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A REVIEW ON RECENT ADVANCES, FORMULATION STRATEGIES AND TRANSLATIONAL CHALLENGES IN NASAL DRUG DELIVERY FOR BRAIN TARGETING

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ABSTRACT
Delivery of therapeutics to the central nervous system (CNS) remains difficult because the blood–brain barrier restricts the entry of many pharmacologically active molecules. Intranasal administration has attracted attention as a non-invasive approach that may increase CNS exposure by exploiting anatomical connections between the nasal cavity and the brain. Drug movement can involve the olfactory region and trigeminal pathways, together with systemic absorption followed by limited passage across the blood–brain barrier. However, successful nose-to-brain delivery is not simply a consequence of placing a drug in the nose. Nasal mucus, mucociliary clearance, enzymatic degradation, limited dose volume, epithelial permeability, formulation instability and variability in nasal anatomy can markedly influence performance. Recent formulation research therefore combines mucoadhesive or mucus-penetrating systems with nanoparticles, liposomes, nanoemulsions, nanogels, in-situ gels, nasal powders and surface-engineered carriers. This review discusses the biological basis of nose-to-brain delivery, major formulation strategies, critical quality attributes, experimental evaluation, therapeutic applications and barriers to clinical translation. Particular attention is given to how formulation design can be connected with residence time, deposition site, drug release and brain exposure. The review also identifies future opportunities in personalized nasal delivery, smart responsive systems, scalable manufacturing and clinically meaningful pharmacokinetic evaluation.

KEYWORDS: Intranasal drug delivery, Nose-to-brain delivery, Brain targeting.

1. INTRODUCTION

The treatment of neurological disorders is strongly influenced by the difficulty of transporting therapeutic molecules to the brain. The blood–brain barrier (BBB) is essential for maintaining the biochemical environment of the CNS, but it also limits the penetration of many hydrophilic molecules, peptides, proteins and other therapeutic agents. Conventional oral and parenteral administration may therefore produce inadequate brain exposure or require systemic doses that increase unwanted effects. Intranasal administration provides an alternative route in which a formulation is deposited directly onto the nasal mucosa and may access the CNS through anatomical pathways associated with the olfactory and trigeminal nerves.

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Recent literature has expanded from simple intranasal solutions toward engineered systems such as nanoparticles, lipid-based carriers, microemulsions, nasal powders, in-situ gels and targeted nanoplatforms. A 2025 review described the field from preclinical work toward clinical translation and highlighted formulation, pharmacokinetic and safety considerations. Another 2025 review specifically examined advanced nasal formulations including microemulsions, in-situ gels, powders and nanocarriers. These publications indicate that the field is moving from the general concept of nose-to-brain delivery toward optimization of formulation performance and clinical feasibility.[1,2]

The purpose of this review is not to reproduce previously published summaries. Instead, it organizes the topic around a formulation-development question: how can nasal dosage-form design improve deposition, residence time, protection of the drug, transport across the nasal interface and reproducible brain exposure. This approach provides a practical framework for students and highlights areas where future research can add value.

2. Objectives of the Review

- To explain the anatomical and physiological basis of nose-to-brain drug delivery.
- To describe the olfactory and trigeminal pathways involved in potential CNS transport.
- To compare conventional and advanced nasal dosage forms for brain targeting.
- To discuss how nanocarriers, mucoadhesive systems and in-situ gels can improve formulation performance.
- To summarize important formulation variables and evaluation parameters.
- To examine applications in neurodegenerative, psychiatric, brain-tumor and other CNS disorders.
- To identify translational challenges related to safety, dose reproducibility, manufacturing and clinical evaluation.

3. Anatomical and physiological basis of nose-to-brain drug delivery

The nasal cavity is lined mainly by respiratory epithelium, while a smaller specialized olfactory region contains olfactory receptor neurons. The olfactory region is particularly important for nose-to-brain research because neuronal structures connect the nasal environment with the olfactory bulb. The trigeminal nerve also supplies portions of the nasal cavity and provides another anatomical route that has been investigated for CNS transport. The precise contribution of each pathway depends on the formulation, deposition location, physicochemical properties of the drug and experimental model.[11,14,19]

The nasal mucosa is not a passive surface. Mucus forms a protective layer, while coordinated ciliary movement continuously transports mucus toward the nasopharynx. This mucociliary clearance can shorten formulation residence time. Enzymes present in the nasal environment may also affect susceptible molecules. Consequently, an effective formulation must balance adhesion and retention with acceptable mucosal compatibility.

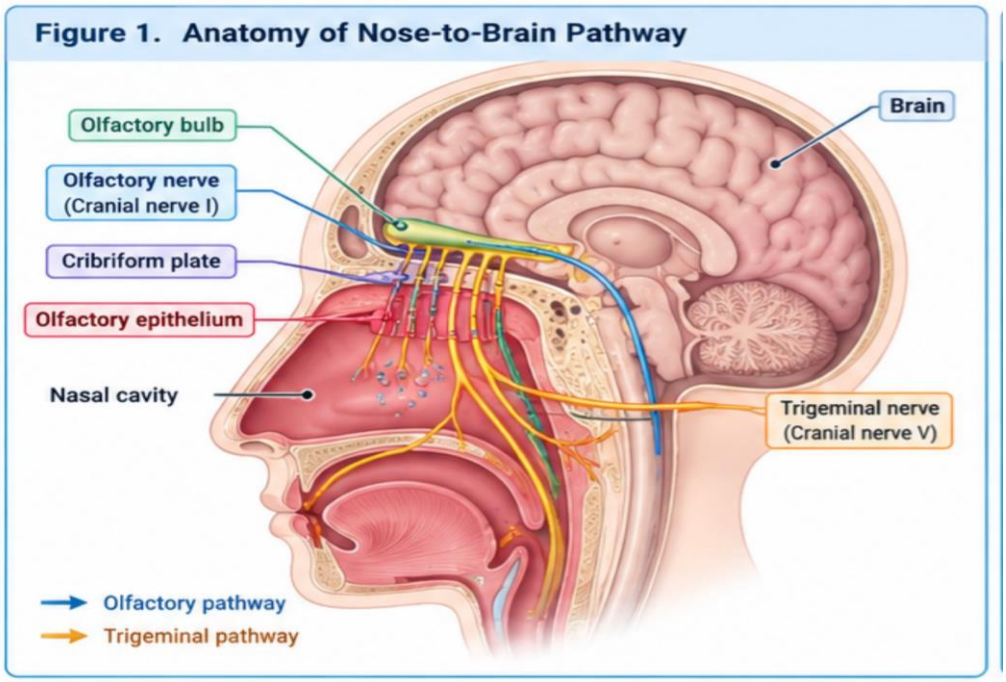

Figure 1: Anatomy of Nose-to-Brain Pathway.

4. Mechanisms of Nose-to-Brain Transport

Four broad processes can be considered when describing intranasal brain delivery: direct neuronal transport, extracellular transport around neural structures, transcellular movement across epithelial cells, and systemic absorption followed by distribution. The olfactory pathway may involve transport along olfactory neurons or associated extracellular spaces. Trigeminal pathways provide connections between the nasal cavity and deeper CNS regions. Nanocarriers can additionally influence uptake, protection from degradation and cellular interactions.

It is important to avoid describing intranasal administration as an automatic 'BBB bypass'. Brain targeting is formulation- and route-dependent, and experimental studies must distinguish direct CNS transport from systemic exposure. Modern reviews emphasize the need for careful pharmacokinetic and biodistribution assessment rather than relying only on increased brain drug concentration.[1,5]

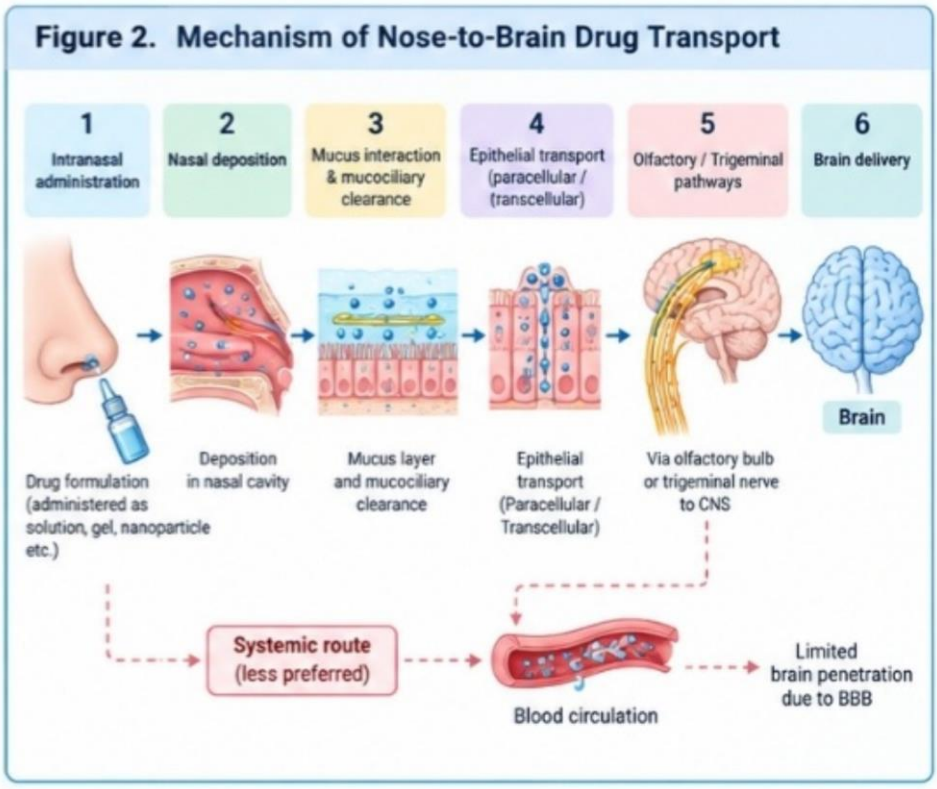

Figure 2: Mechanism of Nose-to-Brain Drug Transport.

5. Barriers Limiting Nasal Brain Delivery

- Mucociliary clearance: rapid removal can reduce residence time and absorption.
- Nasal mucus: the mucus layer can hinder diffusion of some particles and macromolecules.
- Enzymatic degradation: susceptible drugs, peptides and proteins may undergo degradation.
- Limited administration volume: the nasal cavity can accommodate only a relatively small dose volume.
- Variable deposition: device design and patient technique influence where the formulation reaches.
- Epithelial barrier: tight junctions and cellular membranes restrict movement of many molecules.
- Local tolerability: repeated exposure to permeation enhancers or nanoparticles requires careful safety evaluation.
- Inter-individual variability: nasal anatomy, mucus properties, disease state and administration technique can affect performance.
- Scale-up and stability: complex nanocarriers may be difficult to manufacture reproducibly and maintain during storage.

6. Formulation Strategies for Nose-to-Brain Delivery

6.1 Conventional Nasal Solutions and Suspensions: Solutions and suspensions are comparatively simple to manufacture and can provide rapid drug availability. Their major limitation for brain targeting is often short nasal residence time. Optimization of pH, osmolality, viscosity, drug concentration and preservative system is necessary to maintain mucosal compatibility and product stability.

6.2 Nasal Gels and In-Situ Gelling Systems: Gelling systems are designed to undergo a change after administration, such as temperature-, ion- or pH-triggered gelation. The resulting increase in viscosity can reduce immediate drainage and prolong contact with the nasal mucosa. In-situ gels have therefore become an

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important formulation strategy for improving residence time without requiring a permanently highly viscous product during administration. Recent reviews identify in-situ gels as one of the major advanced nasal platforms under investigation.[2]

6.3 Nanoparticles: Polymeric nanoparticles can protect encapsulated molecules and allow controlled release. Materials such as biodegradable polymers have been investigated for CNS delivery. Particle size, surface charge, polymer composition, drug loading and surface modification can influence mucus interaction, epithelial uptake and biodistribution. Importantly, smaller particle size alone does not guarantee better brain targeting; deposition, stability and biological interactions must be evaluated together.

6.4 Liposomes and Other Vesicular Systems

Liposomes can encapsulate hydrophilic or lipophilic drugs and may be modified with mucoadhesive or targeting components. Other vesicular approaches include niosomes and related lipid-based carriers. Their potential advantages include improved drug protection and the ability to modify release. Challenges include physical stability, drug leakage, manufacturing reproducibility and long-term storage.

6.5 Nanoemulsions and Microemulsions

Nanoemulsions and microemulsions can improve the apparent solubilization of poorly water-soluble compounds. Their formulation depends on the choice and concentration of oils, surfactants and co-surfactants. For nasal use, excipient safety and irritation must be considered alongside solubilization performance.

6.6 Nanogels and Mucoadhesive Systems

Nanogels combine features of nanoscale carriers with hydrogel networks. Mucoadhesive polymers can increase contact between the formulation and nasal mucosa, whereas mucus-penetrating approaches attempt to reduce entrapment within the mucus layer. The preferred strategy depends on whether prolonged surface retention or improved movement through mucus is the primary formulation goal.

6.7 Nasal Powders and Dry-Powder Systems

Nasal powders can improve physical stability and may reduce dependence on aqueous preservatives. They can also be engineered for controlled deposition and rapid dissolution. However, powder flow, particle size, moisture sensitivity, device performance and patient administration technique require careful optimization.

6.8 Surface-Modified and Targeted Nanocarriers

Surface modification may be used to alter mucus interaction, cellular uptake or receptor-mediated transport. Cell-penetrating peptides and other targeting ligands have been investigated with liposomes, polymeric nanoparticles and gels. Recent work suggests that such modifications can improve experimental brain delivery, but their long-term safety, manufacturing complexity and clinical benefit require further validation.[6]

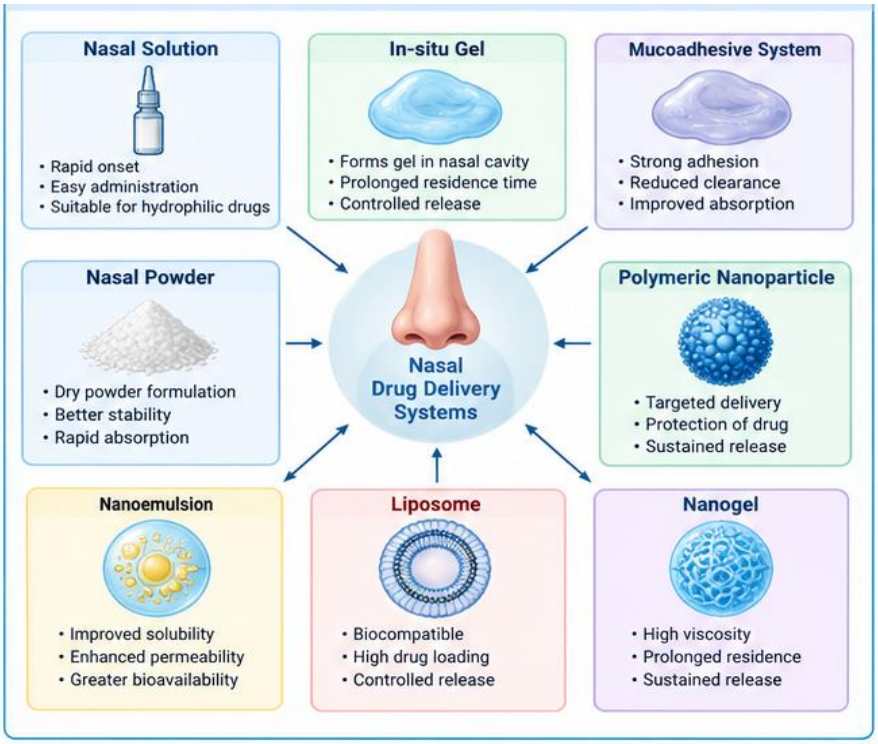

Figure 3: Advanced Nasal Formulation Systems for Brain Targeting.

7. Role of Nanotechnology in Nose-to-Brain Delivery

Nanotechnology provides a formulation toolbox rather than a single delivery mechanism. Nanocarriers can protect drugs from degradation, modify release kinetics, increase apparent solubility and permit surface engineering. Recent reviews have described polymeric nanoparticles, liposomes, nanoemulsions, dendritic systems and other nanoplatforms for nose-to-brain applications.[3,5,7] [12,13,15–19]

A formulation-focused development strategy should connect nanocarrier properties with measurable outcomes. For example, particle size and polydispersity should be connected with physical stability; surface properties should be considered alongside mucus interaction; encapsulation efficiency should be considered with drug loading and release; and nasal deposition should be evaluated together with brain distribution. This integrated approach is more informative than reporting particle size alone.

8. Therapeutic Applications

- Alzheimer's disease: investigation includes delivery of small molecules, peptides, natural compounds and nanocarriers intended to improve CNS exposure.
- Parkinson's disease: intranasal delivery is being investigated for dopaminergic agents, neuroprotective compounds and advanced nanoformulations.
- Brain tumors: intranasal nanocarriers are being studied to improve local brain exposure while reducing dependence on systemic distribution.[4]
- Epilepsy and migraine: intranasal administration is already clinically relevant for selected therapies, demonstrating the practical potential of the nasal route, although not every intranasal product is designed for direct brain targeting.[1]
- Psychiatric and neurological disorders: research includes delivery of CNS-active molecules where rapid onset or improved brain exposure may be beneficial.
- Biologics and nucleic acids: peptides, proteins, siRNA and other macromolecules are being investigated using protective and targeting delivery systems.[6]

9. Critical Formulation Variables

Variable	Why it matters	Typical evaluation
Particle size / PDI	Influences stability, deposition and biological interaction	DLS
Zeta potential	Affects colloidal stability and surface interaction	Zeta potential
Drug loading / encapsulation	Determines dose efficiency	HPLC/UV or validated assay
Mucoadhesion	Can prolong nasal residence	Texture analysis / wash-off / ex vivo methods
Mucus penetration	May influence movement through mucus	Mucus diffusion studies
In-vitro release	Describes release profile	Diffusion or membrane method
Nasal deposition	Influences exposure at target region	Imaging/model-based deposition studies
Histopathology	Assesses local tissue compatibility	Nasal tissue examination
Brain distribution	Supports targeting claim	Brain tissue drug quantification
Stability	Determines shelf-life feasibility	ICH-oriented stability studies

10. Evaluation of Nose-to-Brain Formulations

Evaluation should progress from physicochemical characterization to biological and pharmacokinetic studies. For a nanocarrier, particle size distribution, surface charge, morphology, drug content, encapsulation efficiency and release behavior are common starting parameters. For nasal formulations, pH, osmolality, viscosity, mucoadhesion, spray characteristics and microbial quality may also be relevant.

Ex vivo permeation or retention studies can provide information about interaction with nasal tissue. In vivo studies may compare plasma and brain concentrations after intranasal and conventional administration. Brain-to-plasma ratios, drug targeting efficiency and direct transport-related indices can be useful, but they should be interpreted carefully because mathematical indices can be influenced by systemic exposure and sampling design. Histological assessment is important when permeation enhancers or repeated administration are proposed.

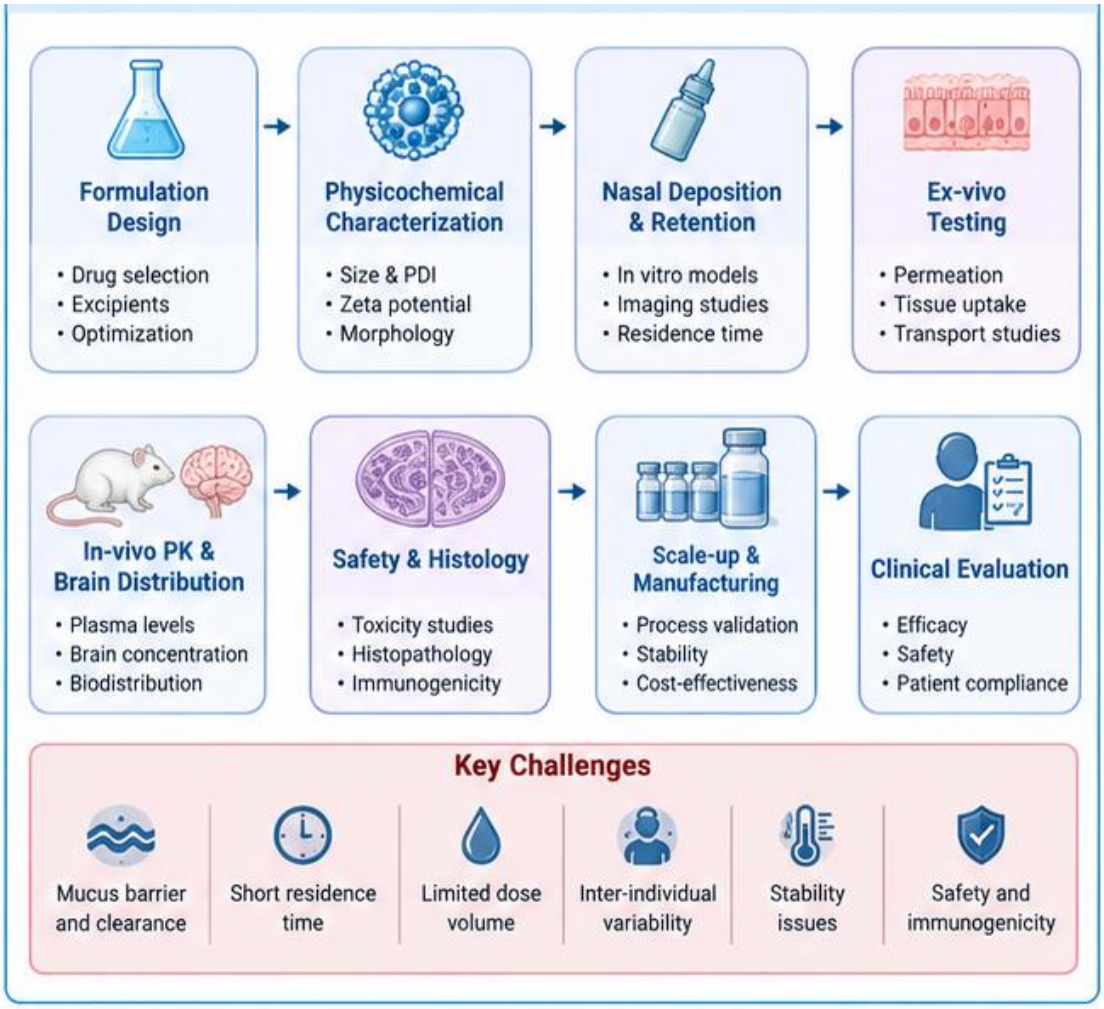

Figure 4: Translational Pathway and Key Challenges in Nose-to-Brain Delivery.

Advantages include non-invasive administration, potential for rapid absorption, avoidance of gastrointestinal degradation, reduced first-pass metabolism for some drugs, the possibility of CNS exposure, and suitability for selected macromolecules when protected by appropriate formulations. The route can also be useful when oral administration is difficult.

Limitations include small nasal dose capacity, mucociliary clearance, enzymatic degradation, variable nasal anatomy, irritation, inconsistent deposition and uncertainty regarding the proportion of drug reaching the brain through direct versus systemic pathways. Advanced nanocarriers introduce additional concerns such as excipient safety, long-term stability, scale-up and regulatory characterization. Current reviews emphasize that these translational barriers remain important even when preclinical brain exposure appears promising.[1,2,6]

- Standardized comparison of brain-targeting performance across different nasal dosage forms is still needed.
- More studies should separate direct nose-to-brain transport from increased brain exposure caused by systemic absorption.
- Patient-to-patient variability in nasal anatomy and administration technique needs greater consideration.
- Device–formulation combinations deserve more attention because deposition is strongly influenced by delivery hardware and technique.
- Long-term nasal safety data are needed for repeated administration of sophisticated nanocarriers.
- Manufacturing and scale-up should be considered earlier rather than only after proof-of-concept studies.
- Personalized nasal delivery may combine patient-specific anatomy, formulation properties and device parameters.
- Future studies should prioritize clinically relevant pharmacokinetic endpoints and reproducible brain exposure rather than relying only on animal biodistribution.

A future nose-to-brain product can be conceptualized as an integrated formulation–device system. The formulation should protect the active ingredient and provide an appropriate residence time, while the device should reproducibly deposit the dose in the desired nasal region. Smart systems that respond to temperature, pH or

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other local conditions may further control retention and release. Personalized approaches could eventually use patient characteristics to select dose, viscosity, spray pattern or administration technique. Translation will require simultaneous attention to efficacy, local tolerability, manufacturing quality and regulatory requirements.[20,21,22]

Nasal drug delivery for brain targeting represents an important area of modern Pharmaceutics because it combines route-specific physiology with advanced formulation science. The olfactory and trigeminal connections provide a rationale for investigating direct CNS delivery, but successful targeting depends on much more than bypassing the BBB. Mucociliary clearance, mucus interaction, epithelial barriers, deposition, formulation stability and patient variability must be considered during development. Nanoparticles, liposomes, nanoemulsions, nanogels, in-situ gels and nasal powders offer different solutions to these barriers. The next stage of the field is likely to depend on better formulation–device integration, standardized pharmacokinetic assessment, long-term safety evaluation and scalable manufacturing. A critical review centered on these formulation and translation issues can therefore provide a useful contribution without simply repeating earlier broad summaries.

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