery of Antidepressant Active Ingredients. *Pharmaceutics* **2022**, *14*, 2070. [CrossRef]
21. Semyachkina-Glushkovskaya, O.; Shirokov, A.; Blokhina, I.; Telnova, V.; Vodovozova, E.; Alekseeva, A.; Boldyrev, I.; Fedosov, I.; Dubrovsky, A.; Khorovodov, A.; et al. Intranasal Delivery of Liposomes to Glioblastoma by Photostimulation of the Lymphatic System. *Pharmaceutics* **2022**, *15*, 36. [CrossRef]
22. Yan, M.; Cheng, L.; Zheng, Z.; Lin, Y.; Qin, D.; Chen, H. Advances in the Understanding of ocular and nasal lymphatics. *BMC Immunol.* **2025**, *26*, 16. [CrossRef] [PubMed]
23. Costa, C.; Moreira, J.N.; Amaral, M.H.; Sousa Lobo, J.M.; Silva, A.C. Nose-to-brain delivery of lipid-based nanosystems for epileptic seizures and anxiety crisis. *J. Control. Release* **2019**, *295*, 187–200. [CrossRef] [PubMed]
24. Kapoor, M.; Cloyd, J.C.; Siegel, R.A. A review of intranasal formulations for the treatment of seizure emergencies. *J. Control. Release* **2016**, *237*, 147–159. [CrossRef] [PubMed]
25. Singh, A.P.; Saraf, S.K.; Saraf, S.A. SLN approach for nose-to-brain delivery of alprazolam. *Drug Deliv. Transl. Res.* **2012**, *2*, 498–507. [CrossRef]
26. Lochhead, J.J.; Yang, J.; Ronaldson, P.T.; Davis, T.P. Structure, Function, and Regulation of the Blood-Brain Barrier Tight Junction in Central Nervous System Disorders. *Front. Physiol.* **2020**, *11*, 914. [CrossRef]
27. Nguyen, T.-T.-L.; Duong, V.-A. Advancements in Nanocarrier Systems for Nose-to-Brain Drug Delivery. *Pharmaceuticals* **2025**, *18*, 615. [CrossRef]
28. Crowe, T.P.; Greenlee, M.H.W.; Kanthasamy, A.G.; Hsu, W.H. Mechanism of intranasal drug delivery directly to the brain. *Life Sci.* **2018**, *195*, 44–52. [CrossRef]
29. Wang, Z.; Xiong, G.; Tsang, W.C.; Schätzlein, A.G.; Uchegbu, I.F. Nose-to-Brain Delivery. *J. Pharmacol. Exp. Ther.* **2019**, *370*, 593–601. [CrossRef]
30. Illum, L. Nasal drug delivery: New developments and strategies. *Drug Discov. Today* **2002**, *7*, 1184–1189. [CrossRef]
31. Pires, P.C.; Santos, A.O. Nanosystems in nose-to-brain drug delivery: A review of non-clinical brain targeting studies. *J. Control. Release* **2018**, *270*, 89–100. [CrossRef] [PubMed]
32. Boyuklieva, R.; Pilicheva, B. Micro- and Nanosized Carriers for Nose-to-Brain Drug Delivery in Neurodegenerative Disorders. *Biomedicines* **2022**, *10*, 1706. [CrossRef]
33. Cunha, S.; Almeida, H.; Amaral, M.H.; Lobo, S.J.M.; Silva, A.C. Intranasal Lipid Nanoparticles for the Treatment of Neurodegenerative Diseases. *Curr. Pharm. Des.* **2017**, *23*, 6553–6562. [CrossRef]
34. Kumbhar, S.A.; Kokare, C.R.; Shrivastava, B.; Gorain, B.; Choudhury, H. Antipsychotic Potential and Safety Profile of TPGS-Based Mucoadhesive Aripiprazole Nanoemulsion: Development and Optimization for Nose-To-Brain Delivery. *J. Pharm. Sci.* **2021**, *110*, 1761–1778. [CrossRef]
35. Uppuluri, C.T.; Ravi, P.R.; Dalvi, A.V. Design, optimization and pharmacokinetic evaluation of Piribedil loaded solid lipid nanoparticles dispersed in nasal in situ gelling system for effective management of Parkinson's disease. *Int. J. Pharm.* **2021**, *606*, 120881. [CrossRef] [PubMed]
36. Yadav, R.K.; Shah, K.; Dewangan, H.K. Intranasal drug delivery of sumatriptan succinate-loaded polymeric solid lipid nanoparticles for brain targeting. *Drug Dev. Ind. Pharm.* **2022**, *48*, 21–28. [CrossRef]
37. Sivadasu, P.; Gowda, D.V.; Subramani, N.K.; Malgur, B.; Vishweshwaraiah, S.S.; Hatna, S. Direct brain targeted nanostructured lipid carriers for sustained release of schizophrenic drug: Formulation, characterization and pharmacokinetic studies. *Brain* **2020**, *9*, 12. [CrossRef]
38. Duan, Z.; Zhou, W.; He, S.; Wang, W.; Huang, H.; Yi, L.; Zhang, R.; Chen, J.; Zan, X.; You, C.; et al. Intranasal Delivery of Curcumin Nanoparticles Improves Neuroinflammation and Neurological Deficits in Mice with Intracerebral Hemorrhage. *Small Methods* **2024**, *8*, e2400304. [CrossRef] [PubMed]
39. Awad, R.; Avital, A.; Sosnik, A. Polymeric nanocarriers for nose-to-brain drug delivery in neurodegenerative diseases and neurodevelopmental disorders. *Acta Pharm. Sin. B* **2023**, *13*, 1866–1886. [CrossRef]
40. Kanoujia, J.; Kishore, A.; Parashar, P. Progress in Polymeric Micelles as Viable Wagons for Brain Targeting. *Curr. Pharm. Des.* **2023**, *29*, 116–125. [CrossRef]
41. Nguyen, T.-T.-L.; Duong, V.-A. Solid Lipid Nanoparticles. *Encyclopedia* **2022**, *2*, 952–973. [CrossRef]
42. Duong, V.-A.; Nguyen, T.-T.-L.; Maeng, H.-J. Preparation of Solid Lipid Nanoparticles and Nanostructured Lipid Carriers for Drug Delivery and the Effects of Preparation Parameters of Solvent Injection Method. *Molecules* **2020**, *25*, 4781. [CrossRef] [PubMed]

43. Ritthidej, G.C. Chapter 3—Nasal Delivery of Peptides and Proteins with Chitosan and Related Mucoadhesive Polymers. In *Peptide and Protein Delivery*; Van Der Walle, C., Ed.; Academic Press: Boston, MA, USA, 2011; pp. 47–68.
44. Sakane, T.; Akizuki, M.; Taki, Y.; Yamashita, S.; Sezaki, H.; Nadai, T. Direct Drug Transport from the Rat Nasal Cavity to the Cerebrospinal Fluid: The Relation to the Molecular Weight of Drugs. *J. Pharm. Pharmacol.* **2011**, *47*, 379–381. [CrossRef]
45. Ulusoy, S.; Bayar Muluk, N.; Karpischenko, S.; Passali, G.C.; Negm, H.; Passali, D.; Milkov, M.; Kopacheva-Barsova, G.; Konstantinidis, I.; Dilber, M.; et al. Mechanisms and solutions for nasal drug delivery—A narrative review. *Eur. Rev. Med. Pharmacol. Sci.* **2022**, *26*, 72–81. [CrossRef] [PubMed]
46. Behl, C.R.; Pimplaskar, H.K.; Sileno, A.P.; deMeireles, J.; Romeo, V.D. Effects of physicochemical properties and other factors on systemic nasal drug delivery. *Adv. Drug Deliv. Rev.* **1998**, *29*, 89–116. [CrossRef]
47. Huang, Q.; Chen, X.; Yu, S.; Gong, G.; Shu, H. Research progress in brain-targeted nasal drug delivery. *Front. Aging Neurosci.* **2024**, *15*, 1341295. [CrossRef]
48. Pires, P.C.; Rodrigues, M.; Alves, G.; Santos, A.O. Strategies to Improve Drug Strength in Nasal Preparations for Brain Delivery of Low Aqueous Solubility Drugs. *Pharmaceutics* **2022**, *14*, 588. [CrossRef]
49. Djupesland, P.G. Nasal drug delivery devices: Characteristics and performance in a clinical perspective-a review. *Drug Deliv. Transl. Res.* **2013**, *3*, 42–62. [CrossRef]
50. England, R.J.; Homer, J.J.; Knight, L.C.; Ell, S.R. Nasal pH measurement: A reliable and repeatable parameter. *Clin. Otolaryngol. Allied Sci.* **1999**, *24*, 67–68. [CrossRef]
51. Ramvikas, M.; Arumugam, M.; Chakrabarti, S.R.; Jaganathan, K.S. Chapter Fifteen—Nasal Vaccine Delivery. In *Micro and Nanotechnology in Vaccine Development*; Skwarczynski, M., Toth, I., Eds.; William Andrew Publishing: Norwich, NY, USA, 2017; pp. 279–301.
52. Alberto, M.; Paiva-Santos, A.C.; Veiga, F.; Pires, P.C. Lipid and Polymeric Nanoparticles: Successful Strategies for Nose-to-Brain Drug Delivery in the Treatment of Depression and Anxiety Disorders. *Pharmaceutics* **2022**, *14*, 2742. [CrossRef]
53. Hussein, N.R.; Omer, H.K.; Elhissi, A.M.; Ahmed, W. Advances in nasal drug delivery systems. In *Advances in Medical and Surgical Engineering*; Elsevier: Amsterdam, The Netherlands, 2020; pp. 279–311.
54. Formica, M.L.; Real, D.A.; Picchio, M.L.; Catlin, E.; Donnelly, R.F.; Paredes, A.J. On a highway to the brain: A review on nose-to-brain drug delivery using nanoparticles. *Appl. Mater. Today* **2022**, *29*, 101631. [CrossRef]
55. Kisku, A.; Nishad, A.; Agrawal, S.; Paliwal, R.; Datusalia, A.K.; Gupta, G.; Singh, S.K.; Dua, K.; Sulakhiya, K. Recent developments in intranasal drug delivery of nanomedicines for the treatment of neuropsychiatric disorders. *Front. Med.* **2024**, *11*, 1463976. [CrossRef]
56. Rassu, G.; Ferraro, L.; Pavan, B.; Giunchedi, P.; Gavini, E.; Dalpiaz, A. The Role of Combined Penetration Enhancers in Nasal Microspheres on In Vivo Drug Bioavailability. *Pharmaceutics* **2018**, *10*, 206. [CrossRef]
57. Madden, S.; Carrazana, E.; Rabinowicz, A.L. Optimizing Absorption for Intranasal Delivery of Drugs Targeting the Central Nervous System Using Alkylsaccharide Permeation Enhancers. *Pharmaceutics* **2023**, *15*, 2119. [CrossRef]
58. Clementino, A.R.; Pellegrini, G.; Banella, S.; Colombo, G.; Cantù, L.; Sonvico, F.; Del Favero, E. Structure and Fate of Nanoparticles Designed for the Nasal Delivery of Poorly Soluble Drugs. *Mol. Pharm.* **2021**, *18*, 3132–3146. [CrossRef] [PubMed]
59. Cingi, C.; Bayar Muluk, N.; Mitsias, D.I.; Papadopoulos, N.G.; Klimek, L.; Laulajainen-Hongisto, A.; Hytönen, M.; Toppila-Salmi, S.K.; Scadding, G.K. The Nose as a Route for Therapy: Part 1. Pharmacotherapy. *Front. Allergy* **2021**, *2*, 638136. [CrossRef] [PubMed]
60. Sosnowski, T.R.; Rapiejko, P.; Sova, J.; Dobrowolska, K. Impact of physicochemical properties of nasal spray products on drug deposition and transport in the pediatric nasal cavity model. *Int. J. Pharm.* **2020**, *574*, 118911. [CrossRef]
61. Gao, M.; Shen, X.; Mao, S. Factors influencing drug deposition in thenasal cavity upon delivery via nasal sprays. *J. Pharm. Investig.* **2020**, *50*, 251–259. [CrossRef]
62. Katare, P.; Pawar Medhe, T.; Nadkarni, A.; Deshpande, M.; Tekade, R.K.; Benival, D.; Jain, A. Nasal Drug Delivery System and Devices: An Overview on Health Effects. *ACS Chem. Health Saf.* **2024**, *31*, 127–143. [CrossRef]
63. Costa, C.P.; Barreiro, S.; Moreira, J.N.; Silva, R.; Almeida, H.; Sousa Lobo, J.M.; Silva, A.C. In Vitro Studies on Nasal Formulations of Nanostructured Lipid Carriers (NLC) and Solid Lipid Nanoparticles (SLN). *Pharmaceuticals* **2021**, *14*, 711. [CrossRef]
64. Ohwaki, T.; Ando, H.; Kakimoto, F.; Uesugi, K.; Watanabe, S.; Miyake, Y.; Kayano, M. Effects of Dose, pH, and Osmolarity on Nasal Absorption of Secretin in Rats II: Histological Aspects of the Nasal Mucosa in Relation to the Absorption Variation Due to the Effects of pH and Osmolarity. *J. Pharm. Sci.* **1987**, *76*, 695–698. [CrossRef]
65. Tan, M.S.A.; Parekh, H.S.; Pandey, P.; Siskind, D.J.; Falconer, J.R. Nose-to-brain delivery of antipsychotics using nanotechnology: A review. *Expert Opin. Drug Deliv.* **2020**, *17*, 839–853. [CrossRef] [PubMed]
66. Kisan, R.J.; Manoj, N.G.; Ishaque, M.S.; Vilarsrao, J.K.; Sambjahi, S.P. Nasal Drug Delivery System-Factors Affecting and Applications. *Curr. Drug Ther.* **2007**, *2*, 27–38. [CrossRef]
67. Deruyver, L.; Rigaut, C.; Lambert, P.; Haut, B.; Goole, J. The importance of pre-formulation studies and of 3D-printed nasal casts in the success of a pharmaceutical product intended for nose-to-brain delivery. *Adv. Drug Deliv. Rev.* **2021**, *175*, 113826. [CrossRef]

68. Ghadiri, M.; Young, P.M.; Traini, D. Strategies to Enhance Drug Absorption via Nasal and Pulmonary Routes. *Pharmaceutics* **2019**, *11*, 113. [CrossRef]
69. Ge, Y.; Xu, X.; Cao, M.; Liu, B.; Wang, Y.; Liao, P.; Wang, J.; Chen, Y.; Yuan, H.; Chen, G. Nasal Drug Delivery and Nose-to-Brain Delivery Technology Development Status and Trend Analysis: Based on Questionnaire Survey and Patent Analysis. *Pharmaceutics* **2024**, *16*, 929. [CrossRef] [PubMed]
70. Sharma, S.; Tyagi, A.; Dang, S. Nose to Brain Delivery of Transferrin conjugated PLGA nanoparticles for clonidine. *Int. J. Biol. Macromol.* **2023**, *252*, 126471. [CrossRef]
71. Sharma, S.; Gauba, P.; Tyagi, A.; Dang, S. Chitosan-modified polymeric nanoparticles for the nose-to-brain drug delivery of paroxetine: An in vitro and in vivo evaluation. *Nanoscale* **2025**, *17*, 1687–1702. [CrossRef]
72. Plapied, L.; Duhem, N.; des Rieux, A.; Préat, V. Fate of polymeric nanocarriers for oral drug delivery. *Curr. Opin. Colloid Interface Sci.* **2011**, *16*, 228–237. [CrossRef]
73. Mukherjee, A.; Bisht, B.; Dutta, S.; Paul, M.K. Current advances in the use of exosomes, liposomes, and bioengineered hybrid nanovesicles in cancer detection and therapy. *Acta Pharmacol. Sin.* **2022**, *43*, 2759–2776. [CrossRef]
74. Duong, V.-A.; Nguyen, T.-T.-L.; Maeng, H.-J.; Chi, S.-C. Nanostructured lipid carriers containing ondansetron hydrochloride by cold high-pressure homogenization method: Preparation, characterization, and pharmacokinetic evaluation. *J. Drug Deliv. Sci. Technol.* **2019**, *53*, 101185. [CrossRef]
75. Duong, V.-A.; Nguyen, T.-T.-L.; Maeng, H.-J.; Chi, S.-C. Preparation of Ondansetron Hydrochloride-Loaded Nanostructured Lipid Carriers Using Solvent Injection Method for Enhancement of Pharmacokinetic Properties. *Pharm. Res.* **2019**, *36*, 138. [CrossRef] [PubMed]
76. Al-Sayadi, G.M.H.; Verma, A.; Choudhary, Y.; Sandal, P.; Patel, P.; Singh, D.; Gupta, G.D.; Kurmi, B.D. Solid Lipid Nanoparticles (SLNs): Advancements in Modification Strategies Toward Drug Delivery Vehicle. *Pharm. Nanotechnol.* **2023**, *11*, 138–154. [CrossRef]
77. Duong, V.-A.; Nguyen, T.-T.-L.; Maeng, H.-J.; Chi, S.-C. Data on optimization and drug release kinetics of nanostructured lipid carriers containing ondansetron hydrochloride prepared by cold high-pressure homogenization method. *Data Brief* **2019**, *26*, 104475. [CrossRef] [PubMed]
78. Souto, E.B.; Baldim, I.; Oliveira, W.P.; Rao, R.; Yadav, N.; Gama, F.M.; Mahant, S. SLN and NLC for topical, dermal, and transdermal drug delivery. *Expert Opin. Drug Deliv.* **2020**, *17*, 357–377. [CrossRef]
79. Dhaval, M.; Vaghela, P.; Patel, K.; Sojitra, K.; Patel, M.; Patel, S.; Dudhat, K.; Shah, S.; Manek, R.; Parmar, R. Lipid-based emulsion drug delivery systems—A comprehensive review. *Drug Deliv. Transl. Res.* **2022**, *12*, 1616–1639. [CrossRef]
80. Nguyen, T.-T.-L.; Duong, V.-A. A Review on Nanosystem-Based Delivery of Tofacitinib for Enhanced Treatment of Autoimmune Diseases and Inflammation. *BioNanoScience* **2024**, *14*, 2048–2064. [CrossRef]
81. Sipos, B.; Csóka, I.; Budai-Szűcs, M.; Kozma, G.; Berkesi, D.; Kónya, Z.; Balogh, G.T.; Katona, G. Development of dexamethasone-loaded mixed polymeric micelles for nasal delivery. *Eur. J. Pharm. Sci.* **2021**, *166*, 105960. [CrossRef]
82. Salem, H.F.; Ali, A.A.; Rabea, Y.K.; Abo El-Ela, F.I.; Khallaf, R.A. Optimization and Appraisal of Chitosan-Grafted PLGA Nanoparticles for Boosting Pharmacokinetic and Pharmacodynamic Effect of Duloxetine HCl Using Box-Benkhen Design. *J. Pharm. Sci.* **2023**, *112*, 544–561. [CrossRef]
83. Khedkar, M.A.; Sharma, V.; Anjum, M.; Singh, S.; Shah, K.; Alam, P.; Dewangan, H.K. Paliperidone-loaded nose to brain targeted NLCS: Optimisation, evaluation, histopathology and pharmacokinetic estimation for schizophernia. *J. Microencapsul.* **2024**, *41*, 832–843. [CrossRef]
84. Agbo, C.P.; Ugwuanyi, T.C.; Ugwuoke, W.I.; McConville, C.; Attama, A.A.; Ofokansi, K.C. Intranasal artesunate-loaded nanostructured lipid carriers: A convenient alternative to parenteral formulations for the treatment of severe and cerebral malaria. *J. Control. Release* **2021**, *334*, 224–236. [CrossRef]
85. Wang, L.; Zhao, X.; Du, J.; Liu, M.; Feng, J.; Hu, K. Improved brain delivery of pueraria flavones via intranasal administration of borneol-modified solid lipid nanoparticles. *Nanomedicine* **2019**, *14*, 2105–2119. [CrossRef] [PubMed]
86. Sun, Y.; Li, L.; Xie, H.; Wang, Y.; Gao, S.; Zhang, L.; Bo, F.; Yang, S.; Feng, A. Primary Studies on Construction and Evaluation of Ion-Sensitive in situ Gel Loaded with Paeonol-Solid Lipid Nanoparticles for Intranasal Drug Delivery. *Int. J. Nanomed.* **2020**, *15*, 3137–3160. [CrossRef] [PubMed]
87. Mistry, A.; Glud, S.Z.; Kjems, J.; Randel, J.; Howard, K.A.; Stolnik, S.; Illum, L. Effect of physicochemical properties on intranasal nanoparticle transit into murine olfactory epithelium. *J. Drug Target.* **2009**, *17*, 543–552. [CrossRef] [PubMed]
88. Ahmad, E.; Feng, Y.; Qi, J.; Fan, W.; Ma, Y.; He, H.; Xia, F.; Dong, X.; Zhao, W.; Lu, Y.; et al. Evidence of nose-to-brain delivery of nanoemulsions: Cargoes but not vehicles. *Nanoscale* **2017**, *9*, 1174–1183. [CrossRef]
89. González-Mariscal, L.; Posadas, Y.; Miranda, J.; Uc, Y.P.; Ortega-Olvera, M.J.; Hernández, S. Strategies that Target Tight Junctions for Enhanced Drug Delivery. *Curr. Pharm. Des.* **2016**, *22*, 5313–5346. [CrossRef]

90. Abourehab, M.A.S.; Khames, A.; Genedy, S.; Mostafa, S.; Khaleel, M.A.; Omar, M.M.; El Sisi, A.M. Sesame Oil-Based Nanostructured Lipid Carriers of Nicergoline, Intranasal Delivery System for Brain Targeting of Synergistic Cerebrovascular Protection. *Pharmaceutics* **2021**, *13*, 581. [CrossRef]
91. Fatouh, A.M.; Elshafeey, A.H.; Abdelbary, A. Agomelatine-based in situ gels for brain targeting via the nasal route: Statistical optimization, in vitro, and in vivo evaluation. *Drug Deliv.* **2017**, *24*, 1077–1085. [CrossRef]
92. Ly, P.-D.; Ly, K.-N.; Phan, H.-L.; Nguyen, H.H.; Duong, V.-A.; Nguyen, H.V. Recent advances in surface decoration of nanoparticles in drug delivery. *Front. Nanotechnol.* **2024**, *6*, 1456939. [CrossRef]
93. Saini, S.; Sharma, T.; Jain, A.; Kaur, H.; Katare, O.P.; Singh, B. Systematically designed chitosan-coated solid lipid nanoparticles of ferulic acid for effective management of Alzheimer's disease: A preclinical evidence. *Colloids Surf. B Biointerfaces* **2021**, *205*, 111838. [CrossRef]
94. Kaur, R.; Gorki, V.; Singh, G.; Kaur, R.; Katare, O.P.; Nirmalan, N.; Singh, B. Intranasal delivery of polymer-anchored lipid nanoconstructs of artemether-lumefantrine in Plasmodium berghei ANKA murine model. *J. Drug Deliv. Sci. Technol.* **2021**, *61*, 102114. [CrossRef]
95. Vieira, A.C.C.; Chaves, L.L.; Pinheiro, S.; Pinto, S.; Pinheiro, M.; Lima, S.C.; Ferreira, D.; Sarmento, B.; Reis, S. Mucoadhesive chitosan-coated solid lipid nanoparticles for better management of tuberculosis. *Int. J. Pharm.* **2018**, *536*, 478–485. [CrossRef] [PubMed]
96. Ahmad, N.; Ahmad, R.; Ahmad, F.J.; Ahmad, W.; Alam, M.A.; Amir, M.; Ali, A. Poloxamer-chitosan-based Naringenin nanoformulation used in brain targeting for the treatment of cerebral ischemia. *Saudi J. Biol. Sci.* **2020**, *27*, 500–517. [CrossRef] [PubMed]
97. Wang, F.; Yang, Z.; Liu, M.; Tao, Y.; Li, Z.; Wu, Z.; Gui, S. Facile nose-to-brain delivery of rotigotine-loaded polymer micelles thermosensitive hydrogels: In vitro characterization and in vivo behavior study. *Int. J. Pharm.* **2020**, *577*, 119046. [CrossRef]
98. Sayed, S.; Elsharkawy, F.M.; Amin, M.M.; Shamsel-Din, H.A.; Ibrahim, A.B. Brain targeting efficiency of intranasal clozapine-loaded mixed micelles following radio labeling with Technetium-99m. *Drug Deliv.* **2021**, *28*, 1524–1538. [CrossRef]
99. Hard, S.; Shivakumar, H.N.; Redhwan, M.A.M. Development and optimization of in-situ gel containing chitosan nanoparticles for possible nose-to-brain delivery of vinpocetine. *Int. J. Biol. Macromol.* **2023**, *253*, 127217. [CrossRef]
100. Uppuluri, C.T.; Ravi, P.R.; Dalvi, A.V. Design and evaluation of thermo-responsive nasal in situ gelling system dispersed with piribedil loaded lecithin-chitosan hybrid nanoparticles for improved brain availability. *Neuropharmacology* **2021**, *201*, 108832. [CrossRef]
101. 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**, *22*, 192. [CrossRef]
102. Rojanaratha, T.; Tienthai, P.; Woradulayapinij, W.; Yimsoo, T.; Boonkanokwong, V.; Ritthidej, G.C. Preparation, physicochemical characterization, ex vivo, and in vivo evaluations of asiatic acid-loaded solid lipid nanoparticles formulated with natural waxes for nose-to-brain delivery. *Eur. J. Pharm. Sci.* **2024**, *203*, 106935. [CrossRef]
103. Islamie, R.; Myint, S.L.L.; Rojanaratha, T.; Ritthidej, G.; Wanakhachornkrai, O.; Wattanathamsan, O.; Rodsiri, R. Neuroprotective effect of nose-to-brain delivery of Asiatic acid in solid lipid nanoparticles and its mechanisms against memory dysfunction induced by Amyloid Beta(1-42) in mice. *BMC Complement. Med. Ther.* **2023**, *23*, 294. [CrossRef]
104. Masjedi, M.; Azadi, A.; Heidari, R.; Mohammadi-Samani, S. Nose-to-brain delivery of sumatriptan-loaded nanostructured lipid carriers: Preparation, optimization, characterization and pharmacokinetic evaluation. *J. Pharm. Pharmacol.* **2020**, *72*, 1341–1351. [CrossRef] [PubMed]
105. Subhash Hinge, N.; Kathuria, H.; Monohar Pandey, M. Rivastigmine-DHA ion-pair complex improved loading in hybrid nanoparticles for better amyloid inhibition and nose-to-brain targeting in Alzheimer's. *Eur. J. Pharm. Biopharm.* **2023**, *190*, 131–149. [CrossRef] [PubMed]
106. Khairnar, S.V.; Pagare, P.; Thakre, A.; Nambiar, A.R.; Junnuthula, V.; Abraham, M.C.; Kolimi, P.; Nyavanandi, D.; Dyawanapelly, S. Review on the Scale-Up Methods for the Preparation of Solid Lipid Nanoparticles. *Pharmaceutics* **2022**, *14*, 1886. [CrossRef] [PubMed]
107. Kulkarni, D.; Sherkar, R.; Shirsathe, C.; Sonwane, R.; Varpe, N.; Shelke, S.; More, M.P.; Pardeshi, S.R.; Dhaneshwar, G.; Junnuthula, V.; et al. Biofabrication of nanoparticles: Sources, synthesis, and biomedical applications. *Front. Bioeng. Biotechnol.* **2023**, *11*, 1159193. [CrossRef]

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