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A Review on Thermosensitive Zolmitriptan Mucoadhesive NanobioGel: Intranasal Delivery for Abortive treatment of Migraine

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ABSTRACT

In order to improve migraine treatment by circumventing the blood-brain barrier and minimizing side effects throughout the body, this study investigates a novel thermosensitive mucoadhesive nanoparticulate biogel for intranasal delivery of zolmitriptan. The limitations of oral zolmitriptan, such as its delayed onset and poor absorption, make it necessary to develop novel drug delivery techniques for migraine, a crippling neurological condition. By utilizing the olfactory mucosa to facilitate the quickest possible drug delivery to the brain, intranasal medicine administration offers a non-invasive method. Zomitriptan-loaded nanoparticles made of biocompatible polymers will be included into the created biogel to improve drug encapsulation, regulate drug release, and strengthen mucoadhesion. Because of its thermosensitivity, it can be administered as a liquid at room temperature and then gelled in situ at body temperature, which guarantees extended contact with the nasal mucosa and improved absorption. Formulation characteristics such drug release, mucoadhesion, encapsulation efficiency, and particle size will be optimized by a design of experiments method. Technetium-labeled formulations will monitor biodistribution, and in vivo trials will evaluate the effectiveness of treating migraines in comparison to oral zolmitriptan. Toxicological tests will evaluate biocompatibility in the nasal cavity and central nervous system. Both small and large molecules can pass through the blood-brain barrier when medications are administered intranasally through the olfactory and trigeminal nerves. PLGA, PEG, and chitosan-based carriers are examples of nanoparticles that provide controlled release and improved delivery specificity. Drug transport is further supported by lipid-based carriers like lipid nanoparticles and liposomes. If this biogel is developed successfully, it has the potential to transform the treatment of migraines by enhancing patient outcomes and lowering treatment costs.

Keywords: *Thermosensitive, Mucoadhesive, Nanoparticulate Nose-To-Brain Delivery*

1. INTRODUCTION

Recurrent episodes of moderate to severe annoyance are the hallmark of migraine, a crippling neurological condition that is frequently accompanied by autonomic symptoms like nausea and vomiting as well as sensory abnormalities like photophobia, phonophobia, and cutaneous allodynia (Jackson et al., 2015; Lonzar et al., 2023). These attacks typically last between 4 and 72 hours if left untreated (Benatto et al., 2020). Migraine affects approximately 14% of the global population and stands out as a primary cause of disability among neurological disorders (Lonzar et al., 2023; Vikelis et al., 2020). The personal, societal, and economic burdens associated with migraine are substantial, considering its effect on work efficiency, healthcare utilisation, and overall excellence of life (Edvinsson, 2017; Şimşek et al., 2020). Diagnosis relies on clinical criteria, a limitation that doesn't fully account for the variety of migraines, including the underlying neurobiological and genetic causes the variety of migraines, including the underlying neurobiological and genetic causes (Ashina et al., 2021). The reliance on patient-reported symptoms for diagnosis underscores the subjectivity involved, potentially leading to diagnostic variability (Macrì et al., 2023).

The pathophysiology of migraine is composite and multifactorial, involving intricate interactions between genetic predisposition, environmental factors, and neurobiological mechanisms (Goschorska et al., 2020; Hargreaves, 2007). Several lines of evidence point to a crucial role for the trigeminovascular system, cortical spreading depression, and central

sensitisation in the beginning and propagation of migraine attacks (Blumenfeld et al., 2021). Triggers such as anxiety, Lack of sleep, go on hunger strike, and sensory stimuli can alter central excitability, sensitising the trigeminal nerve and This results in the secretion of neuropeptides like calcitonin gene-related peptide (CGRP), substance P, and pituitary adenylate cyclase-activating polypeptide (PACAP) (Song et al., 2024). These neuropeptides dilate intracranial blood vessels and cause neurogenic inflammation in the meninges. A slow-moving wave of depolarization in neurons and glial cells, known as cortical spreading depression, is believed to stimulate trigeminal sensory pathways and play a role in the aura phase experienced by certain individuals with migraines (Rocca et al., 2020). Furthermore, central sensitisation, a process of increased neuronal excitability in the central nervous system, amplifies pain signals and contributes to the chronification of migraine. Migraine attacks may be initiated by oxidative stress, as transient receptor potential ankyrin-1 (TRPA1) ion channels located in the dura mater sense this stress and translate it into neural signals, leading to neurogenic inflammation (Borkum, 2017, 2018).Moreover, gut microbiota may play a role in the development of migraines by interacting with the brain through the gut-brain axis, which facilitates two-way communication via neural, hormonal, and immune-related mechanisms.

2. CURRENT TREATMENT STRATEGIES FOR MIGRAINE

Migraine management involves both acute and preventive strategies aimed at lessening the frequency, intensity, and duration of episodes while enhancing the patient's quality of life. Acute treatments focus on alleviating pain and other symptoms during a migraine episode (Goadsby et al., 2017). These may include general pain relievers like nonsteroidal anti-inflammatory drugs (NSAIDs), as well as migraine-specific agents such as triptans and ditans. Triptans, which act as selective serotonin receptor agonists, help by narrowing widened intracranial blood vessels and suppressing neuropeptide release. However, due to their vasoconstrictive properties, they are not recommended for individuals with cardiovascular conditions.Ditans, selective serotonin receptor agonists, offer a potential alternative for patients with cardiovascular risk factors, as they do not possess the same vasoconstrictive properties as triptans. In cases where acute treatments are ineffective or poorly tolerated, antiemetics may be used to alleviate nausea and vomiting (Heckroth et al., 2021), while neuromodulation techniques such as transcranial magnetic stimulation (Daboul et al., 2000) and vagus nerve stimulation can provide non-pharmacological options for acute pain relief (VanderPluym et al., 2021). Furthermore, glutamate receptor antagonists, with their central effects, are under investigation as potential centrally acting antimigraine drugs.

Preventive treatments are indicated for patients experiencing frequent or disabling migraine attacks, with the goal of reducing attack frequency, severity, and duration. First-line preventive medications include beta-blockers (Kumar and Kadian, 2023), calcium channel blockers (Sprenger et al., 2018), tricyclic antidepressants (Smitherman et al., 2013), and anticonvulsants. These medications have been shown to modulate various neurotransmitter systems and neuronal pathways implicated in migraine pathophysiology (Song et al., 2024). More recently, monoclonal antibodies targeting calcitonin gene-related peptide (Scuteri et al., 2019) or its receptor have emerged as effective (Raffaelli and Reuter, 2018) and well-tolerated preventive therapies (Yuan et al., 2017). These antibodies selectively block the CGRP pathway (Messlinger, 2018), which is implicated in migraine pathogenesis (Wattiez et al., 2020), thereby reducing the frequency of migraine attacks (Croop et al., 2019). Lifestyle modifications, such as regular exercise (Agbetou M and Adoukonou, 2022), stress management techniques (Calhoun and Ford, 2007), and dietary changes (Blau et al., 2004), can also play a crucial role in migraine prevention.

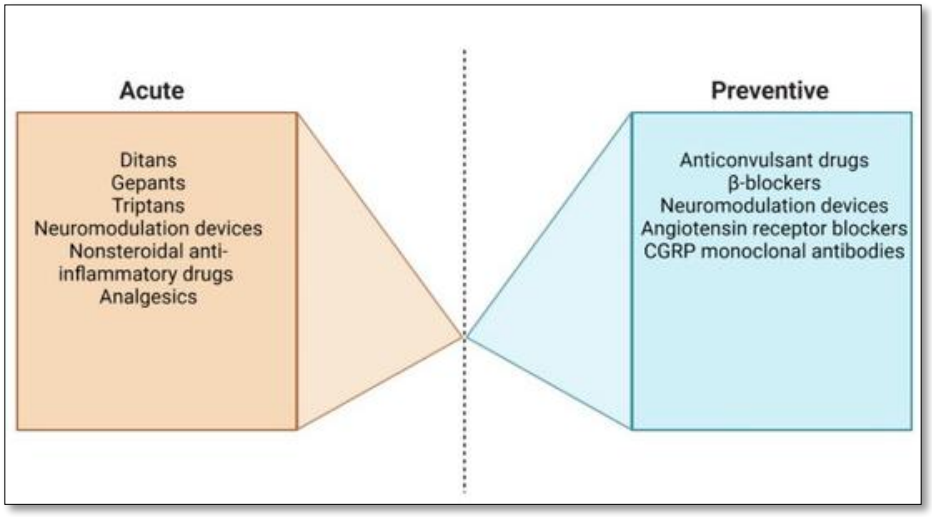
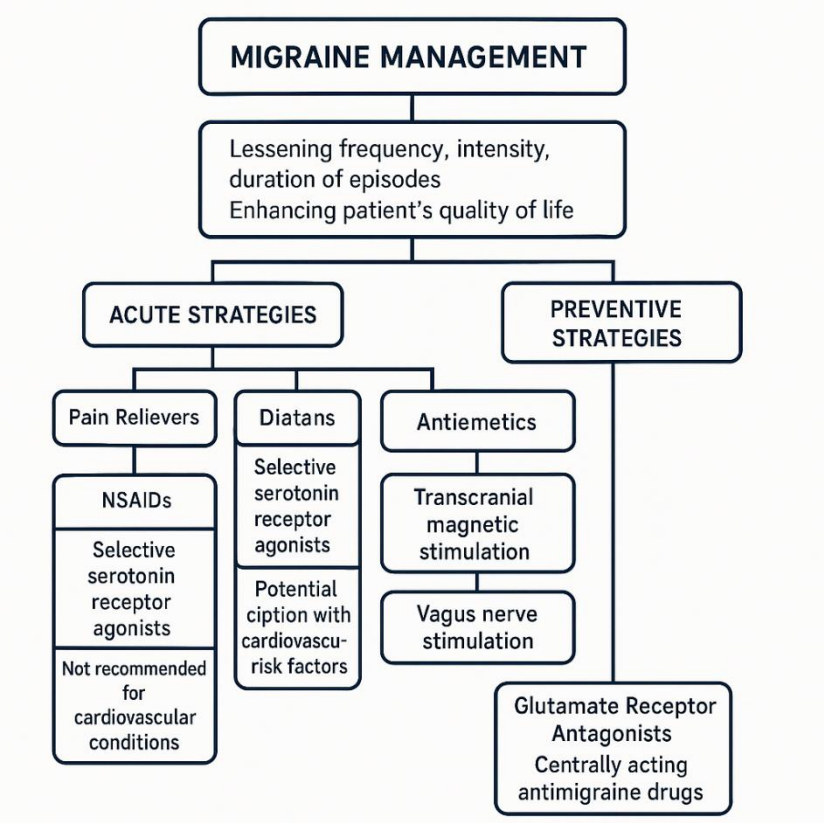


Fig. 1: Migraine Management (Source; Ples *et al.*, 2023)

A patient's unique migraine characteristics, medical history, comorbidities, and preferred course of therapy should all be taken into consideration while choosing acute and preventive medications. A comprehensive management plan should also address modifiable risk factors such as obesity, sleep disorders, and medication overuse. (Baratloo et al., 2017; Marupuru et al., 2023) Many patients are interested in nutraceuticals instead of traditional medicines due to a fear of side effects or addiction. Acupuncture, matches the efficacy of mainstream pharmacological treatments (Nielsen et al., 2022) but also offers a lower risk of side effects (Van Hal et al., 2025), providing patients with a safer and more appealing treatment option (Song et al., 2024). It is worthwhile to pursue music medicine as a non-invasive supplement to existing management techniques (Diamante, 2020). To completely understand these therapies' mechanisms of action and maximize their incorporation into all-encompassing migraine treatment strategies, more research is required(Gauthier et al., 1996; Marupuru et al., 2023).

Non-pharmacological approaches, encompassing physical, psychological, and self-initiated strategies, are also integral to migraine management (Marupuru et al., 2023). Psychosocial interventions, including cognitive behavioural therapy, biofeedback, and relaxation techniques, aim to address psychological factors such as stress (Sturgeon et al., 2023), anxiety (Brown et al., 2012), and depression that can exacerbate migraine (Lunde et al., 2024). These interventions empower patients to develop coping skills, manage triggers, and improve overall well-being (Holroyd & Penzien, 1994). Physical therapy techniques, such as manual therapy and exercise, can help alleviate musculoskeletal pain and improve posture, which may contribute to migraine. Furthermore, Art therapy may help people with migraines by providing insight into their own pain experience and perception, reducing pain through distraction, and enhancing psychological well-being (Smirnoff & Pham, 2024). Individuals with migraines commonly exhibit musculoskeletal and/or vestibular dysfunctions, and the severity of disability can vary depending on the presence of aura or the frequency of migraine attacks (Carvalho et al., 2019).



3. NOSE-TO-BRAIN DRUG DELIVERY: A NOVEL APPROACH FOR MIGRAINE TREATMENT

Bypassing the blood-brain barrier and providing a new method of treating migraines, nose-to-brain drug delivery is a potential, minimally invasive method for delivering medications straight to the central nervous system (Gänger & Schindowski, 2018). This route leverages the unique anatomical and physiological characteristics of the nasal cavity, including its rich vasculature and direct connections to the brain via the olfactory and trigeminal nerves (Mistry et al., 2009). Intranasal administration allows drugs to circumvent systemic circulation, potentially reducing peripheral side effects and increasing drug concentrations in the brain (Mittal et al., 2013). The olfactory and respiratory areas of the nasal cavity are involved in the primarily extracellular and transcellular transfer of therapeutic substances from the nasal cavity to the brain

(Woensel et al., 2013). The olfactory region provides a direct route to the brain via the olfactory nerve, while the trigeminal nerve also contributes to drug transport, especially for compounds with certain physicochemical properties. Several factors can influence the efficiency of nose-to-brain drug delivery, including the drug's molecular weight, lipophilicity, and enzymatic degradation in the nasal cavity (Minn et al., 2002).

Because they provide defense against enzymatic degradation and efflux processes in the nasal canal, nanoparticulate drug delivery devices have become a viable approach to improve nose-to-brain medication transport (Mistry et al., 2009). When compared to conventional drug solutions, studies conducted on animal models show that nanosized drug delivery devices can enhance drug transport to the brain (Mistry et al., 2009). Innovative drug delivery methods like liposomes, nanoparticles, and mucoadhesive microspheres lengthen the duration of a drug's residence in the nasal cavity, increasing absorption and facilitating subsequent brain transfer (Misra & Kher, 2012). Drug stability and absorption in the nasal cavity can be further enhanced by formulation techniques such as the use of enzyme inhibitors and permeation enhancers (Gänger & Schindowski, 2018). Intranasal administration is associated with high drug transfer from nose to brain and drug bioavailability (Hussain, 1998). Therefore, nose-to-brain drug delivery holds significant potential for revolutionising migraine treatment by providing a direct and efficient pathway for delivering therapeutics to the CNS, potentially improving patient outcomes and minimising adverse effects (Şekerdağ, 2017; Sonvico et al., 2018). High drug transfer from the nose to the brain and high drug bioavailability are linked to intranasal delivery (Hussain, 1998). Therefore, by offering a direct and effective conduit for delivering medicines to the central nervous system, nose-to-brain medication administration holds considerable promise to revolutionize migraine therapy, potentially increasing patient outcomes and minimizing unwanted effects (Şekerdağ, 2017; Sonvico et al., 2018).

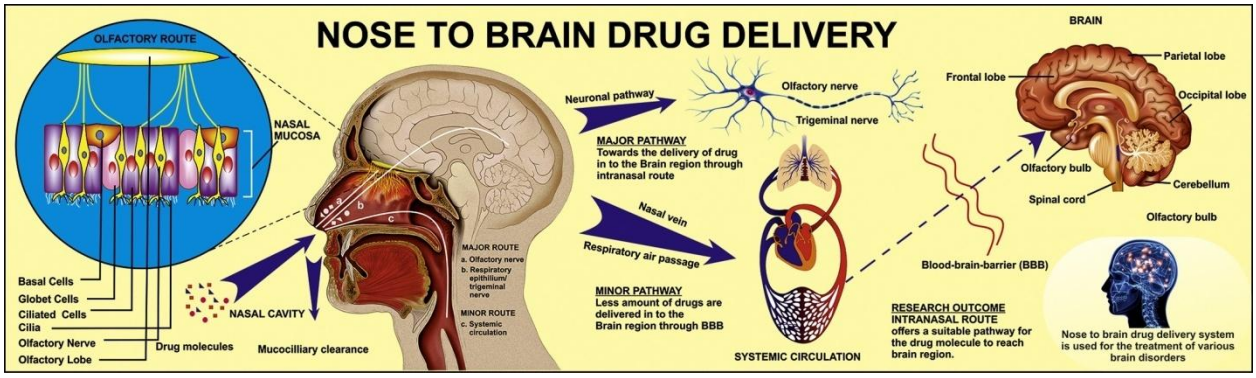


Fig. 2: Nose to Brain Delivery (Source; Agrawal *et al.*, 2018)

4. ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS OF NASAL ROUTE FOR MIGRAINE

Because it can avoid the blood-brain barrier, which is a major barrier for many systemically delivered medications, the nasal route offers a tempting alternative for managing migraines (Gänger & Schindowski, 2018). Direct drug transport to the central nervous system is made possible by the nasal cavity's advantageous position, especially the olfactory mucosa at the base of the skull (Gänger & Schindowski, 2018; Vyas et al., 2005). This is essential for treating migraines, as prompt onset and precise medication administration are critical (Gänger & Schindowski, 2018). By avoiding the liver's first-pass metabolism, which lessens the efficiency of drugs taken orally, intranasal administration is non-invasive and can provide systemic drug distribution with high bioavailability (Devillier et al., 2010; Mittal et al., 2013). Additionally, the nasal cavity's high surface area and rich vascularization facilitate quick medication absorption into the systemic circulation (Şekerdağ, 2017). Furthermore, medications can be directly delivered to parts of the brain linked to migraine pathogenesis through the olfactory and trigeminal nerve pathways (Mistry et al., 2009). Therapeutic drugs can efficiently enter the central nervous system thanks to the extracellular and transcellular transport systems used in intranasal drug administration (Woensel et al., 2013). A thorough understanding of the nose cavity's anatomy, including its epithelial lining, mucus production, and enzymatic activity, is necessary for the design of efficient intranasal drug delivery systems. These factors can affect drug absorption and metabolism (Minn et al., 2002). Both systemic and local immunity are improved by the lymphoid tissue connected to the nasal mucosa (İmani et al., 2024). Additionally, compared to conventional solutions, sophisticated drug delivery technologies like nanoparticles can improve nose-to-brain drug transport, possibly by protecting the medication from efflux or degradation (Mistry et al., 2009). However, research is still ongoing to determine the exact methods by which nanoparticles enable drug transport to the central nervous system (CNS), whether through direct transport via the olfactory or trigeminal nerves or release in the nasal cavity (Mistry et al., 2009). Formulation techniques are always changing to maximize bioavailability, taking into account elements that can restrict drug residence duration and absorption, such as enzymatic degradation and mucociliary clearance (Dudhipala & Narala, 2016). For instance, intranasal fentanyl spray has shown encouraging pharmacokinetic properties, providing a quick start of action and brief duration of effect, which is in line

with the temporal features of breakthrough pain episodes (Dale, 2010). A number of variables, such as the drug's physicochemical qualities, the formulation's features, and the administration method, can affect the drug's pathway into the central nervous system (CNS), making successful intranasal delivery crucial (Dhuria et al., 2009). It is important to carefully consider the possible effects of polymers and surfactants on the nasal mucosa when using them in nasal formulations. Furthermore, intranasal administration reduces systemic exposure and side effects by facilitating focused delivery, which is particularly advantageous for diseases where localized treatment is preferable (Hussain, 1998; İmani et al., 2024; Misra & Kher, 2012; Thomas & Ahsan, 2007).

Formulation strategies, including in-situ gelling systems, represent a cutting-edge approach, using both natural and synthetic polymers (Karavasili & Fatouros, 2015). Utilising cyclodextrins may enhance nasal absorption via increased aqueous solubility (Merkus, 1999). This approach improves patient compliance by reducing hospitalisation costs and ensuring user-friendliness (Kefalides, 1998). Intranasal delivery offers quick drug absorption, increased bioavailability, and direct nose-to-brain transport, which bypasses the blood-brain barrier (Lochhead et al., 2014). Intranasal delivery offers a non-invasive method to deliver both small and large molecules by targeting the olfactory system and connected memory areas (Hanson & Frey, 2008). However, challenges exist, including variability in nasal deposition, mucociliary clearance, enzymatic degradation, and potential toxicity. Addressing these challenges requires careful consideration of formulation strategies and delivery devices to optimise drug absorption and therapeutic outcomes.

The initial region is the outermost section of the nasal cavity, which is lined with ciliated hairs and a mucous membrane, limiting the entry of foreign particles, antigens, and infections. The respiratory region is supplied with trigeminal sensory neurones and blood vessels. The olfactory region is situated in the top portion of the nasal canal, characterised by an epithelium composed of supporting cells, basal cells, and olfactory sensory neurones. This region is in proximity to the olfactory bulb (OB) of the brain via the olfactory nerves, situated beneath the cribriform plate of the skull. The trigeminal nerves are located in this region. Upon deposition of a therapeutic formulation within the nasal cavity, it must surmount mucociliary clearance in the vestibular region. Upon entering the nasal cavity, the medication can access the central nervous system through the olfactory or trigeminal nerves, or indirectly via systemic circulation (Bourganis et al., 2018). The trigeminal and olfactory routes in the nasal cavity facilitate direct transport to the brain, enhancing the pharmacokinetic/pharmacodynamic (PK/PD) profiles of central nervous system (CNS) medications. The medication can access the olfactory bulb by traversing the olfactory mucosa or the cerebrospinal fluid, then mingling with the interstitial fluid in the brain. The therapeutic substances must traverse the cribriform plate and the olfactory nerve subsequent to their interaction with olfactory receptors on olfactory neurones. The direct delivery of pharmaceuticals to the brain via various olfactory nerve transport systems includes both intraneuronal and extraneuronal pathways, with transport occurring along axons and through perineural channels, respectively (Costa et al., 2021). The trigeminal route encompasses branches of the trigeminal nerves that innervate the respiratory and olfactory mucosa, facilitating the delivery of therapeutically active chemicals to the brainstem and associated tissues. These branches penetrate the brainstem at the pons and continue to the hindbrain and forebrain. This system facilitates intracellular transport via axons and extracellular transport through diffusion and bulk flow via perineuronal channels, perivascular gaps, or lymphatic channels linked to the cerebrospinal fluid and brain tissues. The drug's physicochemical qualities will dictate whether transport occurs intracellularly or extracellularly (Costa et al., 2019). Conversely, the respiratory area is highly vascularised, facilitating systemic medication absorption. Small lipophilic compounds can more easily penetrate the bloodstream and traverse the blood-brain barrier compared to hydrophilic and high molecular weight ones. Upon entering the nasal blood vessels, the medication can access the carotid artery, subsequently reaching the brain and spinal cord. This route is less favoured due to the constraints imposed by the blood-brain barrier on medication access to the central nervous system and the potential adverse peripheral effects resulting from systemic distribution (Cunha et al., 2021). Notwithstanding the advantages and possibilities of the nose-to-brain delivery method, substantial obstacles must be addressed for pharmaceuticals to access the central nervous system, including the anatomical, physiological, and biochemical attributes of the target region. One of the primary challenges pertains to the retention of mucus in the nasal mucosa, along with ciliary movement, as these are the initial barriers to surmount when drugs are administered via the intranasal route. Both factors can restrict the retention time of the drug formulation in the nasal cavity and impede molecular movement towards the central nervous system. The limited capacity for formulation distribution in each nostril may hinder effective drug delivery to the brain.The physical position of the olfactory epithelium is a significant barrier for this route, as the dose form must first access this place. Metabolic enzymes located in the olfactory mucosa should be taken into account when formulating for the nose-to-brain pathway. Therefore, IN formulations must consist of biocompatible and odourless excipients while preventing fast removal by mucociliary clearance and/or enzymatic degradation (Selvaraj et al., 2018).

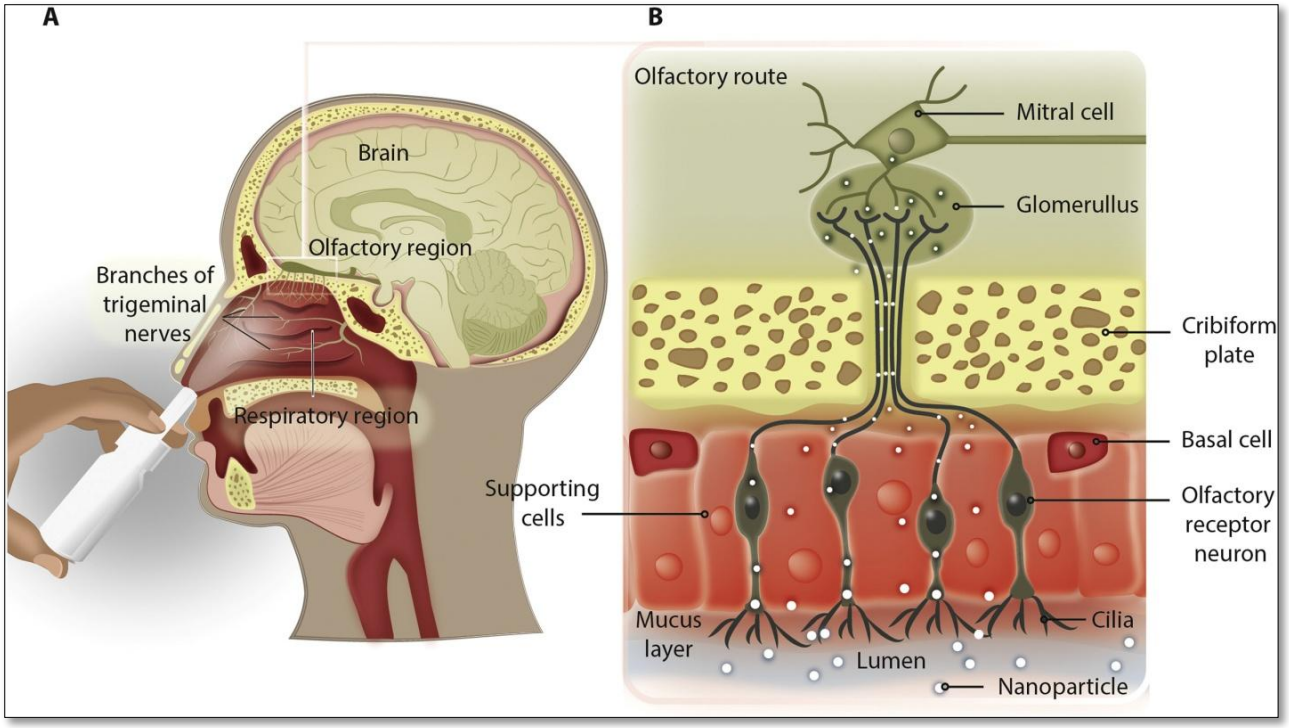


Fig.3: Anatomical features of the intranasal route (A), including key structures involved in nose-to-brain drug delivery (B). (Source; Formica et al., 2022)

5. ADVANTAGES OVER CONVENTIONAL DRUG DELIVERY METHODS FOR MIGRAINE

Novel drug delivery systems offer substantial advantages over conventional methods for migraine treatment, addressing limitations related to drug bioavailability, targeted delivery, and patient compliance. Traditional oral medications often suffer from erratic absorption rates in the gastrointestinal tract, leading to inconsistent therapeutic effects and the need for higher doses to achieve the desired outcome (Langer, 1990). Nanocarrier systems, which can encapsulate or complex with drug molecules, protect the drug from degradation in the gastrointestinal environment and facilitate controlled release, ensuring a sustained and consistent therapeutic level (Ding & Li, 2017). This is especially important when it comes to managing migraines, since keeping a steady medication concentration helps lessen the frequency of attacks and avoid breakthrough headaches. Additionally, systemic exposure is minimized and the likelihood of negative side effects is decreased by the capacity to precisely target medication delivery to the trigeminal nerve or other pertinent brain regions involved in migraine pathogenesis(Hargreaves, 2007). Nanotechnology-based drug delivery systems, such as nanoparticles, nanocapsules (Patra et al., 2018), and micelles, offer several advantages over conventional delivery systems (Anselmo and Mitragotri, 2016), including improved drug solubility, reduced tissue damage, and enhanced selectivity for target tissues (Ülker & Erkey, 2014). These systems can be designed to improve the therapeutic efficacy of migraine treatments by overcoming the blood-brain barrier, which is a significant obstacle in the delivery of pharmaceuticals to the central nervous system(Domínguez et al., 2014). Intranasal delivery represents another promising avenue, enabling rapid drug absorption and direct access to the brain via the olfactory(İmani et al., 2024) or trigeminal pathways(Mistry et al., 2009). Nanoparticles, administered via the nose, can enhance drug delivery to the brain (Formica et al., 2022) compared to traditional solutions, potentially because they protect preventing the medication from deteriorating or leaking into the nasal cavity (Mistry et al., 2009). This approach bypasses the first-pass metabolism in the liver, which can significantly reduce (Choonara et al., 2014) the bioavailability of orally administered drugs (Lin et al., 2017), offering a faster onset of action and improved therapeutic outcomes for acute migraine attacks (Mittal et al., 2013; Vyas et al., 2005). Additionally, the use of nanodrugs enables improved pharmacokinetic behavior, speedier creation of new medications with a broad safety margin, increased safety and biocompatibility, and targeted drug administration (Onoue et al., 2014). In order to enhance drug accumulation at the site of action and restrict drug release in healthy tissues, nanocarriers can alter drug pharmacokinetics and biodistribution (Jang & Gho, 2014; Rosa et al., 2011). Additional uses of nanotechnology include the creation of transdermal patches with innovative drug formulations that offer co-administering capabilities and a non-invasive, prolonged drug release that is beneficial for the prevention of migraines.

6. ZOLMITRIPTAN: A POTENTIAL DRUG FOR MIGRAINE MANAGEMENT

Zolmitriptan, a member of the triptan class of medications, which are selective serotonin receptor agonists, is a noteworthy development in the immediate treatment of migraine headaches(Zobdeh et al., 2021). Migraine, a complex neurological disorder, involves intricate mechanisms within the central nervous system, encompassing dysfunction, trigeminovascular activation, and altered pain perception, thereby requiring targeted pharmacological interventions (Hargreaves, 2007). Triptans, including zolmitriptan, have become a cornerstone in migraine management due to their ability to directly address these underlying mechanisms, offering relief from the debilitating symptoms associated with migraine attacks (Marupuru et al., 2023). The efficacy of zolmitriptan and other triptans underscores a shift towards viewing migraine as primarily a neural phenomenon, emphasizing the role of neuronal pathways and neurotransmitter systems in the pathophysiology of this condition (Goadsby et al., 2017). While non-steroidal anti-inflammatory drugs and acetaminophen remain relevant for mild to moderate migraine attacks (Akopian et al., 2000), triptans are often preferred for moderate to severe episodes ((Baratloo et al., 2017) or when NSAIDs are ineffective (Marupuru et al., 2023). The development and subsequent clinical application of zolmitriptan have significantly improved the quality of life for numerous migraine sufferers, allowing them to regain functionality during acute attacks, and emphasizing the need of ongoing study and advancement in migraine treatments(Lonzar et al., 2023).

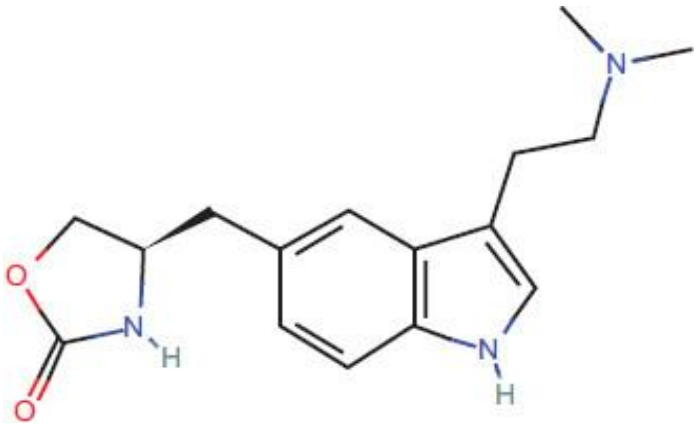


Fig. 4: Chemical structure of zolmitriptan (Source; Rapoport et al., 2007)

6.1 Mechanism of Action

The therapeutic efficacy of zolmitriptan is primarily attributed to its potent agonistic activity at serotonin 5-HT1B and 5-HT1D receptors (Dowson et al., 2002). These receptors are strategically located in various key areas implicated in migraine pathophysiology, including the intracranial blood vessels (Iyengar et al., 2019) and the trigeminal nerve endings (Leone et al., 2017). Activation of 5-HT1B receptors on intracranial blood vessels induces vasoconstriction, effectively counteracting the vasodilation that is believed to contribute to migraine pain (Song et al., 2024). Simultaneously, zolmitriptan acts on 5-HT1D receptors present on the trigeminal nerve endings, inhibiting the release of pro-inflammatory neuropeptides (McKeage, 2016) such as substance P (Abram et al., 2023) and calcitonin gene-related peptide (Song et al., 2024). CGRP, in particular, theatres a vitalpart in the neuroinflammatory response associated with migraine, and its inhibition helps to reduce the sensitization of the trigeminal nervous system.

Furthermore, zolmitriptan's mechanism extends beyond vasoconstriction and neuropeptide inhibition, influencing the transmission of pain signals (Hoffmann et al., 2019) within the trigeminal nucleus caudalis in the brainstem (May et al., 1999). By modulating the activity of this central pain processing area, zolmitriptan can diminish the perception of migraine pain (Dowson and Charlesworth, 2022) and associated symptoms such as nausea (Loder et al., 2005), photophobia (Charlesworth et al., 2003), and phonophobia (McKeage, 2016). The drug's multifaceted action on both peripheral (Pleș et al., 2023) and central components (Stovner et al., 2007) of the migraine pathway underscores its effectiveness in providing comprehensive relief. The ability of zolmitriptan to target multiple sites within the migraine pathway highlights the complexity of this neurological condition and the importance of multi-targeted therapeutic approaches.

The exploration of central sensitization in migraine, marked by heightened neuronal excitability, reveals that drugs capable of interrupting this process, such as dihydroergotamine, may be crucial in migraine treatment (Dodick & Silberstein, 2006). While the precise mechanisms underlying central sensitization remain a subject of ongoing research, interventions like neuromodulation, which seek to reverse maladaptive brain plasticity, are being investigated as potential prophylactic treatments for chronic migraine (Viganò et al., 2019). Recent studies have identified genetic mutations and polymorphisms strongly correlated with migraine, alongside altered levels of specific molecules, Emphasizing the importance of tailoring medical treatments to individual patient needs.

The intricate interplay of neuronal systems in migraine, as revealed by advanced imaging techniques, highlights the importance of understanding brain network disorders in the development of effective therapies.

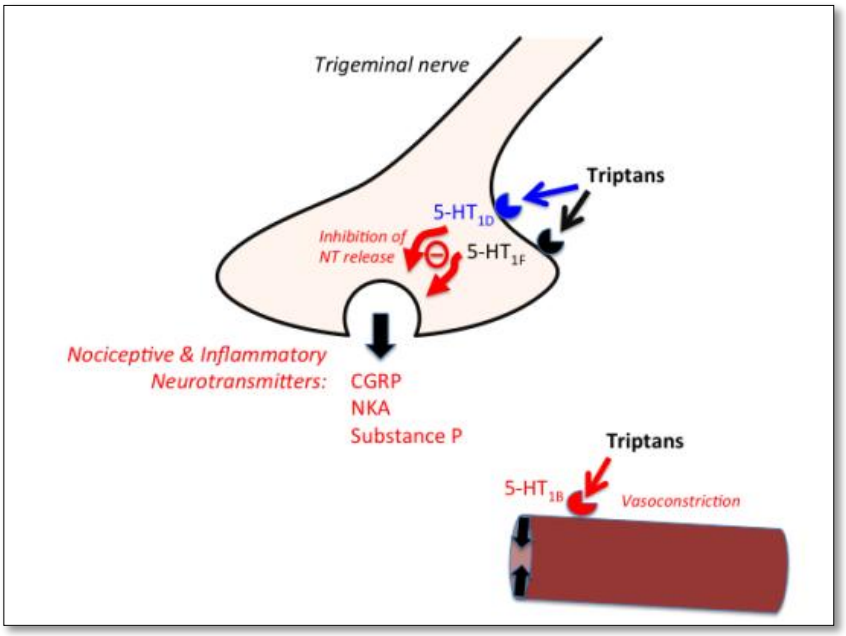


Fig. 5: Antimigraine Mechanism of Action (Source; Goadsby et al., 2017)

6.2 Pharmacokinetics

Zolmitriptan exhibits favourable pharmacokinetic properties that contribute to its clinical utility in acute migraine management. Following oral administration, zolmitriptan is speedily absorbed from the gastrointestinal tract (Dixon, 1997), achieving peak plasma concentrations within approximately 1 to 2 hours (Seaber et al., 1998). This rapid absorption is essential for providing timely relief during a migraine attack, allowing patients to quickly regain functionality and alleviate debilitating symptoms. Zolmitriptan is subject to first-pass metabolism in the liver (Naoto et al., 2005), primarily through the cytochrome P450 enzyme system (Wild et al., 1999), specifically CYP1A2, which results in the formation of an active metabolite, N-desmethylzolmitriptan. This metabolite possesses similar potency to the parent compound at 5-HT1B/1D receptors, contributing to the overall therapeutic effect.

The bioavailability of zolmitriptan is approximately 40-50%, which is influenced by the extent of first-pass metabolism (Kalanuria & Lee, 2009). Zolmitriptan is widely distributed throughout the body (Dowson et al., 2005), with a volume of distribution of around 7 L/kg (Dodick et al., 2005), indicating good tissue penetration. About 25% of the medication is bound to plasma proteins, meaning that a sizable portion is free for receptor engagement and therapeutic activity.

The elimination half-life of zolmitriptan is approximately 2.5 to 3 hours (Seaber et al., 1997), which is relatively short compared to some other triptans. Zolmitriptan and its metabolites are primarily excreted in the urine (Seaber et al., 1996), with a smaller proportion eliminated in the faeces. Because the medication is metabolized in the liver, dosage modifications (Dafonteet al., 2023) may be necessary in individuals with hepatic impairment (Bateman et al., 1980).

7. CHALLENGES IN ORAL ADMINISTRATION

Despite its therapeutic benefits, oral administration of zolmitriptan faces several challenges that can impact its efficacy and patient compliance. One major challenge is the variability in absorption due to factors such as gastric emptying rate, food intake, and individual differences in gastrointestinal physiology. Because zolmitriptan is metabolized by the cytochrome P450 enzyme system, potential drug interactions with other medications that inhibit or induce these enzymes can alter its plasma concentrations and therapeutic effects (Cubała et al., 2007). Nausea and vomiting, common symptoms of migraine, can further complicate oral administration by reducing drug absorption and leading to inconsistent clinical responses.

To mitigate these challenges, alternative formulations such as nasal sprays, sublingual tablets, and transdermal patches have been developed to bypass the gastrointestinal tract and liver metabolism. These alternative routes of administration offer the potential for faster absorption, reduced variability, and improved bioavailability, particularly in patients experiencing nausea or vomiting. Since intranasal delivery has been shown to be effective for brain targeting (Kumar et al., 2008), this approach may improve drug delivery to the central nervous system and hence improve therapeutic results (Abdelbary & Tadros, 2013).

Additionally, studies on new drug delivery methods, such as nanoemulsions and microparticles, seek to improve the solubility, stability, and targeted transport of zolmitriptan to the brain(Kumar et al., 2008). Personalized medicine approaches, considering genetic factors, comorbidities, and concomitant medications, can optimize zolmitriptan dosing and administration strategies for individual patients.

8. MUCOADHESIVE NANOPARTICULATE BIOGEL: A SMART DRUG DELIVERY SYSTEM FOR MIGRAINE

Mucoadhesive nanoparticulate biogels represent an innovative approach to migraine treatment by combining the advantages of mucoadhesion and nanoparticle drug delivery within a biocompatible hydrogel matrix (Asthana, 2017; Ways et al., 2018). These systems provide localized and extended drug release by adhering to mucosal surfaces like the nasal or buccal mucosa, which is especially advantageous for the treatment of migraines(Sosnik & Seremeta, 2017). Nanogels, a specific type of hydrogel, have garnered significant attention as drug delivery carriers due to their exceptional attributes (Soni et al., 2016), including high drug loading capacity (Vinogradov, 2006), remarkable stability (Galmarini et al., 2006), and responsiveness to environmental stimuli like ionic strength (Moscovici et al., 2017), pH (Kim et al., 2009), and temperature (Oberoi et al., 2012), setting them apart from conventional pharmaceutical nanocarriers (Kabanov & Vinogradov, 2009). The mixing of nanoparticles in the biogel structure lets for enhanced drug encapsulation (Fang et al., 2011), protection against enzymatic degradation (Sahay et al., 2010), and controlled release kinetics, optimising therapeutic efficacy while minimising systemic side effects (Gao et al., 2016). The use of nanoparticulate carriers has been proposed as a viable strategy to overcome biological barriers (Henrich-Noack et al., 2019). Nanotherapeutics, which involve utilising nanocarriers to transport medications across the blood-brain barrier, are gaining traction due to their capacity to facilitate effective medication delivery methods (Tiwari et al., 2019).

One of the key benefits of using mucoadhesive nanoparticulate biogels is their potential to support direct drug delivery from the nasal cavity to the brain, which holds significant promise for treating conditions like migraines (Mistry et al., 2009). Administering drugs intranasally allows them to circumvent the blood-brain barrier—a major hurdle in the treatment of neurological diseases (İmani et al., 2024). This route enables a greater concentration of the drug to reach the brain, potentially increasing therapeutic effectiveness while minimizing systemic exposure and related side effects (Mistry et al., 2009).

The anatomical structure at the base of the skull, particularly the roof of the nasal cavity, is located near the central nervous system and is lined with olfactory mucosa, making it a strategic site for targeting nose-to-brain delivery (Gänger & Schindowski, 2018). The olfactory neuroepithelium is especially noteworthy as it represents the only region of the CNS that lacks the protective blood-brain barrier, thereby allowing direct interaction with externally administered substances (Sonvico et al., 2018).

To develop effective formulations for this delivery route, it is essential to understand the mucosal architecture and its physical and chemical properties. Biogels often incorporate mucoadhesive agents like chitosan, carbomers, and hyaluronic acid to enhance adherence to the nasal mucosa, thereby prolonging the contact time and improving drug uptake. Furthermore, nanoparticles composed of biocompatible materials such as PLGA, PEG, and chitosan show great potential for delivering mRNA. These systems improve mRNA stability, enhance cellular internalization, and enable efficient release into the cytoplasm, which supports translation into proteins capable of triggering strong immune responses (İmani et al., 2024).

The "smart" aspect of these drug delivery systems stems from their responsiveness to specific stimuli, which can be tailored to trigger drug release at the desired location (Salehi et al., 2023) or in response to a particular physiological condition (Amina and Guo, 2020). For instance, pH-sensitive polymers can be incorporated into the biogel matrix to release the drug in response to changes in pH levels associated with inflammation or migraine onset (Bai et al., 2022). Temperature-sensitive polymers can also be used to create biogels that undergo a phase transition at body temperature (Boustta et al., 2014), forming a gel-like structure that adheres to the mucosa (Cao et al.,2019) and releases the drug in a controlled manner. To further improve medication delivery to the central nervous system, the nanoparticles' surface can be altered with targeting ligands, including peptides or antibodies, to increase their affinity for particular receptors on the brain endothelium.These nanoparticles provide controlled mRNA release and protect it from degradation. The incorporation of tailored adjuvants into mRNA vaccines significantly enhances defence by maximising immunostimulation, delivery, and immunity (İmani et al., 2024).

Designing mucoadhesive nanoparticulate biogels for effective migraine therapy involves multiple critical considerations, such as selecting appropriate mucoadhesive polymers, determining the ideal nanoparticle composition, optimizing drug encapsulation and release profiles, and incorporating specific targeting ligands. Ensuring the safety and compatibility of the materials used in the formulation is especially important, given that such systems are often intended for repeated use. Recent advancements in the development of novel amino lipids have aimed to improve the effectiveness and tolerability of lipid-based nanoparticles, with particular focus on the role of the amino lipid component (Paloncýová et al., 2021).

To validate the clinical potential of these biogels, extensive preclinical and clinical evaluations must be conducted using migraine-specific models and patient trials. As innovative delivery platforms, mucoadhesive nanoparticulate biogels represent a promising strategy for migraine treatment by potentially increasing therapeutic efficacy while minimizing

unwanted systemic effects (Hoare et al., 2011). In recent years, progress in nanotechnology and materials science has significantly advanced the development of brain-targeted delivery systems (Wu et al., 2023). Additionally, polymeric micelles have been shown to enhance drug solubility and bioavailability (Abdelbary & Tadros, 2013). In situ gel-forming systems have also gained attention as a favorable delivery method due to their ability to increase mucosal retention, improve patient compliance, and simplify administration.

9. THERMOSENSITIVE BIOGEL: AN INNOVATIVE DRUG CARRIER FOR MIGRAINE TREATMENT

Thermosensitive biogels represent a promising avenue for innovative drug delivery systems, particularly in the context of migraine treatment, where besieged and controlled release is paramount (Song et al., 2021). Migraine, a debilitating neurological disorder, necessitates therapeutic strategies that can effectively manage pain and associated symptoms while minimizing systemic side effects (Ferroni et al., 2018). Traditional pharmacological treatments for migraine often exhibit limited efficacy and are accompanied by undesirable side effects, underscoring the need for novel drug delivery approaches (Viganò et al., 2019). In targeted drug delivery research, biomimetic hydrogels have attracted a lot of interest due to their potential for better drug loading, increased cellular uptake, and sustained drug release within target cells(Sheikhpour et al., 2017).

Hydrogels possess a unique structural framework that enables them to encapsulate therapeutic agents, offering protection and allowing for prolonged or even externally controlled release. This capability has sparked considerable interest in using hydrogels for the administration of both small-molecule drugs and biopharmaceuticals (Dreiss, 2020). Among the various types, thermosensitive biogels have gained attention due to their ability to undergo sol-to-gel transitions in response to temperature fluctuations, enabling targeted drug release precisely at migraine-affected regions (Hoare et al., 2011). These smart materials combine the robustness of cross-linked networks with adaptable features like self-healing and adhesive capabilities, which can be fine-tuned through functionalized side chains to react to specific environmental stimuli (Knipe & Peppas, 2014).

The exceptional fluid absorption capacity of hydrogels stems from their hydrophilic functional groups—such as amino, hydroxyl, carboxyl, and sulfonate—embedded within their polymer matrix. These groups allow noncovalent bonding with various biological tissues, enhancing integration and compatibility (Coşman et al., 2022). Hydrogels can also be engineered to mimic the mechanical and chemical characteristics of biological tissues, making them suitable platforms in tissue engineering applications (Boz et al., 2022).

Injectable hydrogels represent a significant advancement in this field, offering site-specific drug delivery through minimally invasive techniques (Kulkarni et al., 2023). Their porous architecture, which can be adjusted by modifying cross-link density and water affinity, plays a key role in regulating drug diffusion and release kinetics (Hoare & Kohane, 2008). Due to their high water content and structural similarity to the extracellular matrix, these materials show excellent compatibility with biological systems (Hoare & Kohane, 2008).

In migraine therapy, thermosensitive hydrogels can be precisely applied to administer medications to pain-associated sites such as the trigeminal nerve. Their cross-linked design also shields drugs from enzymatic degradation or adverse environments (Coşman et al., 2022). The combination of features such as biocompatibility, water absorption, and resistance to thermal and mechanical stress makes them ideal for drug delivery and biomimetic functions (Almawash et al., 2022; Kim & Park, 2003). By leveraging their temperature-responsive behavior, these biogels can enable controlled release of analgesics in response to local temperature spikes during migraine attacks, potentially minimizing reliance on systemic drugs. Furthermore, their biodegradability and safe interaction with human tissues reinforce their suitability for use in a wide range of biomedical and pharmaceutical applications (Buwalda et al., 2016; Martínez-Serrano et al., 2023).

10. CLINICAL PERSPECTIVES AND FUTURE PROSPECTS

10.1 Potential Clinical Applications

The nose-to-brain (N2B) delivery pathway has gained attention as an effective, non-invasive alternative to conventional methods of targeting the central nervous system (CNS) (Gänger & Schindowski, 2018). This method takes advantage of the nasal cavity's distinct anatomical and physiological features, allowing drugs to bypass the blood-brain barrier (BBB)—a major hurdle in CNS drug delivery due to its selective permeability (Misra & Kher, 2012). By utilizing olfactory and trigeminal nerve routes, N2B delivery facilitates direct drug transport to the brain, presenting a transformative opportunity for managing various neurological disorders (Mistry et al., 2009). Though modern research has refined the approach over the past two decades, its foundational concepts can be traced back to ancient practices (Vyas et al., 2005).

One of the major advantages of this technique is its ability to avoid the restrictive nature of the BBB, which often impedes the therapeutic efficacy of systemically administered drugs aimed at treating CNS disorders (Domínguez et al., 2014). Conditions such as schizophrenia, Alzheimer's disease, Parkinson's disease, meningitis, and migraines require medications to reach specific areas of the brain for effective intervention (Mistry et al., 2009). The N2B approach is particularly well-suited for such applications, as it can deliver active compounds directly to the brain, thereby overcoming one of the greatest

limitations in neuropharmacology (Mittal et al., 2013).

In addition to targeting efficiency, this method reduces the risk of infection and complications commonly associated with invasive delivery methods. Since it bypasses hepatic first-pass metabolism, it can enhance drug bioavailability, allowing for the use of lower drug doses and potentially reducing adverse effects. Intranasal administration, a long-standing method for delivering poorly absorbed drugs, facilitates both systemic and CNS access via nasal mucosa absorption (Woensel et al., 2013). Moreover, emerging evidence suggests that even xenobiotics and a wide variety of therapeutic agents can access the brain through this route (Veronesi et al., 2017).

Direct brain targeting through the nasal cavity continues to gain traction, particularly with advancements in nano-drug delivery systems. Preclinical studies have shown that nanoparticle-based carriers, such as liposomes, dendrimers, micelles, and carbon nanotubes, enhance CNS drug delivery when compared to conventional solution-based formulations (Mistry et al., 2009; Teleanu et al., 2018). These nanosystems can be tailored for controlled release, improved bio-distribution, and targeted delivery, presenting a significant advancement in CNS therapy.

Additionally, this route offers the potential to localize drug delivery to specific brain regions, improving treatment outcomes and reducing systemic side effects. This is particularly valuable in neurodegenerative diseases like Parkinson's, where degeneration of dopamine-producing neurons in the substantia nigra leads to motor dysfunction. Delivering dopamine agonists or neuroprotective drugs directly to these regions could offer symptom relief and potentially slow disease progression (Rosa et al., 2011).

10.2 Challenges and Regulatory Considerations

Although nose-to-brain (N2B) drug delivery presents significant therapeutic potential, several technical and regulatory hurdles must be overcome before it can be fully integrated into clinical practice. One of the primary obstacles lies in the nasal cavity's complex anatomy and physiology, which can influence the extent and consistency of drug absorption. The nasal cavity offers a limited surface area for absorption, and factors such as mucus secretion and mucociliary clearance can impede drug transport and reduce retention time. The intricate nasal architecture requires a deep understanding of its biological and physical characteristics to develop effective drug formulations. Moreover, the presence of metabolizing enzymes within the nasal mucosa can degrade drug molecules before they reach the brain, diminishing their bioavailability (Minn et al., 2002).

To address these limitations, researchers are working on advanced drug delivery systems designed to improve drug uptake, enhance residence time in the nasal cavity, and shield active compounds from enzymatic degradation. Strategies under investigation include the use of nanoparticles, mucoadhesive carriers, liposomes, and hydrogels (Sonvico et al., 2018).

Another significant concern is the variability in nasal physiology between individuals. Differences in age, gender, underlying health conditions, and nasal pathologies can influence nasal patency, mucus viscosity, and the efficiency of mucociliary clearance. These variations can lead to inconsistent drug absorption and therapeutic response, emphasizing the need for patient-specific approaches in N2B drug delivery design.

From a regulatory standpoint, the lack of dedicated guidelines specific to nose-to-brain drug delivery adds another layer of complexity. Regulatory bodies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have not yet released detailed frameworks for assessing the safety and efficacy of these specialized systems. The absence of such protocols can hinder the pace of innovation and contribute to uncertainty in the approval process.

To facilitate clinical translation, it is essential to perform rigorous preclinical and clinical investigations that evaluate key parameters such as pharmacokinetics, biodistribution, safety, immunogenicity, and potential nasal toxicity. These studies must also examine drug transport efficiency to the brain and assess any off-target effects in peripheral tissues. Standardized evaluation tools and performance metrics should be established to measure the effectiveness of nasal delivery systems.

Notably, nanoformulations have demonstrated improved efficiency in transporting drugs to the brain in animal models compared to traditional drug solutions (Dhuria et al., 2009; Şekerdağ, 2017). The development of these systems, combined with collaborative efforts among academia, industry stakeholders, and regulatory agencies, is vital for creating a clear regulatory framework. Such cooperation will support the safe advancement and approval of innovative N2B drug delivery technologies.

10.3 Future Trends in Nose-to-Brain Drug Delivery

The landscape of nose-to-brain (N2B) drug delivery is advancing rapidly, with several emerging trends poised to shape its future application and development. A notable direction is the growing reliance on nanotechnology to engineer innovative delivery platforms aimed at improving brain-targeted therapy (Furtado et al., 2018). Nano-carriers such as liposomes and polymeric nanoparticles are increasingly being developed to encapsulate drugs, safeguard them from enzymatic breakdown, and direct them efficiently to designated brain regions (Brown et al., 2020). Additionally, microfluidic technologies are being explored to enhance the design and performance of these nano-systems, improving pharmacokinetic parameters like efficacy and bioavailability (Ahn et al., 2018; Hussain, 1998). Surface functionalization of nanoparticles with ligands targeting specific receptors on neuronal cells further refines their brain specificity, promoting precise drug localization (Lockman et

al., 2002).

Another critical trend is the integration of personalized medicine into N2B delivery strategies. Tailoring treatment plans based on individual variability—such as age, gender, health status, and genetic predisposition—offers the potential to improve therapeutic efficacy while reducing adverse effects. For instance, patients experiencing reduced nasal airflow or increased mucous secretion may require modified formulations, delivery devices, or dosing strategies, such as nasal sprays or dry powders, to achieve optimal outcomes. This personalization is particularly crucial in the context of intranasal cellular therapies, where replicability and delivery efficiency are often inconsistent.

Furthermore, the application of non-invasive imaging techniques, including magnetic resonance imaging (MRI) and positron emission tomography (PET), is gaining traction for assessing drug biodistribution and therapeutic action within the brain (Jiang et al., 2011). These imaging modalities offer critical insights into drug penetration, localization, and functional outcomes, enabling the real-time optimization of dosing strategies and identification of responsive patient subgroups. This data-driven approach can significantly accelerate the development of effective N2B treatments.

The use of artificial intelligence (AI) and machine learning (ML) tools is also transforming the design and refinement of nose-to-brain delivery systems. These technologies allow researchers to process complex datasets from both preclinical and clinical studies, revealing patterns that can inform formulation design, predict pharmacological behavior, and personalize treatment regimens (Onoue et al., 2014). Moreover, advanced computational modelling is now being used to simulate nasal drug transport and interaction with the blood-brain barrier. These simulations help researchers fine-tune formulation parameters, predict outcomes, and ultimately reduce the time and cost associated with product development.

Together, these trends highlight a future where nose-to-brain drug delivery becomes more precise, efficient, and patient-specific, offering new avenues for treating challenging neurological conditions.

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