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Nose-to-Brain Delivery for Migraine: A Review of Recent Technological and Formulation Advances

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ABSTRACT

Migraine is a debilitating neurological disorder that demands fast and effective therapeutic intervention. Traditional oral and parenteral routes are often limited by gastrointestinal disturbances, hepatic first-pass metabolism, delayed onset of action, and poor patient compliance, especially during acute attacks. Nose-to-brain drug delivery presents a promising, non-invasive alternative that bypasses the blood-brain barrier (BBB) via the olfactory and trigeminal nerve pathways, enabling direct drug transport to the central nervous system (CNS). This review comprehensively explores recent technological and formulation advancements in intranasal drug delivery systems for migraine therapy. Emphasis is placed on novel carriers such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, micelles, and nanoemulsions, which enhance drug solubility, retention, and CNS targeting. Advanced delivery devices such as Precision Olfactory Delivery (POD®) systems and breath-powered nasal applicators have demonstrated improved deposition into the upper nasal cavity, enhancing therapeutic outcomes. Preclinical and clinical studies, including FDA-approved formulations like Zomig, ONZETRA Xsail, and Zavzpret (zavegepant), are discussed to highlight their efficacy, safety, and patient-centric benefits. Additionally, the integration of mucoadhesive and in-situ gelling systems, thermosensitive polymers, and combination therapies has further improved nasal drug retention and bioavailability. Future directions include personalized nasal delivery platforms, smart responsive materials, and AI-integrated biosensor-enabled systems for real-time monitoring and targeted administration. Collectively, these advancements underscore the growing potential of nose-to-brain strategies to revolutionize migraine treatment by providing rapid, targeted, and patient-friendly therapeutic solutions.

Keywords: *nose-to-brain delivery, migraine, intranasal therapy, nanoparticles, drug targeting, nasal formulations, CNS delivery.*

1. Introduction

Migraine is a complex and disabling neurological disorder that extends far beyond a simple headache, affecting over a billion individuals globally. It is characterized by intense unilateral throbbing pain, often accompanied by nausea, vomiting, photophobia, and phonophobia, with some patients experiencing sensory disturbances or "aura" before onset. The condition predominantly affects women between the ages of 20 and 50, representing a major cause of lost productivity and reduced quality of life during prime working years [1][2]. Despite progress in understanding its underlying mechanisms, migraine pathophysiology remains incompletely elucidated. Current evidence implicates altered neuronal excitability, vascular changes, and neurogenic inflammation mediated by neurotransmitters and peptides such as serotonin, calcitonin gene-related peptide (CGRP), substance P, and nitric oxide, which collectively contribute to pain transmission and vasodilation [2][3].

Pharmacological management of migraine includes acute and preventive strategies. Triptans (e.g., sumatriptan) are the first-line drugs for acute episodes, while NSAIDs, ergot alkaloids, and antiemetics are used adjunctively. Preventive regimens involve beta-blockers, antiepileptics, and antidepressants. However, these therapies have several drawbacks. Oral triptans, though effective for many, exhibit delayed absorption during attacks due to migraine-induced gastric stasis, resulting in suboptimal efficacy. Moreover, their use is limited by cardiovascular contraindications, incomplete pain relief, and recurrence of headaches [3][4]. Routes such as injections and intravenous infusions offer faster relief but are invasive and impractical for regular use, emphasizing the need for a non-invasive, rapid-acting alternative [4][5].

Intranasal drug delivery has emerged as a promising approach to overcome these limitations. The nasal route offers direct access to the systemic circulation and potentially to the brain, bypassing gastrointestinal degradation and hepatic first-pass metabolism. Crucially, the olfactory and trigeminal neural pathways provide a unique anatomical connection to the central nervous system, enabling "nose-to-brain" transport of therapeutic agents [5][6]. The olfactory mucosa, situated beneath the cribriform plate, allows for direct drug diffusion to the olfactory bulb, while the trigeminal pathway connects to

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migraine-relevant brain structures such as the brainstem and thalamus. These routes facilitate rapid onset of action, dose minimization, and reduced systemic side effects [6][7].

Commercially available intranasal formulations, including zolmitriptan and sumatriptan nasal sprays, have demonstrated clinical viability and patient acceptability. Nevertheless, nasal delivery faces inherent challenges, including mucociliary clearance, enzymatic degradation, and limited drug residence time, which can restrict therapeutic efficacy [7][8]. To address these barriers, innovative formulation strategies have been developed. Nanoparticulate carriers such as solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) enhance mucosal permeation, protect labile drugs, and prolong retention in the nasal cavity. Similarly, in-situ gelling systems undergo sol-to-gel transition upon contact with nasal mucosa, maintaining prolonged contact and controlled release [8][9].

The incorporation of mucoadhesive polymers such as chitosan, carbopol, and hydroxypropyl methylcellulose (HPMC) further augments drug absorption by increasing formulation adherence and resistance to nasal clearance [9]. Together, these advanced delivery systems represent a paradigm shift in migraine therapy, enabling faster relief, improved bioavailability, and enhanced patient compliance.

This review will comprehensively discuss recent progress in nasal drug delivery systems for migraine management, focusing on formulation innovations, mechanistic insights into nose-to-brain transport, and emerging clinical outcomes. It will also highlight the persistent challenges and future perspectives essential for optimizing intranasal therapeutics aimed at providing rapid, targeted, and patient-friendly migraine relief.

2. Anatomical and Physiological Basis of Nose-to-Brain Drug Delivery

Delivering drugs to the brain through the nose is a fascinating concept that hinges on the unique structure and function of the nasal cavity. This region of the body isn't just for breathing and smelling, it can also serve as a gateway for targeted therapies aimed at the central nervous system (CNS). To understand how this works, let's explore the anatomy of the nasal cavity and how different areas contribute to drug transport.

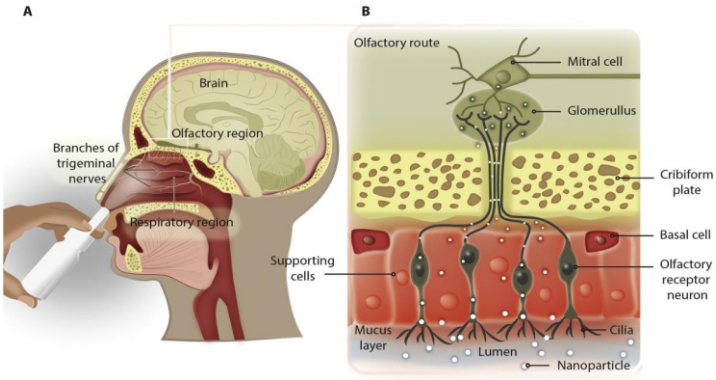

Fig. 1. Anatomical features of the intranasal route (A), including key structures involved in nose-to-brain drug delivery (B) [9]

2.1 Nasal Cavity Structure and Regions Involved in Brain Targeting

The nasal cavity, measuring about 12–15 cm in length, is divided into two symmetrical halves by the nasal septum and extends from the nostrils to the nasopharynx [10]. Despite its compact size, it offers a large surface area of approximately 150–200 cm^2 due to the presence of turbinates, which enhance drug absorption [11]. Structurally and functionally, the nasal cavity comprises three main regions.

The vestibular region, lined with coarse hairs and tough epithelium, primarily filters inhaled particles and contributes minimally to drug absorption. The respiratory region is the largest, richly vascularized, and covered with ciliated epithelium and mucus-secreting glands, making it ideal for rapid systemic absorption. The olfactory region, located at the roof of the nasal cavity, contains olfactory sensory neurons that directly connect to the brain's olfactory bulb, enabling drugs to bypass the blood–brain barrier. This region is crucial for nose-to-brain drug delivery targeting neurological disorders [12].

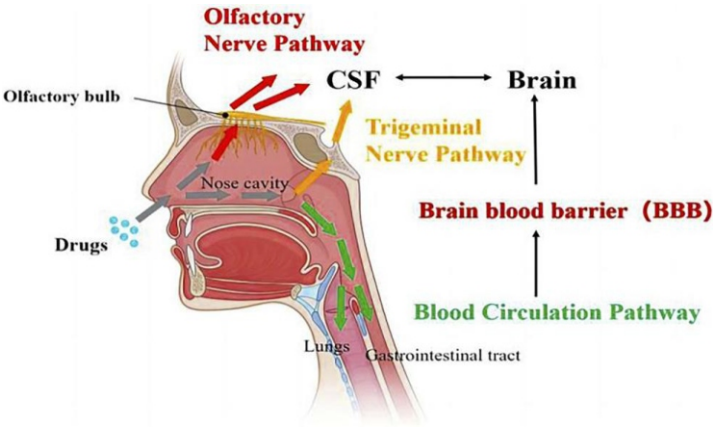

Fig.2. Transport pathways of drugs from nose- to brain [10].

2.2 Nasal Routes Pathways for Drug Transport

One of the most fascinating aspects of nasal drug delivery systems (NDDS) is their potential to exploit the direct anatomical and physiological link between the nasal cavity and the brain. Drugs administered intranasally can reach the central nervous system (CNS) through multiple routes, notably via the olfactory and trigeminal nerve pathways, after crossing the nasal epithelium of either the olfactory or respiratory regions [13][19]. Once within the cranial compartment, these molecules can access the cerebrospinal fluid (CSF) through the olfactory bulb or along the trigeminal nerve, subsequently diffusing into deeper brain tissues to exert therapeutic effects. Some drugs may alternatively enter systemic circulation and reach the brain through the blood–brain barrier (BBB).

The olfactory nerve pathway represents the most direct and efficient nose-to-brain route, bypassing the restrictive BBB a key advantage in treating neurological disorders. Several substances, including neurotropic viruses, steroid hormones, and metal ions, naturally utilize this route. Drugs are absorbed through the olfactory mucosa via pinocytosis, endocytosis, or passive diffusion by olfactory sensory neurons (OSNs), traveling along neuronal axons across the cribriform plate to the olfactory bulb and into brain regions such as the rhinencephalon [14]. However, a limitation of this route is the variable and sometimes slow axonal transport rate, which can delay drug onset ranging from 1–2 hours to even 24 hours in certain cases [12][15].

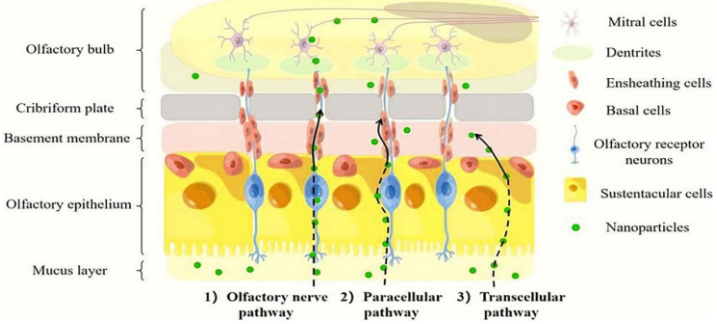

Fig.3. Mechanisms involved in direct nose-to-brain nanoparticle transport from the olfactory region [11]

The epithelial mucosal olfactory pathway enables rapid and efficient drug delivery from the nasal cavity to the brain, bypassing the blood–brain barrier (BBB). Small molecules like lidocaine, dopamine, and insulin can reach the CNS within minutes through either the transcellular or paracellular routes [16][17]. In the transcellular route, drugs cross olfactory epithelial cells via diffusion or carrier-mediated transport, while in the paracellular route, they move between cells through intercellular junctions to reach the cerebrospinal fluid (CSF) or systemic circulation. This pathway offers faster delivery than axonal transport, supporting rapid-onset nose-to-brain targeting for neurological therapeutics [17].

2.3 Barriers to Effective Nose-to-Brain Delivery

While nasal delivery holds great promise, several biological and anatomical barriers can limit its success:

- Mucociliary clearance: The nasal lining constantly works to expel foreign particles, including drug formulations, through mucus movement. This reduces the time available for the drug to be absorbed.
- Enzymatic degradation: The nasal mucosa contains enzymes that can break down drugs, particularly peptides and proteins, before they have a chance to reach the brain.
- Tight junctions: These are closely packed connections between epithelial cells that make it difficult for large or water-loving (hydrophilic) molecules to pass through, especially via the paracellular route.
- Limited surface area: The olfactory region, which is critical for brain targeting, occupies only a small portion of the nasal cavity.
- Physiological variability: Factors like age, infections, or nasal inflammation can alter drug absorption patterns.
- Volume limitations: Only small volumes (generally less than 200 μL) can be administered intranasally, which restricts the total dose that can be delivered.
- These challenges highlight the need for careful formulation strategies to ensure efficient and consistent nose-to-brain delivery.

3. Advantages of Nasal Delivery for Migraine Therapy

The epithelial mucosal olfactory pathway serves as a rapid and efficient route for delivering drugs from the nasal cavity directly to the brain, bypassing the restrictive blood–brain barrier (BBB). Small molecules such as lidocaine, dopamine, and insulin can enter the central nervous system (CNS) within minutes through transcellular or paracellular mechanisms. In the transcellular route, drugs diffuse or are actively transported through epithelial cells, whereas in the paracellular route, they pass between cells via intercellular junctions to reach the cerebrospinal fluid (CSF) or systemic circulation. This mechanism enables faster therapeutic onset compared to slower neuronal axonal transport [16][17].

4. Challenges and Limitations in Nose-to-Brain Delivery

While nose-to-brain delivery offers a promising, non-invasive strategy to bypass the blood–brain barrier (BBB), its effectiveness is challenged by several physiological and biochemical barriers that limit drug absorption and clinical success [21].

4.1 Mucociliary Clearance: A Natural Barrier

The nasal cavity's self-cleaning mechanism, mucociliary clearance (MCC), uses cilia to move mucus and trapped particles toward the throat for elimination. Although essential for protection, MCC reduces drug residence time on the nasal mucosa, as the mucus layer renews every 10–20 minutes, causing premature drug removal [22][23]. To counter this, mucoadhesive agents such as chitosan and carbopol are employed to prolong mucosal contact and enhance absorption [24].

4.2 Enzymatic Degradation in the Nasal Cavity

Enzymes like cytochrome P450, peptidases, and proteases in the nasal mucosa degrade drugs—especially peptides and proteins—before brain uptake [23][25]. Strategies include prodrug design, enzyme inhibitors, and nanocarrier systems that shield drugs until delivery.

4.3 Limited Drug Retention Due to Small Nasal Cavity Volume

The nasal cavity's limited volume (17–20 cm^3) and the small olfactory region (3–5%) constrain dosage and absorption [23][35]. In-situ gelling systems, which transform into gels upon administration, enhance viscosity and retention, improving drug absorption and therapeutic efficiency.

5. Recent Technological Advancements in Nasal Drug Delivery Systems

Recent innovations in nasal drug delivery focus on enhancing drug stability, mucoadhesion, retention, and targeted nose-to-brain transport. Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) enable controlled release and improved drug loading, with NLCs showing superior brain targeting in curcumin formulations [26][27][36][37]. Polymeric nanoparticles like PLGA, modified with targeting ligands, enhance neuroactive drug bioavailability [27]. Liposomes protect drugs from enzymatic degradation and prolong nasal residence, while niosomes, composed of cholesterol and nonionic surfactants, offer better stability and sustained release [28]. Nanoemulsions (NEs) and Microemulsions (MEs) improve solubility, permeability, and brain delivery efficiency for drugs such as memantine and ibuprofen [26][29][30]. Additionally, dendrimers and micelles enhance solubility, targeting precision, and CNS penetration PAMAM dendrimers notably improved haloperidol brain uptake [30]. Collectively, these nanocarriers represent major progress toward efficient, non-invasive brain drug delivery.

6. Advanced Migraine Targeting Formulation Techniques

The need for fast-acting, well-tolerated, and effective migraine treatments has driven the innovation of novel nasal formulations. These strategies are tailored to overcome nasal delivery challenges while offering rapid relief.

6.1 Mucoadhesive Systems

Mucoadhesive formulations are designed to stick to the nasal mucosa, increasing the residence time and enhancing drug absorption.

- Especially useful in migraine therapy, where a quick onset is needed
- Studies show that mucoadhesive in-situ gels offer better drug retention and therapeutic efficacy [31]

6.2 In-situ Gelling Systems

These formulations are liquid at room temperature but gel upon contact with the nasal mucosa, triggered by pH or temperature changes [32]. Benefits include reduced mucociliary clearance and sustained release.

For example, poloxamer-based nasal gels containing naratriptan hydrochloride demonstrated:
- Extended drug release
- Improved patient compliance in migraine management [33][34]

6.3 Thermosensitive and pH-Sensitive Formulations
These advanced systems allow:
- Thermosensitive gels remain liquid at room temperature and gel at body temperature
- pH-sensitive gels to gel in response to the nasal cavity's pH [32]

A formulation of sumatriptan succinate using thermosensitive in-situ gel technology showed:
- Prolonged drug release
- Improved bioavailability in migraine patients [35][36][37]

6.4 Dry Powder and Nasal Spray Technologies
Dry powder formulations offer several advantages:
- Better drug stability
- No preservatives
- Enhanced absorption

A recent example is Atzumi, a dihydroergotamine (DHE) dry powder nasal spray, which was FDA-approved for treating acute migraines. Clinical trials demonstrated:
- Fast absorption
- High tolerability
- Better performance than conventional DHE formulations [38]

7. Drug Candidates and Therapeutics Explored for Nasal Delivery in Migraine
Nasal drug delivery is emerging as an effective and patient-friendly approach in the treatment of migraines, especially for individuals who experience nausea, vomiting, or gastrointestinal disturbances during an attack, conditions that often limit the effectiveness of oral medications.

This route offers several advantages:
- Rapid onset of action, crucial for managing acute migraine episodes
- Bypassing the gastrointestinal tract makes it ideal for patients with compromised GI motility
- Avoidance of first-pass metabolism, leading to better drug bioavailability
- Improved patient compliance, as nasal sprays or powders are non-invasive and easy to use during an attack.

7.1 Recent Patents and Commercial Formulations
Nasal drug delivery has become a practical and effective approach for migraine management, with products like Zomig and Imitrex providing rapid relief by bypassing the digestive tract, especially for patients with nausea or vomiting. Recent innovations include nanoparticle-based formulations, mucoadhesive gels, dry powders, and smart nasal devices, enhancing drug stability, residence time, and direct nose-to-brain transport. Newer therapies such as Zavzpret and ONZETRA Xsail offer targeted, fast-acting migraine relief, including options suitable for patients with cardiovascular risks. Repurposing drugs like naratriptan and DHE using nano- and in-situ gelling systems further improves brain penetration and sustained action.

These advances underscore a growing clinical and commercial interest in efficient, patient-friendly nasal migraine therapies.

7.2 Emerging Trends
Recent research in nasal migraine therapy is shifting toward advanced and multifunctional delivery platforms that enhance drug efficacy and patient outcomes. One major trend involves dual-drug-loaded nanoparticles, which combine multiple therapeutics for synergistic effects. Additionally, smart formulations that respond to changes in nasal pH or temperature offer controlled and site-specific drug release. The use of nanocarriers such as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and micelles has significantly improved bioavailability. Targeting the upper nasal cavity, which offers better vascularization and lower clearance, is also gaining attention for direct brain delivery and faster therapeutic onset.

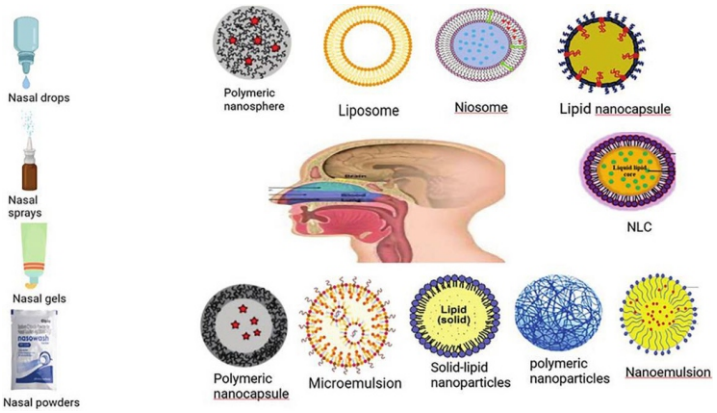

Fig.4. Various conventional and advanced systems for intranasal drug delivery [12, 13]

7.3 Natural Compounds and Phyto-constituents in Nasal Migraine Therapy
Recent nasal drug delivery advances include natural compounds and combination therapies for migraine. Intranasal herbal remedies like Centella asiatica and PA-free Petasites hybridus show preventive and frequency-reducing effects [39]. Combination therapies with triptans, NSAIDs, or caffeine, supported by nanocarriers (SLNs, NLCs), enhance brain targeting, efficacy, and safety [40].

8. Formulation Strategies and Considerations for Nasal Drug Delivery
Effective nasal drug delivery, particularly for brain targeting, depends on careful formulation design to ensure absorption, retention, and therapeutic efficacy. Particle size, surface charge, and pH are critical; nanoparticles (<200 nm) can cross mucosal barriers, while a slight positive surface charge enhances adhesion to the negatively charged nasal lining. Formulations should match nasal pH (5.5–6.5) to avoid irritation and maintain ciliary function. Permeation enhancers like chitosan, cyclodextrins, and surfactants improve absorption by temporarily opening tight junctions or disrupting the mucosal barrier. Bioadhesive polymers such as Carbopol, HPMC, and chitosan counteract mucociliary clearance, prolonging residence time and improving patient compliance. Drug loading and entrapment efficiency are optimized in carriers like liposomes, niosomes, and nanoparticles to ensure sustained release and therapeutic effectiveness. Finally, stability and viscosity are essential; in-situ gelling agents balance comfort and retention while antioxidants, stabilizers, and preservatives maintain long-term physical and chemical stability.

9. Evaluation Techniques and Pharmacokinetics in Nasal Drug Delivery

Effective nasal drug delivery, particularly for brain-targeted therapies like migraine, requires comprehensive evaluation and pharmacokinetic studies. In vitro assessments examine mucoadhesion and drug release, ensuring formulations adhere to nasal mucosa and release drugs at a controlled rate for optimal absorption. Ex vivo studies use animal nasal tissues to evaluate drug permeation, absorption rate, and the impact of enhancers or bioadhesive agents, bridging the gap between lab and in vivo conditions. In vivo pharmacokinetic studies in animal models track biodistribution, absorption, Cmax, Tmax, and elimination half-life, providing insights into drug delivery efficiency to the brain. A critical parameter is the brain/plasma ratio, which indicates the extent of direct nose-to-brain delivery via olfactory and trigeminal pathways. High brain targeting efficiency ensures rapid and focused drug action in the CNS, essential for timely relief in migraine and other neurological disorders.

10. Preclinical and Clinical Studies Supporting Nasal Delivery for Migraine

Nasal drug delivery for migraine has strong support from preclinical and clinical research, demonstrating rapid, targeted, and effective treatment. Preclinical studies include intranasal sumatriptan-loaded Nanostructured Lipid Carriers (NLCs) in rats, showing high Drug Targeting Efficiency (258%) and Direct Transport Percentage (61%), confirming efficient brain delivery [41]. TNX-1900, a magnesium-enhanced intranasal oxytocin, exhibited analgesic effects on trigeminal neurons, highlighting its potential for migraine prevention. Clinical trials further validate nasal therapies: zavegepant nasal spray achieved 24% pain-free rates within 2 hours versus 15% for placebo, resolving bothersome symptoms in 40% of patients [42]. Regulatory approvals reinforce these findings: intranasal sumatriptan demonstrated significant pain reduction (RR 1.70) [43]; Zavzpret was FDA-approved in 2023 as the first intranasal CGRP antagonist [44]; and ONZETRA Xsai, a breath-powered sumatriptan powder, enhances nasal deposition. TNX-1900 has received IND clearance, reflecting regulatory encouragement for further development. Collectively, these studies underscore nasal delivery as a fast, targeted, and clinically viable approach for migraine management.

11. Future Directions and Perspectives in Nasal Drug Delivery

The future of nasal drug delivery focuses on precision, personalization, and advanced technologies to improve brain targeting for conditions like migraine and neurodegenerative diseases. Personalized systems optimize deposition to regions such as the olfactory area, enhancing drug retention and efficacy, exemplified by dexamethasone-loaded microspheres [45]. Smart formulations respond to triggers like pH or temperature, using nanocarriers to achieve faster and more effective brain delivery [26][46]. Emerging in vitro models, such as organ-on-chip platforms, aid in realistic testing [47]. Integration of AI and biosensors allows real-time monitoring of biomarkers, enabling adaptive dosing via devices with electronic atomizers and precision pumps [41][48]. These innovations collectively promise safer, faster, and more targeted nasal therapies, paving the way for personalized, patient-centric neurological treatments.

12. Conclusion

The nasal route has emerged as a highly promising strategy for migraine therapy, primarily by bypassing the blood-brain barrier (BBB) and enabling direct nose-to-brain delivery via olfactory and trigeminal nerve pathways [48]. This approach allows faster and more targeted drug action in the central nervous system. Advanced formulation technologies, including solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, and nanoemulsions, have enhanced drug solubility, retention, and bioavailability. For example, sumatriptan-loaded NLCs achieved over 250% drug targeting efficiency in preclinical studies [41].

Innovative delivery devices, such as Precision Olfactory Delivery (POD®) and breath-powered systems, improve deposition in the upper nasal cavity, providing rapid onset and higher patient compliance during migraine attacks when oral drugs may be ineffective [49][50]. Clinically, FDA-approved nasal therapies like Zomig®, Imitrex®, ONZETRA® Xsail, and Zavegepant (Zavzpret) demonstrate rapid, non-invasive pain relief with improved tolerability [51].

Future directions include personalized delivery systems, responsive smart materials, and AI-integrated devices, promising precise, patient-centric migraine management. Overall, nose-to-brain delivery combines speed, efficacy, and convenience, positioning intranasal therapy as a cornerstone in migraine treatment.

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