IJPSR (2025), Volume 16, Issue 10 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 March 2025; received in revised form, 23 April 2025; accepted, 26 April 2025; published 01 October 2025

INNOVATIONS IN NASAL FORMULATIONS: ADVANCES IN TREMOR TREATMENT

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Keywords:

Tremors, Parkinsonian tremor, Nasal drug delivery, Sustained release, Transfersomes

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ABSTRACT: Tremors are a neurodegenerative disorder (ND) characterized by the involuntary movement of body parts such as the soft palate, hands, jaw, tongue, and head. As of February 2020, the Online Mendelian Inheritance in Man (OMIM) database contained over 594 genetic conditions. Tremors can originate due to improper functioning of certain areas of the brain or due to genetic inheritance and is prominently observed in people above 60 years of age and mostly in males. It is present as symptoms in many neurodegenerative disorders like stroke, Parkinson's, and multiple sclerosis. Many dosage forms have been developed for the treatment of tremors, which include tablets, transdermal patches, sustained release, injectables, and sublingual. The intranasal route of drug delivery is an emerging type of novel delivery system and can be a useful tool for treatment. By following pathways like the trigeminal and olfactory nerve pathways, prominent drug bioavailability in the brain, rapid absorption of drugs, and reduced side effects are achieved. In this review, we have discussed the classification of tremors, the drugs used by nasal delivery, the barriers in nasal delivery, advanced formulations, and ongoing research in nasal delivery.

INTRODUCTION: Tremor is one of clinical practice's most frequently observed involuntary movement disorders. A tremor is a rhythmical, involuntary oscillatory movement of body parts, mainly produced by alternating the contractions of reciprocally inverted muscles [1]. The tremor was described in the Movement Disorder Society in 1998, and this was further revised in 2018 [2]. Tremors are a common feature in many genetic disorders. A search in the Online Mendelian Inheritance in Man (OMIM) database in February 2020 found 594 genetic conditions or genes linked to tremors [3]. As the most common type of movement disorder, tremors can have multiple origins, including essential, Parkinsonism, dystonic, neuropathic, and functional causes [1].

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DOI: 10.13040/IJPSR.0975-8232.16(10).2707-19

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.16(10).2707-19

In some neurological conditions, tremors are not restricted to limbs but may involve body parts like the head, jaw, tongue, and soft palate [4]. While tremor is most frequently seen in middle-aged and older adults, it can develop at any age. The condition affects both men and women equally [5]. When evaluating a patient with a tremor, it is crucial to consider the characteristics of the tremor itself [4]. The consistency of tremor rhythms varies, and there is no universally agreed-upon minimum level of rhythmicity for a tremor. Successful treatment usually reduces rhythmicity, while worsening tremors tend to become more rhythmic due to stronger involvement of motor pathways [2].

There are many treatment options for tremors, and the treatment choice largely depends on the underlying causes. Treatment depends on the individual's severity, the degree of durability, or the impairment experienced by the patient[4]. Tremors can have various causes and underlying mechanisms. Major causes include neurodegenerative diseases, strokes, head injuries,

certain medications and toxins, demyelinating disorders, systemic illnesses, and metabolic conditions. When evaluating a patient with tremors, key factors to consider are the type and characteristics of the tremor, the presence of other neurological symptoms, and how medications or alcohol affect the tremor. A thorough medical history and detailed neurological examination are usually essential in identifying the cause [5].

Neurodegenerative disorders (NDs) are conditions that primarily affect the nervous system, leading to progressive nerve cell damage. This deterioration causes cognitive decline (such as dementia) or movement disorders (like tremors). Since nerve cells control bodily functions, their damage is a key feature of NDs. Most of these diseases are severe and have no cure, though treatments can help manage symptoms and improve quality of life. Diseases like Parkinson's, Huntington's, Tremors, and Alzheimer's are the most common in aging populations, driving increased research interest in their causes and treatment. Delivering drugs effectively to the brain and central nervous system (CNS) is challenging due to the brain's protective structure. The effectiveness of a therapeutic agent depends not only on its bioavailability but also on its ability to cross key barriers like the blood-brain barrier (BBB) and cerebrospinal fluid (CSF), which are significant obstacles in treating nervous system conditions.

Intranasal drug delivery is an effective method due to its simple and efficient transport of pharmaceutical formulations [6]. Nasal drug delivery has gained considerable attention in recent years as a convenient and effective method for administering drugs, both locally and systemically. The nasal route can be used for both local and systemic drug delivery. For local action, it is commonly used for nasal conditions like congestion, rhinitis, sinusitis, and allergies. Various drugs, including corticosteroids, antihistamines, anticholinergics, and vasoconstrictors, can be administered directly to the nasal cavity. Recently, there has been growing interest in using the nasal route for systemic drug delivery. Nasal drug delivery methods such as nasal sprays, drops, gels, and powders are commonly used to treat various conditions and are intended for both local and systemic effects. Meanwhile, newer delivery systems like liposomes, nanoparticles, microspheres, microemulsions, and intranasal vaccines are still under research and development, with efforts underway to bring them to market. These advanced systems are gaining attention due to their potential to deliver drugs directly to the brain and overcome the limitations of conventional methods. For example, nasal drops can lack accurate dosing, pose a risk of contamination, and may lead to leakage or swallowing of the medication. In contrast, micro- and nanoparticle-based systems offer advantages like prolonged residence time in the nasal cavity, making them more effective for targeted delivery [7].

Intranasal drug delivery bypasses the blood-brain barrier (BBB) and provides a non-invasive route for delivering therapeutic agents directly to the central nervous system (CNS). This method has since gained significant attention for its potential in treating neurological disorders such as Alzheimer's disease, Parkinson's disease, and brain tumors. By leveraging the olfactory and trigeminal nerve pathways, intranasal administration ensures rapid drug absorption, reducing systemic side effects and enhancing drug bioavailability in the brain. Researchers establish specific parameters for pharmaceutical products to maximize their potency and effectiveness.

A key requirement is that the drug must be well-tolerated, avoiding any nasal irritation or discomfort. Additionally, it should not generate toxic metabolites that could compromise patient safety. The drug must be odorless and possess long-term stability to ensure efficacy. It should have sufficient solubility, with a minimum of 100 mg/mL, to facilitate proper formulation. Additionally, it should exhibit efficient nasal absorption and remain effective at a low dosage, ideally below 25 mg per dose. There are various methods for the treatment of tremors. In the present article, we have used one of the most convenient methods for treating tremors, the nasal route [6].

Tremor and its Classification: A tremor is an involuntary, rhythmic, and oscillatory movement that can involve one or multiple body parts, frequently affecting the hands, head, arms, or legs [8]. These movements are typically the result of abnormal muscle contractions stemming from the

nervous system's inability to adequately regulate motor functions. Although tremors are generally not life-threatening, they may pose significant challenges and can lead to disabilities, thereby complicating everyday activities such as writing, typing, eating, and dressing. The primary causes of tremors are often associated with dysfunctions in the areas of the brain responsible for movement control. Most types of tremors do not have a known genetic origin; however, certain forms may display hereditary patterns within families. Tremors may present as an isolated phenomenon or as symptoms of various neurological disorders, including Parkinson's disease, multiple sclerosis, and strokes. Moreover, tremors can also arise from a range of medical conditions, including but not limited to:

- Pharmacological agents
- Exposure to heavy metals and other neurotoxins
- Caffeine consumption
- Thyroid disorders
- Liver or kidney dysfunction
- Diabetes
- Psychological factors such as stress, anxiety, or fatigue [9].

Pathophysiology: The pathophysiology of tremors is intricate and varies significantly based on the underlying medical condition. Tremors frequently stem from disruptions in the brain's motor control systems, particularly in critical areas such as the basal ganglia, cerebellum, and brainstem. These disruptions may be attributed to various factors, including abnormal oscillatory neural activity, neurotransmitter imbalances, and genetic predispositions. Each of these factors can contribute to the onset and exacerbation of tremors, leading to varying clinical presentations.

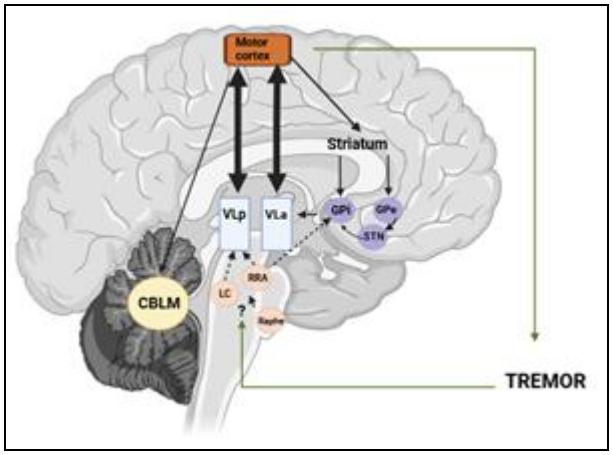

FIG. 1: THE PATHOPHYSIOLOGY OF TREMOR: MC = motor cortex, GPe = globus pallidus externa, GPi = globus pallidus interna, STN = subthalamic nucleus, VLa = anterior ventrolateral nucleus of the thalamus, CBLM = cerebellum, LC = locus coeruleus, RRA = retrobulbar area

The **Fig. 1** depicts the hypothetical cerebral circuit responsible for the initiation and propagation of rest tremors. According to the dimmer-switch hypothesis, the basal ganglia (highlighted in blue) play a pivotal role in the initiation of tremor episodes, while the cerebellar-thalamo-cortical circuit (illustrated in red) is involved in modulating the amplitude of the tremor. These two circuits interact and converge at the motor cortex, allowing for coordinated motor control. Numerous neurotransmitter systems are implicated in this pathway. For instance, the dopaminergic retrobulbar area has a significant influence on the cerebral tremor circuit via its connections with the basal ganglia and the ventrolateral nucleus (VLp). Additionally, the serotonergic raphe nuclei are also involved, although the specific targeting of this region within the cerebral tremor circuit remains to be fully elucidated. Furthermore, afferent activity originating from the muscles that are actively trembling may converge with cerebral networks, potentially at the level of the cerebellum and/or thalamus. This interaction is an area of ongoing research, as further investigations are needed to clarify the mechanisms underlying these connections.

The yellow bolts depicted in the figure indicate potential targets for deep brain stimulation (DBS) and neurosurgical lesioning, which are therapeutic approaches aimed at alleviating tremors. In contrast, the green bolts represent potential targets for non-invasive brain stimulation techniques, which may offer alternative treatment options [10].

Epidemiology: The prevalence of tremors is observed to increase with advancing age, particularly among individuals aged 60 years and older. Furthermore, epidemiological data consistently indicate that the incidence of tremors is higher in males than in females throughout the lifespan. In 2020, the global prevalence of tremors in the general population was reported at 0.32%, with variations ranging from 0.04% in individuals under the age of 20 to 2.87% in those aged 80 years and above. It is estimated that approximately 24.19 million individuals worldwide were affected by tremors in 2020 [11].

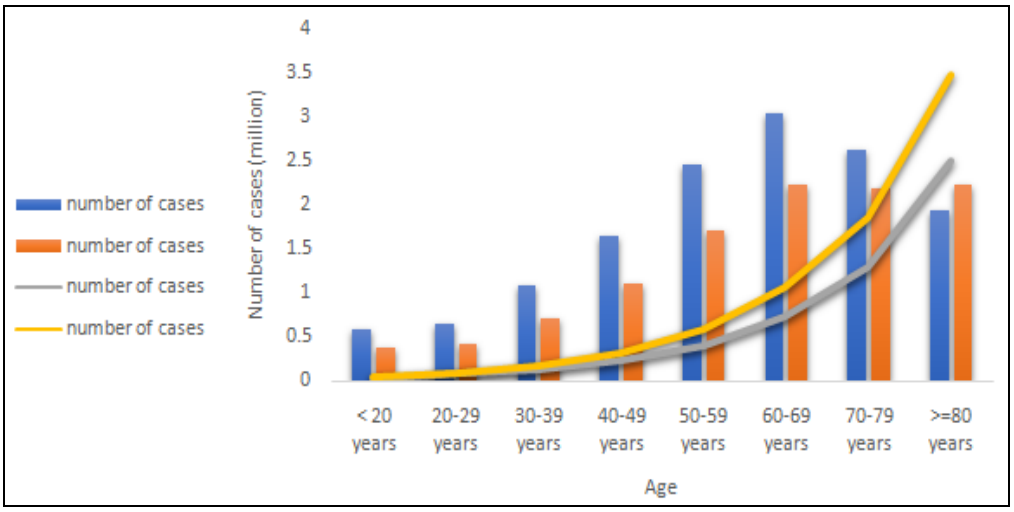

FIG. 2: TREMORS CASE PREVALENCE BASED ON AGE AND SEX

Symptoms may include:

- Trembling of the hands and arms
- A quivering voice
- Difficulty in writing and drawing
- Challenges in manipulating utensils, tools, and other objects
- A gradual onset of symptoms, which are typically more pronounced on one side of the body
- Worsening of tremors during movement
- Initial presentation in the hands, potentially affecting one hand or both hands
- Possible “yes-yes” or “no-no” nodding or shaking motions of the head
- Exacerbation of symptoms in response to emotional stress, fatigue, caffeine intake, or extreme temperature conditions [12].

The diagnosis of a tremor involves a comprehensive evaluation conducted by a physician, which includes a detailed physical examination and a thorough review of the individual's medical history. The physician will perform a neurological assessment, which encompasses an evaluation of muscle tone and strength, reflexes, balance, and speech.

Key factors to be evaluated include:

- The occurrence of the tremor at rest versus during activity.
- The specific location of the tremor within the body, noting whether it affects one side or both sides.
- The characteristics of the tremor, including its frequency and amplitude.

In addition, the physician may request blood or urine samples to eliminate potential underlying factors contributing to the tremor. Diagnostic imaging may be utilized to ascertain whether the

tremor is attributable to any brain damage. An electromyogram (EMG), which assesses involuntary muscle activity and muscle response to nerve stimulation, may also be employed to identify any muscle or nerve-related abnormalities [13].

Treatment Options for Tremor: Effective treatment for tremor encompasses a range of strategies, including medications, exercises, lifestyle modifications, and, in severe cases, surgical interventions such as deep brain stimulation.

The medications for Tremor include Beta-blockers are effective in reducing tremors. Anticonvulsants can help manage tremor symptoms. Benzodiazepines are useful for reducing anxiety-related tremors. Botulinum toxin (Botox) injections can provide significant relief from tremors [14].

The tremor Exercises include Hand and Wrist Exercises are Crucial for improving dexterity and control. Balance and Coordination Exercises are Essential for enhancing stability. And Occupational Therapy is Vital for developing practical skills and strategies. Diet for Essential Tremor includes Avoiding Caffeine is imperative to minimize tremor triggers. Limit Alcohol intake. Proper hydration is crucial for overall health. Maintaining balanced Nutrition and a well-rounded diet supports optimal functioning.

Tremors require Lifestyle Changes, which include Stress management techniques, essential to reduce stress as stress is one of the triggers for tremors, utilization of adaptive tools, maintaining and prioritizing sleep hygiene with quality sleep, and limitation of stimulants like minimizing nicotine intake.

Tremors have some surgical options in case of severe conditions, like deep brain stimulation, which is a highly effective option for tremors. A non-invasive treatment like focused ultrasound can provide significant relief. Another effective surgical procedure is Thalamotomy, which helps in the reduction of tremors. By taking this assertive approach to treatment, individuals can gain better control over their tremor symptoms and improve their quality of life [15].

Classification of Tremors: Tremors can be intricately classified into a variety of categories, taking into account several crucial factors, including their underlying cause, activation conditions, and oscillation frequency. Understanding these classifications is essential for accurately diagnosing and treating different types of tremors. The major classification systems include clinical, etiological, and phenomenological approaches.

Based on Activation Condition: Tremors can be primarily categorized into two main groups, depending on whether they manifest when the body is at rest or during voluntary movement.

Rest Tremor: This type of tremor occurs when the affected body part is completely at rest, such as a hand resting on a table. Notably, it often fades away with any voluntary movement, providing a stark contrast between stillness and activity. Rest tremors are most commonly associated with Parkinson's disease (PD), where they might present as rhythmic oscillations that can range between 4 to 6 Hertz. For example, a Parkinsonian tremor typically manifests in asymmetrical patterns, affecting one side of the body more than the other.

Action Tremor: Action tremors occur during voluntary muscle contractions and are further subdivided into several distinct types:

Postural Tremor: This tremor is evident when an individual strives to maintain a position against gravity, such as holding their arms outstretched. Essential tremor is a prevalent example, often affecting the hands and voice.

Kinetic Tremor: Engaged during purposeful motions, kinetic tremors can be further classified into simple kinetic tremors and intention tremors, such as those seen in cerebellar dysfunction. As individuals reach for an object, these tremors may become more pronounced, especially as they near their target.

Task-Specific Tremor: This unique tremor only manifests during specific activities, such as writing. Known as primary writing tremor, it emphasizes the idea that not all tremors are constant.

Isometric Tremor: This occurs when the muscles contract against a stationary object without producing movement. An example is the dystonic tremor, often seen when a person is attempting to push against an unyielding surface [16].

Based on Etiology: Tremors can also be classified according to their underlying causes, allowing healthcare providers to differentiate between various pathological conditions that may lead to tremor development.

Physiological Tremor: This natural, subtle tremor exists in all individuals, typically operating at an unnoticed level. However, it can be amplified by factors such as anxiety, fatigue, caffeine consumption, or hyperthyroidism. Generally, physiological tremors oscillate between 8 to 12 Hertz and exemplify the body's intricate response to stressors.

Essential Tremor (ET): As the most prevalent movement disorder, essential tremor mainly affects the hands, head, and voice, leading to involuntary movements that can range from mild to debilitating. A significant genetic component is often observed, indicating a hereditary predisposition. Frequencies for essential tremor usually fall between 4 to 12 Hertz.

Parkinsonian Tremor: Identified as a hallmark symptom of Parkinson's disease, this tremor frequently presents asymmetrically. It predominantly occurs at rest and may persist during movement, especially in the later stages of the disease. The characteristic oscillation frequency lies between 4 to 6 Hertz, often leading to challenges in daily activities due to its rhythmic fluctuations.

Cerebellar Tremor: Resulting from dysfunction in the cerebellum often due to conditions like stroke or multiple sclerosis cerebellar tremors are marked by intentional tremors that worsen as an individual approaches a target during movement. These tremors typically have a low frequency, often less than 5 Hertz, highlighting the coordination issues faced by affected individuals.

Dystonic Tremor: This unique tremor is associated with dystonia and manifests in the body parts affected by this condition. Dystonic tremors can vary widely in their presentation, often appearing irregular and fluctuating in intensity. Some individuals might find that specific sensory tricks can help alleviate these tremors, leading to an intriguing interplay between perception and motor function.

Psychogenic (Functional) Tremor: Psychogenic tremors are characterized by their inconsistent nature, often changing in intensity or pattern with distraction. Typically linked to psychological conditions such as conversion disorders, these tremors do not have any identifiable structural neurological cause, presenting a challenge for diagnosis and treatment.

Drug-Induced Tremor: Certain medications, including beta-adrenergic agonists, lithium, or valproate, can lead to the development of tremors as a side effect. These tremors usually resolve once the offending medication is discontinued, underscoring the importance of medication management in affected individuals.

Neuropathic Tremor: This type of tremor is seen in patients with peripheral neuropathy, often linked to conditions such as Charcot-Marie-Tooth disease. Neuropathic tremors result from nerve damage and can significantly impact coordination and motor control [17].

Based on Frequency: Tremors can also be differentiated according to their frequency of oscillation:

High-Frequency Tremor (>7 Hz): This category includes physiological tremors, enhanced physiological tremors, and various cases of essential tremors, which exhibit rapid rhythmic movements.

Medium-Frequency Tremor (4–7 Hz): Essential tremors and Parkinsonian tremors typically fall into this category, providing a moderate oscillatory experience that can disrupt everyday functions.

Low-Frequency Tremor (<4 Hz): This includes cerebellar tremors, dystonic tremors, and Holmes tremors, which are generally characterized by slower oscillations and a greater challenge for the individual to manage.

Understanding these classifications deepens insight into the complex world of tremors, helping guide appropriate interventions and improve the quality of life for those affected [4].

Nasal Drug Delivery: Traditional drug delivery methods like oral tablets and extended-release formulations often have a delayed onset of action. In contrast, nasal drug delivery via sprays or powders, such as levodopa or benzodiazepines, allows for rapid absorption through the nasal mucosa, resulting in a quicker therapeutic effect. Oral medications are also hindered by first-pass metabolism, which reduces bioavailability as the liver breaks down the drug before it can enter systemic circulation. Nasal delivery bypasses this process, enhancing bioavailability.

Additionally, systemic side effects like dizziness and fatigue are common with oral and transdermal medications. Nasal drug delivery can specifically target the brain, minimizing peripheral side effects and allowing for lower drug doses. Issues with consistent absorption in oral and transdermal routes can be improved using mucoadhesive nasal gels or nanoparticles that enhance drug residence time and control release.

For elderly patients who struggle with oral medications, nasal sprays or powders provide a non-invasive alternative. They also act as a practical solution for patients requiring injectable treatments, which often come with pain and infection risks.

Another challenge with various delivery methods is the short duration of action, leading to frequent dosing. Nasal microspheres, hydrogels, or nano-emulsions can address this by enabling sustained drug release, reducing the need for multiple doses. Moreover, nasal formulations are generally more cost-effective than injections, requiring less healthcare oversight and making them accessible to more patients [18].

TABLE 1: COMMERCIAL DOSAGE FORMS WITH LIMITATIONS

Dosage forms	Examples	Limitations
Oral tablets	Propranolol, primidone, carbidopa- levodopa	Delayed onset of action and first-pass metabolism reduce bioavailability. This may cause systemic side effects such as dizziness and fatigue.
Extended-release tablets	Propranolol ER, gabapentin ER	Inconsistent absorption of medication, the risk of dose dumping, and limited flexibility for adjusting doses.
Oral capsules	Topiramate, primidone, gabapentin	Difficulty swallowing in elderly patients, slow onset of action, and consistent dosing required for efficacy.
Transdermal patches	Rotigotine patch	Skin irritation and allergic reactions can occur, drug permeability is limited, and daily application is required, but it may detach prematurely.
Injectable (IV, IM, SC)	Clonazepam IV	Invasive and painful; requires administration by a healthcare professional, with a risk of infection at the injection site.
Sublingual/buccal films	Clonazepam ODT	There is limited availability for tremor treatment, and it requires frequent dosing due to its short duration of action.
Intranasal sprays	Midazolam	Nasal discomfort and irritation, inconsistent absorption due to nasal mucosa conditions, and a short duration of action.
Inhalable formulations	Levodopa inhalation powder	Proper inhalation technique is required, and it can be expensive. Additionally, it may not be suitable for all types of tremors [6].

Anatomy and Physiology of the Nose and Blood-Brain Barrier (BBB): The nasal cavity is a crucial part of the respiratory system, serving functions beyond breathing. It is a complex structure bounded by bone and cartilage, divided into two halves by the nasal septum. The lateral walls contain bony projections called conchae, which increase the surface area and create turbulent airflow. This turbulence plays an essential role in warming, humidifying, and filtering the air we inhale, a process aided by the mucus-producing nasal mucosa, which is rich in blood vessels and lined with protective cilia. The nasal vestibule at the entrance further filters the incoming air with coarse hairs. In the upper part of the nasal cavity is the olfactory region, which contains specialized receptors for the sense of smell. Surrounding the nasal cavity are the paranasal sinuses air-filled spaces that help reduce the weight of the skull, enhance voice resonance, and provide additional air conditioning. Functionally, the nasal cavity serves as the primary pathway for air, protects the lower respiratory tract from irritants, and speech aids, and facilitates drainage from the sinuses.

Clinically, the nasal cavity can be affected by various conditions such as rhinitis, sinusitis, deviated septum, and nasal polyps, underscoring its significance to overall health. The nasal cavity stretches from the nostrils to the throat and consists of several regions. The vestibular region at the front contains hair and mucus to protect against irritants. The curved conchae on the sides trap foreign particles, filtering and humidifying the air. The respiratory region in the middle is vital for breathing, while the olfactory region at the top helps us smell through olfactory neurons connecting to the brain [19, 20]. The brain is separated from the nasal cavity by the cribriform plate of the ethmoid bone and is protected by the blood-brain barrier (BBB). The BBB, made up of endothelial cells with tight junctions, prevents most substances from entering the brain, ensuring a stable internal environment. Supportive cells like astrocytes and pericytes also play a role in this protective barrier [21].

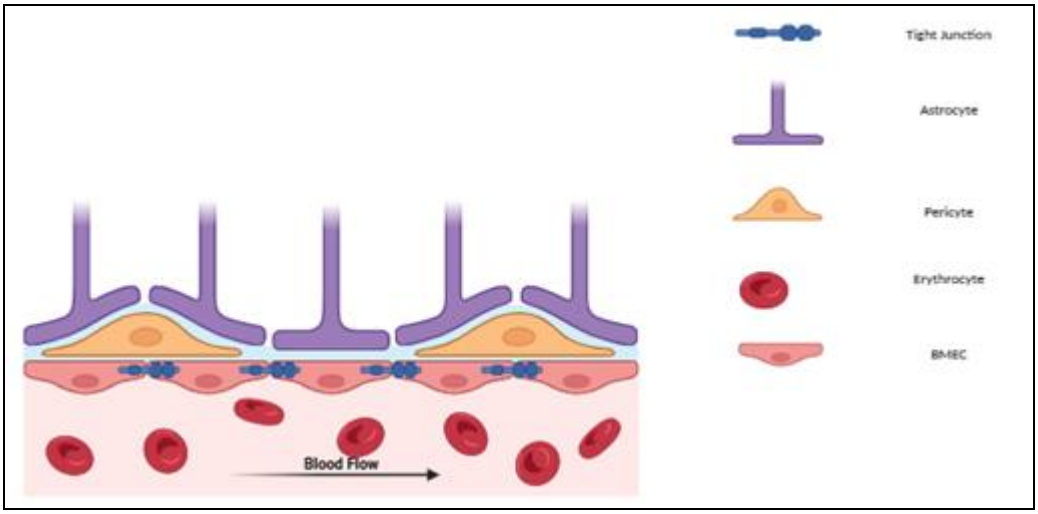

FIG. 3: CELLS IN THE BLOOD-BRAIN BARRIER SYSTEM

Enzymes in the Nasal Cavity: Enzymes present in the nasal cavity can hinder drug absorption and lead to the degradation of drugs. Various enzymes, such as aldehyde cytochrome-dependent monooxygenases, are found in the nasal mucosa. Additionally, P-glycoproteins, organic anion transporters (OAT), and several xenobiotic-metabolizing enzymes are present in the olfactory perineural space [19, 22]. Other enzymes, such as aminopeptidases and carboxylesterases, exhibit the highest activity in the nasal epithelium [23].

TABLE 2: ENZYMES WITH LOCATION AND FUNCTION

Enzyme	Location in the nasal cavity	Function
Cytochrome P450	Nasal epithelium, olfactory mucosa	Metabolism of xenobiotics and drugs[24]
Carboxylesterases (CES)	Nasal epithelium	Hydrolysis of esters, metabolism of prodrugs[19]
Glutathione S-transferases	Nasal epithelium	Detoxification of xenobiotics via glutathione conjugation[6]
Alcohol dehydrogenase	Nasal mucosa	Oxidation of alcohols to aldehydes
Aldehyde dehydrogenase	Nasal mucosa, olfactory tissue	Converts aldehyde to carboxylic acid[25]
Aminopeptidases	Nasal epithelium, submucosa	Breakdown of peptides and proteins[24]
Neprilysin	Nasal epithelium	Degradation of neuropeptides and peptides like bradykinin
Monoamino oxidase	Olfactory bulb, nasal epithelium	Metabolism of neurotransmitters
Cyclooxygenase (COX-1, COX-2)	Nasal mucosa	Prostaglandin synthesis, inflammation regulation
Hyaluronidase	Submucosa, nasal connective tissue	Degrades hyaluronic acid affects tissue permeability
p- glycoproteins	Olfactory perineural space	Metabolism of xenobiotics and drugs[22]

Pathways for Nasal-brain Delivery of Drugs: The nasal cavity serves not only as a passage for air but also as an effective and promising route for drug delivery, known in Ayurveda as Nasya Karma

[26, 27]. Due to its rich blood supply, large surface area, and proximity to the brain, the nasal cavity allows for rapid drug absorption. This method can bypass the digestive system and escape first-pass metabolism; also, in some cases, it can even circumvent the blood-brain barrier.

Nasal drug delivery addresses many advantages that are associated with oral administration, leading to improved drug stabilization, enhanced transport mechanisms, and better physicochemical properties, such as increased bioavailability. Systemic absorption occurs through the highly vascularized nasal mucosa, facilitating quick absorption into the bloodstream, which results in a fast onset of action and improved bioavailability.

Drugs can directly enter the brain *via* the olfactory nerve and the trigeminal nerve [26]. Simple diffusion, endocytosis, and paracellular transport through the junctions between cells allow drugs to traverse olfactory epithelial cells [19, 23]. Drug delivery through the olfactory nerve typically occurs within 1.5 to 6 hours, while absorption through olfactory epithelial cells may take only a few minutes [19].

The trigeminal nerve also extends into the nasal cavity, offering an alternative pathway for drug delivery to various brain regions, including the brainstem and spinal cord. However, the olfactory route is generally faster than the trigeminal pathway [20].

Additionally, some drugs utilize the nasal-brain lymphatic system, entering through the nasal-associated lymphoid tissue (NALT) to reach the systemic circulation. NALT primarily functions as an immune organ that prevents foreign particles from invading the nasal cavity and upper respiratory tract [19].

It contains M cells, which have been shown to absorb nanoparticles effectively. Therefore, drugs administered nasally can indirectly enter the brain through systemic circulation [20].

The nasal route of drug delivery offers several advantages. It is a short and simple method compared to other administration routes, can bypass first-pass metabolism, provides longer-lasting effects than other systems, and enables rapid onset of action [26].

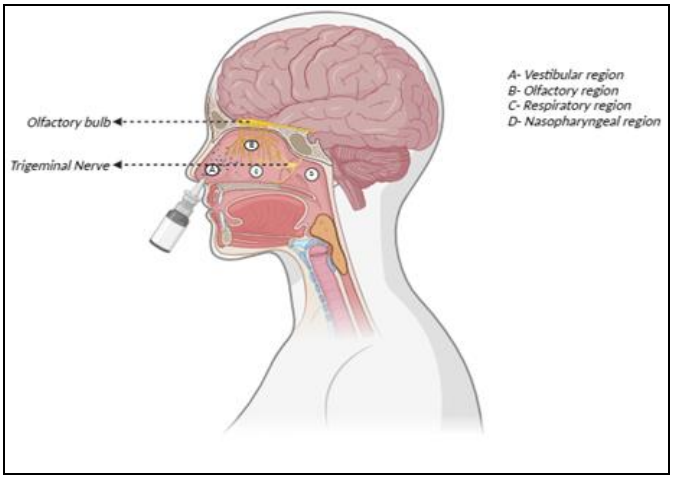

FIG. 4: REGIONS FOR NASAL DELIVERY

Limitations for the Nasal Drug Delivery System: While nasal drug delivery presents advantages such as rapid onset and the ability to bypass first-pass metabolism, it also has several limitations that can impact its efficacy, safety, and patient compliance. These limitations can be divided into physiological and formulation-related categories.

Physiological Limitations:

Limited Nasal Absorption Area: The human nasal cavity has a relatively small surface area (approximately 150 cm^2) for drug absorption, which restricts the amount of drug that can be effectively delivered. Only small molecules and lipophilic drugs are absorbed efficiently, while large hydrophilic molecules have poor permeability [28].

Mucociliary Clearance (MCC): The nasal epithelium features a self-cleaning mechanism known as mucociliary clearance, which quickly removes foreign particles, including drugs, from the nasal cavity. The half-clearance time for nasal formulations is about 15 to 20 minutes, which means that drugs must remain in the nasal cavity for a longer duration to have an effect [23,28].

Enzymatic Degradation: Nasal enzymes metabolize drugs before they can be absorbed, including cytochrome enzymes, carboxylesterases, and peptidases. Peptides and proteins, such as biologics, are degraded by proteases, making them less effective when delivered via the nasal route [19, 28].

Limited Dose Volume and Concentration: The maximum liquid volume that can be administered

per nostril is 200 to 250 µL, which limits drug concentration. Higher doses necessitate multiple sprays, which may lead to drug loss and reduced patient compliance [28].

Interindividual Variability: Nasal conditions (e.g., allergic rhinitis, sinusitis, nasal congestion, and deviated septum) can diminish drug absorption and increase variability in efficacy. Age-related changes in mucosal thickness and clearance rates also affect drug pharmacokinetics.

Formulation-Related Limitations:

Drug Stability Issues: Certain drugs, particularly proteins and peptides, can be unstable in aqueous nasal formulations. Factors such as oxidation, hydrolysis, and microbial contamination can lead to the degradation of these drugs over time.

Irritation and Toxicity: Some excipients (for example, preservatives and absorption enhancers) may cause nasal irritation, dryness, and burning sensations. Prolonged use of nasal formulations can potentially damage nasal cilia, resulting in chronic inflammation.

Poor Permeability of Hydrophilic Drugs: Water-soluble drugs often find it difficult to penetrate the nasal epithelium. This may require the use of permeation enhancers (like chitosan and bile salts), which could raise toxicity concerns [28].

Short Retention Time: Liquid sprays and solutions are rapidly cleared from the nasal passage due to drainage, leading to low bioavailability. While strategies utilizing mucoadhesive polymers (such as chitosan and carbopol) can improve retention, they may cause discomfort and negatively affect patient compliance.

Applicable Formulations: Solution-based formulations are popular in nasal drug delivery due to their ease of preparation, rapid absorption, and patient-friendly use. These formulations dissolve the active pharmaceutical ingredient (API) in a liquid vehicle, often incorporating excipients for improved stability and absorption. Nasal sprays, which deliver drugs as a fine mist via metered dose pumps, are commonly used for medications like midazolam. However, their effectiveness can be limited by short nasal residence time and the risk of postnasal drip. The nasal drops are another cost-effective option, but they offer less precise dosing and may drain into the throat. Saline-based nasal irrigations are primarily for cleansing the nasal cavity rather than targeted drug delivery, despite improving absorption for subsequent treatments. For deeper penetration, nasal nebulizers create a fine mist, ensuring even distribution of drugs. Although nebulizers are less portable and more costly, solution-based formulations remain a preferred choice for quick therapeutic action. Advances in mucoadhesive agents and other enhancers continue to improve their effectiveness, solidifying their role in modern nasal drug delivery systems [28, 29].

Nanoparticle-based formulations are a promising approach for nasal drug delivery in treating tremors. These systems encapsulate drugs such as levodopa, benzodiazepines, and beta-blockers in nanoparticles made from biodegradable polymers like PLGA or chitosan, as well as lipid carriers like liposomes. The small size of these carriers helps them penetrate the nasal mucosa effectively and transport drugs to the brain, bypassing the blood-brain barrier. This targeted delivery enhances drug bioavailability and provides controlled, sustained release, leading to faster therapeutic effects and fewer side effects. Moreover, nanoparticles can be designed with mucoadhesive properties to increase retention time in the nasal cavity, further improving absorption. While still under research, these formulations have significant potential to enhance tremor management through precise dosing and improved patient compliance [20, 29].

Hydrogel-based formulations for nasal drug delivery enhance tremor management by improving drug retention and controlled release. These systems incorporate tremor-relieving agents, like levodopa or benzodiazepines, within a water-retaining polymer network that adheres to the nasal mucosa. This prolonged residence time allows for sustained release into the bloodstream or through nose-to-brain pathways. Composed of biocompatible polymers such as chitosan or carbopol, these hydrogels respond to temperature changes, maintaining their gel-like consistency. Their mucoadhesive properties minimize rapid clearance, reduce dosing frequency, and improve therapeutic outcomes by providing stable drug levels and enhanced bioavailability. Overall, these

formulations increase drug contact time with the nasal mucosa, improving absorption and ensuring more consistent therapeutic effects [30, 31].

Lipid-based formulations for nasal drug delivery in tremor treatment enhance drug absorption and target the brain effectively. These systems, including liposomes, nanoemulsions, and solid lipid nanoparticles (SLNs), encapsulate tremor-relieving agents like levodopa or benzodiazepines, protecting them from degradation and ensuring controlled release. By facilitating transport across the nasal epithelium and potentially through the olfactory pathway, these formulations can bypass the blood-brain barrier. Their lipid composition can also be customized to improve mucoadhesion, increasing residence time and bioavailability. This results in a rapid onset of action while minimizing systemic side effects, making these formulations promising for tremor management. Specialized vesicles such as liposomes, transfersomes, and ethosomes enhance brain targeting. Liposomes provide stability, transfersomes penetrate membranes easily, and ethosomes use ethanol for improved permeability [20, 28].

Microparticulate systems for nasal drug delivery encapsulate tremor-relieving agents, like levodopa or benzodiazepines, in microparticles ranging from 1 to 100 micrometers. Using biodegradable polymers such as chitosan, alginate, or PLGA, these systems enable controlled drug release and protect against enzymatic degradation in the nasal cavity. By adhering to the nasal mucosa, they prolong drug residence time, enhancing absorption and providing a sustained therapeutic effect, which is especially helpful for managing tremors. While they may not penetrate as deeply as nanoparticles, their consistent release and improved dosing accuracy can reduce dosing frequency and systemic side effects. Overall, these systems efficiently deliver drugs directly to the brain via the nasal route, potentially improving treatment efficacy and patient compliance. Microneedles can also create small openings in the nasal mucosa to boost absorption further, minimizing side effects [28].

Powder formulations for nasal drug delivery utilize micronized particles to deliver tremor-relieving agents like levodopa or benzodiazepines directly through the nasal cavity. These powders offer advantages over liquids, including improved drug stability, a longer shelf life, and the elimination of irritating preservatives. By incorporating mucoadhesive properties and optimizing particle size, these formulations enhance deposition and enable controlled, sustained release of the active ingredient. This leads to faster therapeutic effects and consistent drug levels, reducing dosing frequency and minimizing side effects. Effectiveness depends on specialized delivery devices for accurate dosing and uniform dispersion, as well as addressing factors like particle aggregation and patient variability. Overall, powder formulations provide a stable alternative to liquids, with enhanced retention and solubility, particularly for moisture-sensitive drugs.

Each strategy has unique advantages, with choices made based on drug properties and patient needs. Ongoing research in nanotechnology and bioengineering continues to enhance the reliability and efficiency of nasal drug delivery, offering new hope for patients with neurological disorders [31].

Other Advances and Ongoing Research in Nasal Delivery and Tremors: The intranasal drug delivery system draws the interest of many scientists for further development and research due to advantages like good bioavailability, prevention of first-pass metabolism, good patient compliance, and varied clinical applications in areas like mental disorders, osteoporosis, chronic allergic reactions, mucosal inflammation, rhinitis, and sinusitis (asthma), sexual dysfunction, and bacterial and viral infections. Nanotechnology, along with nasal delivery, gives better results with compliance problems and improves bioavailability.

For systemic action, drugs like NSAIDs and calcitonin (for osteoporosis treatment) are already available in the market, and other similar drugs are to be released [32]. For severe equine asthma treatment, the Immunomodulatory CpG-ODN, bound to gelatin nanoparticles, was introduced into the horse as an animal model by inhalation. This immunotherapy showed a significant decrease in allergic and inflammatory responses. This sheds light on the possibility of human asthma treatment [33]. For Parkinson's disease (PD), the silymarin lipophilic mucoadhesive microemulsion (SLMMME) was developed and compared with

that of silymarin solution (SLMS) on rats as the animal model. The SLMMME-treated rats were observed to have a significant improvement in neuroprotection than that of SLM-treated rats [34].

For the treatment of glioblastoma (GBM), a formulation of self-emulsifying nano intranasal administration of butylidenephthalide (Bdph) was optimized to improve drug loading capacity and studied on the rat model. It was observed that the same survival time, i.e., 37 days seen with optimized Bdph (160 mg/kg) and non-optimized stock Bdph (320 mg/kg) [35].

Tuberculosis (TB) vaccine ID93+GLA-SE was optimized into an intranasal and pulmonary dry powder formulation against Mycobacterium tuberculosis (Mtb). The murine studies showed controlled Mtb in infected mice and a 10- 44% drug dose delivery by the intranasal route [36].

CONCLUSION: Based on the type of tremor, there are many treatment options such as beta-blockers, anticholinergics, thalamotomy, deep-brain stimulation surgery, dopamine agonists, anti-seizure drugs, and more that are being used in present medical practice. Tremors also act as indications for other disorders like Parkinson's disease, multiple sclerosis, alcohol withdrawal, and stroke. Therefore, a brief understanding of tremors and finding easier and more efficient ways for treatment is of great importance.

There has been research and development in the novel nasal delivery of drugs for the treatment of tremors. When compared with oral delivery, the drawbacks of oral drug delivery can be overcome by nasal delivery. The advantages of this route are that rapid drug absorption occurs due to the large surface area, proximity to the brain, and rich blood supply, thereby preventing first-pass metabolism. Targeted brain delivery can also be achieved by nasal-associated lymphoid tissue (NALT) along with the trigeminal and olfactory nerve routes. The M cells of lymphoid tissue absorb nanoparticles prominently. The novel dosage forms like nasal sprays, nasal powders, nano-emulsions, hydrogels, and lipid-based formulations are some of the developed products that provide the advantages like controlled and sustained release, better permeability (even in the brain), solubility, bioavailability, moderating hydration, and enhancing the efficiency of the drug. With the evident results in research as provided in this article, it can be said that the nasal-brain delivery has immense potential in the treatment of tremors and other related disorders.

ACKNOWLEDGEMENTS: Nil

CONFLICTS OF INTREST: Nil

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How to cite this article:
Monica PU, Priyanka J, Padmaja V and Kumar PL: Innovations in nasal formulations: advances in tremor treatment. Int J Pharm Sci & Res 2025; 16(10): 2707-19. doi: 10.13040/IJPSR.0975-8232.16(10).2707-19.