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Nanoparticle-Enabled Nose-to-Brain Delivery: A Review on Management of Migraine Therapy

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ABSTRACT:

Migraine, a prevalent and disabling neurological disorder, remains inadequately managed by conventional oral therapies due to challenges like slow onset, low bioavailability, and significant first-pass metabolism. By enabling direct medication administration from the nose to the brain and avoiding the blood-brain barrier and hepatic metabolism, the intranasal route presents an appealing option. This review critically examines the application of nanoparticle-based systems for the enhanced intranasal delivery of antimigraine drugs. We explore the mechanistic pathways involved in neuronal transport via the olfactory and trigeminal nerves, which enable rapid and targeted drug delivery to the central nervous system. The focus of this article is advanced nanocarriers, such as polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and mucoadhesive in situ gels, which together enhance drug stability, extend nasal residence time, and offer controlled release profiles. Compared to conventional oral formulations, these nanotechnological techniques can achieve a surprisingly fast start of action (within 15–30 minutes) and much better brain bioavailability (up to 80–90%), according to substantial data from recent preclinical and clinical investigations. Beyond that, this delivery system's personalized design reduces systemic medication exposure, which lowers peripheral side effects and improves patient compliance. In conclusion, intranasal administration facilitated by nanoparticles is a potential and revolutionary approach to improving migraine treatment, bridging the gap between cutting-edge formulation research and observable patient benefits.

Keywords: Drug targeting, Intranasal delivery, Migraine, Nanoparticles, Nose-to-brain transport.

INTRODUCTION:

Migraine is a complex neurobiological disorder affecting about 15% of women and 6% of men. It is characterized by a unilateral, pulsating headache, often accompanied by nausea, vomiting, and light sensitivity. Reduced serotonin (5-hydroxytryptamine, 5-HT) causes cerebral vasodilation and activation of trigeminovascular pathways, driving the intense pain of migraine attacks. The condition imposes a significant burden on quality of life and healthcare systems. [1]

Oral medications, including triptans and NSAIDs (Nonsteroidal Anti-Inflammatory Drugs), remain the primary therapy but are limited by poor gastrointestinal absorption, hepatic metabolism, delayed onset, and systemic side effects. These constraints highlight the need for faster, more targeted drug delivery strategies. Intranasal administration offers a promising alternative. The nasal cavity provides rapid systemic absorption and direct access to the brain via olfactory and trigeminal nerves, bypassing the gastrointestinal tract and first-pass metabolism. This nose-to-brain route can achieve faster and more consistent relief compared to oral therapies. [2][3]

However, conventional nasal sprays are often cleared rapidly by the mucociliary system, reducing drug absorption. Nanoparticle-based in-situ gels address these limitations by encapsulating drugs within nanoscale carriers and undergoing sol-to-gel transition in the nasal cavity. This approach enhances stability, prolongs residence time, allows controlled release, and facilitates targeted transport to the central nervous system, improving therapeutic efficacy and patient compliance. [4][5]

Despite their promise, challenges remain in optimizing particle properties, mucoadhesion, safety, and clinical translation. Systematic studies are needed to establish standardized protocols and fully realize the potential of nanoparticle-enabled nose-to-brain delivery for migraine management. Nose-to-brain drug delivery provides a promising alternative to conventional drug delivery systems for brain disorders like migraine, offering enhanced brain targeting, rapid onset, and reduced systemic side effects. [4][6][7]

Advantages of Nose-to-Brain Drug Delivery [8]

- Bypasses the blood-brain barrier (BBB) and hepatic first-pass metabolism, ensuring higher drug concentrations reach the brain than oral or intravenous routes.
- Enables non-invasive, patient-friendly administration, particularly suitable for unconscious, paediatric, and geriatric populations.
- Reduces peripheral (systemic) side effects by minimizing drug exposure to non-targeted organs.
- Novel carriers (e.g., nanoparticles, liposomes) protect drugs from enzymatic degradation and promote controlled, prolonged brain drug release.

Challenges in Nasal Drug Delivery [9]

- **Mucociliary clearance**: The nasal cavity has its own protective mechanism that swiftly expels foreign substances, which unfortunately leads to the rapid removal of drug formulations and reduces their contact time with the absorption surface.
- **Enzymatic degradation**: A variety of nasal enzymes can metabolize delicate molecules, particularly peptides and proteins before they exert any therapeutic effect, resulting in reduced drug availability.
- **Limited residence time**: Because of constant mucus movement and physiological turnover, most formulations remain in the nasal cavity only briefly, restricting effective absorption.
- **Restricted absorption surface**: The nasal cavity offers a relatively small surface area compared to other routes, limiting the total amount of drug that can be absorbed.
- **Physicochemical barriers**: Drugs with poor solubility, low lipid affinity, or chemical instability struggle to permeate the nasal epithelium effectively.

Significance of Nanoparticle-Based Nose-to-Brain Delivery [10][11][12]

- **Protection of sensitive molecules**: Nanoparticles can encapsulate therapeutic agents, shielding them from enzymatic degradation and maintaining their structural integrity.
- **Improved solubility and penetration**: By enhancing solubility and promoting interaction with the nasal membrane, nanocarriers facilitate efficient transport of drugs that would otherwise show poor absorption.
- **Prolonged mucosal residence**: Surface-modified nanoparticles exhibit strong mucoadhesion, allowing them to stay longer at the nasal site and increase the window for absorption.
- **Targeted brain delivery**: The nanoscale size enables nanoparticles to access olfactory and trigeminal pathways, providing a direct route to the brain while bypassing the blood–brain barrier.
- **Controlled and sustained release**: These systems can be engineered to release the drug gradually, maintaining consistent therapeutic levels over an extended period.
- **Enhanced bioavailability**: The combined effects of protection, retention, and efficient transport result in significantly improved drug bioavailability within the central nervous system.

MECHANISM OF NOSE-TO-BRAIN DRUG DELIVERY

The nasal cavity provides a direct anatomical link to the central nervous system (CNS), offering a non-invasive route that bypasses the restrictive blood-brain barrier. Drugs administered intranasally follow distinct transport pathways that deliver them either directly into the brain or indirectly through systemic circulation [13], as shown in Figure 1.

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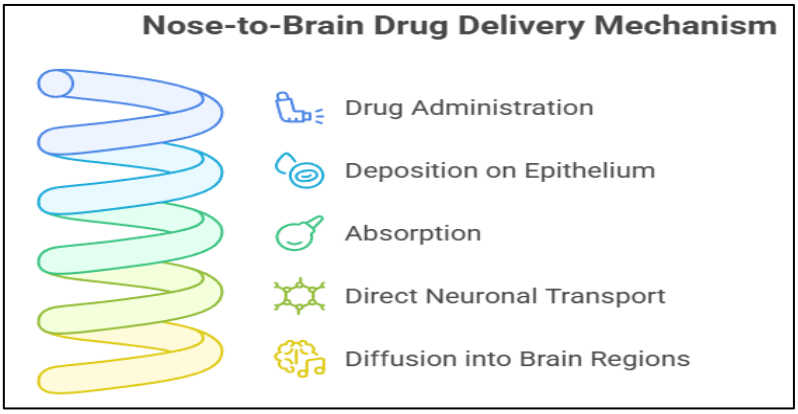

Figure 1: Nose-to-Brain Drug Delivery Mechanism

I. **Deposition and Initial Absorption** [14][15]

After administration, drug particles deposit on two regions: the olfactory epithelium in the upper nasal cavity and the respiratory epithelium covering the majority of the surface. The epithelial layer is thin and highly vascularized, allowing rapid absorption.

II. **Direct Neuronal Transport** [6][16][17]

1. **Olfactory Pathway**: Drugs administered intranasally can penetrate the olfactory epithelium and reach the olfactory bulb via sensory neurons, followed by diffusion into cortical and subcortical brain regions. The olfactory pathway, located in the upper nasal cavity, serves as a key route for brain targeting. This region contains olfactory receptor neurons (ORNs) along with supporting cells, also known as sustentacular, basal, or microvillar cells. ORNs transmit sensory information from the nasal environment to the CNS. Beneath the epithelium lie Bowman's glands (mucus-secreting), axons, lymphatic and blood vessels, and connective tissue. Dendrites of olfactory neurons extend into the mucus layer, while their axons pass through the cribriform plate into the subarachnoid space containing CSF and then project to brain regions such as the olfactory tract, piriform cortex, anterior olfactory nucleus, amygdala, and hypothalamus.

Drug transport across the olfactory epithelium generally occurs via three pathways: [16][17]

- **Transcellular pathway:** Mainly through sustentacular cells, involving endocytosis or passive diffusion. This route primarily favors lipophilic drugs.

- **Paracellular pathway:** Between sustentacular cells, facilitating transport of hydrophilic drugs. The absorption rate depends on the drug's molecular weight, with effective bioavailability for molecules up to ~1000 Daltons or higher when absorption enhancers are used.

- **Olfactory nerve pathway:** Drugs are internalized by neurons through endocytosis and transported intracellularly along axons to the olfactory bulb.

2. **Trigeminal Pathway:** The trigeminal nerve innervates both the olfactory and respiratory regions. Drugs absorbed here travel via trigeminal branches to the brainstem and higher pain-processing centers, making this pathway particularly relevant for migraine therapy. The respiratory region differs from the olfactory region in cellular composition, consisting mainly of ciliated epithelium interspersed with goblet cells that clear mucus and foreign particles. The trigeminal nerve transmits sensory information from the oral and nasal cavities, eyelids, and cornea to the CNS through its ophthalmic, maxillary, and mandibular divisions. Unlike the olfactory nerve, trigeminal fibers from the respiratory region enter the brain at two points: near the olfactory bulb via the cribriform plate and at the pons. Other cranial nerves and sensory structures in the nasal cavity may also serve as additional entry routes. Overall, the trigeminal nerve provides a key route for nasal drug delivery to the CNS. [9][18]

III. **Paracellular and Intracellular Routes** [19]

Small hydrophilic drugs primarily traverse the nasal epithelium through paracellular pathways, passing between cells via tight junctions. Lipophilic compounds and nanoparticles are mainly absorbed through transcellular mechanisms, which include passive

diffusion across cell membranes or active vesicular transport such as endocytosis and exocytosis. Additionally, axonal transport along neuronal pathways and perineural diffusion allow direct access to the brain, bypassing systemic circulation.

IV. **Systemic Absorption** [9][16]

A fraction of the intranasally administered drug enters the rich network of nasal blood vessels, rapidly reaching systemic circulation while avoiding first-pass hepatic metabolism. This systemic uptake supports both central nervous system and peripheral effects, enhancing the overall efficacy of anti-migraine agents.

V. **Blood-Brain Barrier and Migraine Pharmacotherapy** [20][21]

The BBB is a dynamic interface composed of endothelial cells, astrocytes, pericytes, and a basement membrane, collectively restricting paracellular transport and expressing efflux pumps like P-glycoprotein (P-gp). This limits the brain uptake of many antimigraine drugs, including sumatriptan and rizatriptan, which have low BBB (Blood-Brain Barrier) permeability.

Migraine and BBB Permeability [22]

Migraine attacks may transiently disrupt the BBB due to neuroinflammation and vasodilation, creating a therapeutic window for nanoparticle delivery. However, this disruption is unpredictable and not reliable for consistent drug delivery.

Nanoparticle Strategies to Cross the BBB [2][15]

Nanoparticles can cross the BBB via:

- Receptor-mediated transcytosis: Using ligands like transferrin or lactoferrin.
- Adsorptive-mediated transcytosis: Cationic nanoparticles interact with negatively charged cell membranes.
- Tight junction modulation: Borneol and chitosan can reversibly open tight junctions.These mechanisms enhance brain targeting while minimizing systemic exposure.

VI. **Distribution within the Brain** [15][22]

Once drugs reach the CNS, they disperse through cerebrospinal fluid and interstitial fluid, targeting key structures involved in migraine pathophysiology, including trigeminal nuclei, the thalamus, and cortical pain-processing centers. Together, these mechanisms account for the faster onset of action, lower dosing requirements, and improved therapeutic outcomes observed with nasal anti-migraine formulations compared to conventional oral therapies.

Comparative Efficacy with Other Drug Delivery Methods [18][33]

Table 1: Comparative Efficacy with Other Drug Delivery Systems

Delivery Method	Onset Time	Bioavailability	Patient Compliance
Oral	30–60 min	40–60%	Moderate
Injectable	10–15 min	90–100%	Low
Transdermal	60–90 min	70–80%	Moderate
Nasal Nanoparticles	15–30 min	80–90%	High

STRATEGIES USED TO DEVELOP SUSTAINED-RELEASE MIGRAINE FORMULATIONS

Sustained-release formulations for migraine are developed using several innovative strategies that enhance drug retention, prolong therapeutic effects, and improve brain targeting, particularly via the intranasal (nose-to-brain) route [2], as shown in Figure 2.

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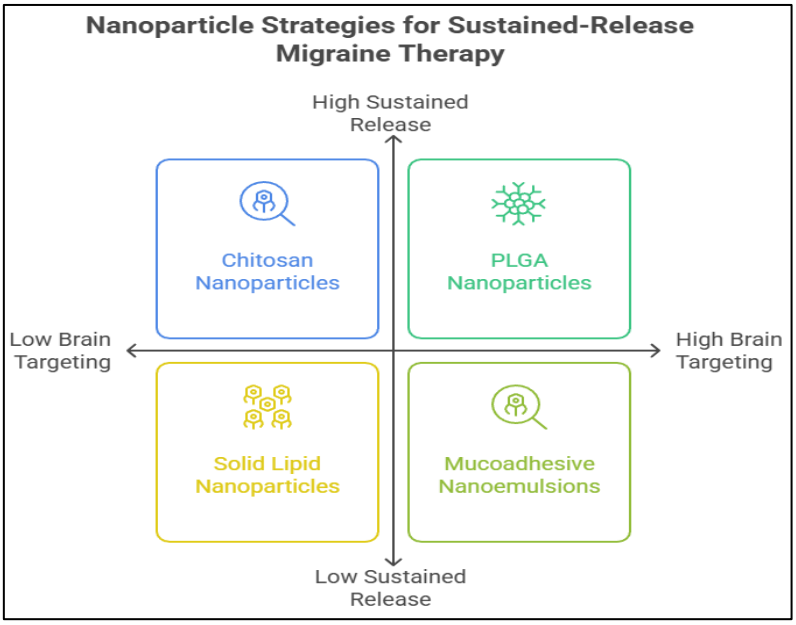

Figure 2: Nanoparticle Strategies for Sustained-Release Migraine Therapy

I. Polymeric Nanoparticles

1. PLGA Nanoparticles [23]

Poly (lactic-co-glycolic acid) (PLGA) nanoparticles are biodegradable, biocompatible, and FDA-approved for drug delivery. They provide sustained release of drugs like topiramate and ubrogepant, with studies showing brain concentrations 2.5-fold higher than oral administration. PLGA nanoparticles embedded in thermosensitive in situ gels offer controlled release over 24 hours, ideal for migraine prophylaxis.

2. Chitosan Nanoparticles [24]

Chitosan, a natural polysaccharide, exhibits mucoadhesive properties and enhances nasal residence time. Sumatriptan-loaded chitosan nanoparticles show high entrapment efficiency (75–85%) and sustained release over 28 hours, with an improved brain targeting index (Drug Targeting Efficiency (DTI) > 2.3).

II. Lipid-Based Nanoparticles

1. Solid lipid nanoparticles (SLNs) [25]

SLNs are developed to encapsulate migraine drugs, offering biocompatibility, controlled release, prolonged drug action and protection of drugs from degradation and improving bioavailability. Rizatriptan-loaded SLNs demonstrated a Maximum Concentration (Cmax) of 473.56 ng/mL and an Area Under the Curve (AUC) of 3706.95 ng/mL, significantly outperforming oral formulations.

2. Nanostructured lipid carriers (NLCs) [26]

NLCs are composed of a blend of solid and liquid lipids to improve drug loading and stability, surpassing the limitations of conventional SLNs.

III.Mucoadhesive In Situ Gelling Systems [4][27]

Mucoadhesive in situ gels incorporate nanoparticles or dissolved drugs and undergo sol-to-gel transition upon contact with the nasal mucosa, providing extended residence time and sustained release.

These gels ensure constant and higher drug absorption over a prolonged period, as demonstrated in drug-loaded SLN gels for migraine therapy.

IV.Liposomes and Nanoemulsions [28][29]

Liposomes (phospholipid vesicles) and nanoemulsions increase drug stability, enhance brain targeting, and provide controlled/sustained release while protecting drugs from enzymatic degradation.

Mucoadhesive nanoemulsions also enhance brain delivery of antimigraine drugs, showing prolonged presence and efficacy.

V. Dendrimers and Inorganic Nanoparticles [11][30]

Dendrimers are highly branched, multifunctional polymers that enable high drug loading, controlled release, and improved brain targeting. They can be incorporated into mucoadhesive gels to further sustain release.

Inorganic nanoparticles such as gold- or silica-based carriers are being explored for their controlled release properties, though safety and mucosal irritation must be assessed.

VI.Additional Strategies

1. Surface Functionalization [11][30][31]

PEGylation reduces immunogenicity and enhances circulation time. Ligands such as borneol, transferrin, or lactoferrin can target specific receptors to increase nose-to-brain transport efficiency. Borneol-modified nanoparticles have demonstrated opening of tight junctions and enhanced penetration across the BBB.

Surface modification (e.g., with ligands or polymers) enhances mucoadhesion, uptake, and targeted release.

Incorporation of enzyme inhibitors and permeation enhancers helps protect drugs from degradation and extends their effective presence.

2. Patient-Centric Perspective and Compliance [25][31][32]

Nasal nanoparticle delivery systems offer a practical, non-invasive alternative to painful injections and slow-acting oral tablets, which is especially beneficial during acute migraine episodes when nausea and gastric stasis compromise drug absorption. Devices optimized for nasal drug deposition, such as breath-powered nasal powders, improve precision and user acceptability. Clinical trials indicate patient preference, improved adherence, and faster onset of relief with nasal nanoparticles compared to traditional forms.

Proper patient education on device usage and administration techniques is essential to maximize treatment compliance and efficacy. These advantages suggest that nasal nanoparticle delivery aligns well with patient-centered care paradigms in migraine management.

EXPLORATION OF FORMULATIONS [18][20][21]

Recent formulations include PLGA nanoparticles embedded in thermo-responsive in situ gels maintaining stability and controlled drug release over 24 hours, enhancing brain accumulation after nasal administration in animal models. Chitosan-based nanoemulsions and borneol-modified lipid carriers have demonstrated significant improvement in permeability and neuroprotective effects targeting migraine-relevant pathways. Particle size (ideally <200 nm), positive zeta potential, and high drug encapsulation efficiencies remain critical formulation parameters.

Recent advances include:

- **In situ gels:** Thermo-responsive systems for sustained release.
- **Borneol-modified nanoparticles:** Enhanced BBB penetration.
- **Hybrid systems:** Lipid-polymer nanoparticles for dual functionality.

Table 2: Nanoformulation-Based Strategies for Intranasal Migraine Therapy

Formulation Type	Study Findings	Examples
Polymeric Nanoparticles	Nanoparticles sustained release for up to 24 hours and their easy penetration of the nasal mucosa due to their formulation and particle size may assist in cutting down the number of daily doses to just one.	Sumatriptan [2]
	Intranasal medication delivery may be a useful tool for migraine treatment, according to ex vivo drug permeation experiments that show regulated drug release for up to 24 hours.	Zolmitriptan [34]
	decreases the first-pass metabolism and increases bioavailability following nasal medication administration for migraine treatment	Eletriptan Hydrobromide [35]
Solid lipid nanoparticles (SLN)	Nasal SLN was observed to be preferable to the commercial oral formulation and drug solutions administered by the IV route, with Cmax 473.56 ng/ml, Tmax 1 hr, AUC 3706.95 ng/ml, and T1/2 of 5.7 hr.	Rizatriptan Benzoate [36]
	The findings showed that the drug was delivered to the brain quickly within 10 minutes, and the safety of the nano-formulation for nasal administration was validated by toxicological studies.	Almotriptan [37]
Nasal Emulsions/ Nanoemulsions	The drug's brain targeting was greater with intranasal nanoemulsions (AUC=302.52 µg min/g) than with intranasal gels (AUC=115 µg min/g) and intravenous treatment (AUC=109.63 µg min/g).	Rizatriptan Benzoate [38]
	In nasal drug administration for the treatment of migraines, nanoemulsion demonstrated a high drug loading, a repeatable drug release profile, a reduced droplet size, and a good zeta potential.	Flunarizine Dihydrochloride [12]
	The drug's solubility and release in a simulated nasal fluid are enhanced by solid-liquid nanoemulsion. The mixture as a whole was determined to be appropriate for nasal medication administration.	Flunarizine Dihydrochloride [39]
Nanostructured lipid carriers (NLCs)	Adequate drug deposition in the brain. For NLCs delivered intranasally, the DTE and DTP were determined to be 258.02% and 61.23%, respectively.	Sumatriptan [26]
Nasal Sprays (MDI / Pump sprays)	Rapid and efficient migraine symptom alleviation was achieved with sumatriptan nasal spray, particularly the 20 mg dosage. Notable pain reduction was observed as early as 15 minutes, and 62–63% of patients reported minimal or no pain at 2 hours, compared to 29–35% for a placebo. Overall, the treatment was favourably received.	Sumatriptan nasal spray [40]
Polymeric Nanoparticles (PLGA, Chitosan, etc.)	Polymeric nanoparticles help deliver drugs to the CNS by crossing the blood-brain barrier safely and providing controlled release. They are biodegradable, can carry diverse drugs, and show promise in treating neurological disorders, though clinical use is still developing.	PLGA nanoparticles for CNS drugs [2][24]
Micellar nanocarriers	When compared to the drug's intravenous and nasal solutions, in vivo biodistribution experiments demonstrated the superiority of the created nanocarrier for brain targeting. A potential nose-to-brain transport channel for the labeled medication was identified by brain localization experiments.	Zolmitriptan [41]
Nanoparticle-based In-Situ Gel/ In-Situ Gel	The nasal ubrogepant nanoparticle gel achieved rapid and sustained brain delivery, improving migraine relief and reducing inflammation more effectively than oral or plain formulations.	Ubrogepant [4]
	The optimized nasal in-situ gel of rizatriptan showed rapid gelation, sustained release, and significantly improved brain bioavailability, providing faster and more effective migraine relief than oral formulations	Rizatriptan [42]

KEY CONSIDERATIONS AND STRATEGIES WHEN DEVELOPING A NASAL NOSE-TO-BRAIN MIGRAINE FORMULATION

Design factors and development priorities are as follows:

1. Choice of active and dosage form [43]

It's critical to select a drug with enough potency and chemical stability to be effective in the small volumes allowed by nasal delivery. Molecules like zavegepant, Ubrogepant, etc. were specifically engineered for this, making them suitable as a nasal administration.

2. Maximizing absorption and residence time [38][44]

For a drug that needs quick relief, the formulation should enable fast uptake through the nasal mucosa. In contrast, if longer-lasting exposure is needed, strategies such as in situ gelling systems or mucoadhesive excipients can help the drug stay in contact with the nasal lining for extended periods.

3. Droplet size and delivery mechanics [6][45]

Precise particle or droplet size matters for targeting the upper nasal cavity, especially the olfactory region, which provides a more direct pathway to the brain. Formulation design should be paired with delivery devices capable of depositing the drug in the superior/posterior nasal vault, where nose-to-brain transport is most effective.

4. Minimizing irritation and adverse local effects [10][46]

Side effects like nasal burning, irritation, an unpleasant taste, or nosebleeds may discourage use. This makes careful excipient selection, preservative design, and patient-friendly sensory properties essential.

5. Stability and manufacturability [3][47]

The drug must remain stable under formulation and storage conditions. For APIs that are unstable in liquid form, dry-powder nasal formulations may offer a viable alternative. Consider pH adjustments, ionic strength, or stabilizing excipients to enhance shelf life.

6. PK/PD and regulatory expectations [48][49]

If the formulation is meant for rapid systemic relief, demonstrating fast plasma exposure is key. If the therapeutic target is central, biomarkers or clinical endpoints showing CNS activity should be included. Regulatory agencies also expect robust safety and tolerability data, especially with repeated dosing and interaction studies (e.g., with common migraine rescue therapies).

7. Clinical endpoints and populations [51][52]

For acute migraine studies, the gold-standard primary outcomes are pain relief or complete pain freedom at 2 hours. Additional endpoints may include sustained relief, the ability to function normally, and tolerability measures (like absence of taste disturbances). For preventive indications, endpoints typically focus on reducing Monthly Migraine Days (MMDs).

8. Drug interaction and safety monitoring [52][53]

New migraine molecules, particularly gepants, require thorough evaluation of liver safety, cardiovascular risk, and compatibility when used alongside preventive treatments or rescue medications. Most gene therapies have shown acceptable safety profiles, but careful monitoring during trials is key.

CONCLUSION

Nanoparticle-enabled nose-to-brain delivery represents a promising breakthrough in migraine management by enabling rapid relief with minimal side effects. These advanced systems overcome key barriers such as the blood-brain barrier and first-pass metabolism, ensuring efficient brain targeting. Polymeric nanoparticles, lipid carriers, and mucoadhesive in-situ gels enhance drug residence time within the nasal cavity and enable controlled, sustained release. Clinical studies demonstrate superior performance compared to conventional oral therapies, with onset times of 15-30 minutes and bioavailability reaching up to 80-90%.

The direct nose-to-brain pathway supports precise delivery to migraine-relevant regions while limiting systemic exposure, resulting in improved therapeutic efficacy and patient compliance. Continued research should focus on optimizing safety profiles, manufacturing scalability, and regulatory compliance to enable clinical translation. The convergence of nanotechnology and intranasal delivery holds immense potential to redefine migraine therapy and significantly enhance patient's quality of life.

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