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Intranasal Nanoemulgels: An Innovative Approach for Direct Brain Targeting in the Treatment of Neurological Disorders

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ABSTRACT

Neurological disorders such as dementia, epilepsy, migraine, Parkinson's, and Alzheimer's disease are significant worldwide health issues due to the blood-brain barrier (BBB) being so restrictive that around 98% of tiny-molecule therapy is ineffective. Safety considerations limit the widespread use of classic invasive techniques (intracerebral, intraventricular, or parenchymal injections), while systemic distribution typically results in issues with low brain bioavailability, systemic toxicity, and degradation. Because it bypasses the blood-brain barrier and reduces first-pass metabolism, the intranasal route has emerged as a promising non-invasive option for straight drug transportation from the nose to the brain through the olfactory and trigeminal pathways. As innovative brain-specific transporters, nanoemulgels—hybrid techniques that combine lipid-based nano-emulsions with a mucoadhesive gel matrix—have recently attracted attention. In models of epilepsy, glioblastoma, schizophrenia, and dementia, experimental research on medications like carbamazepine, naringin, quetiapine, sorafenib, and azilsartan has shown increases in brain uptake, better pharmacological efficacy, and therapeutic advantages. There are still issues with long-term safety, device compatibility, and regulatory uniformity despite their benefits. Still, by combining enhanced therapeutic outcomes, rapid brain targeting, & non-invasiveness, intranasal nanoemulgels present a novel and versatile platform that has the potential to completely transform the delivery of CNS medications. Future research should focus on clinical translation, large-scale manufacturing, and approval from regulators in order to establish nanoemulgels as a standard treatment for neurological illnesses.

Keywords:

Nanoemulgels, Intra-nasal drug Delivery, Neurological Disorders, Alzheimer's Disease.

INTRODUCTION:

The high rate of morbidity and death in the world necessitates intensive clinical care for brain diseases, such as brain tumors, autoimmune neurological conditions (Parkinson's, Alzheimer's, and prisoner's syndrome), having epilepsy, dementia, migraine, and acute ischemic brain hemorrhage. Ineffective at producing adequate therapeutic effects, the majority of developed brain-targeting drugs alleviate symptoms of brain dysregulation. There are three main problems:

(i)the blood-brain barrier (BBB) is lipophilic;

(ii)the brain's microenvironment is complicated; &

(iii)Aberrant protein status.

Arterioles and venules are found in normal, continuous, non-apertured arteries of the neurological system. The control and interchange of ions and chemicals among brain cells are mediated by these arteries. [1] The brain is protected by the spread of infectious agents, poisons, or allergens by the blood-brain barriers function with the distinctive form of CNS capillaries. The BBB diverts blood from the interstitial fluid and serves as an effective barrier to keep most active chemicals from diffusing to the receptors in the central nervous system. It functions as a dynamic regulator that moves nutrients and prevents heavy, unwanted (lipophilic) substances from entering the brain's extracellular fluid. The BBB can be freely penetrated by lipophilic compounds with an average molecular weight of 600 Daltons and an optimal Log P of 1.5–2.7.

The walls of the blood arteries in the brain are made up of brain endothelial cells (BECs), which are very polarized compared to the endothelial cells in other organs. Tight junctions that bind BECs together restrict the para-cellular flux of ions & the transcellular exchange (transcytosis and pinocytosis) among brain cells & blood cells. BECs govern the body's health and pathological circumstances by utilizing the interplay of numerous neural, vascular, and neurological components to coordinate a variety of metabolic, transportation, and physiological functions.[2] Restricting the flow of bioactive/macromolecules and their receptor binding via BBB-adorned p-glycoprotein efflux transporters also produces a desired pharmacological response. Toxin-removing efflux transporters, like p-gp, typically diffuse cell membranes

passively, whereas influx transporters act as an type of carriers to carry ions and nutrients to brain cell. The BBB not only acts as an active barrier for cellular self-defense, but it also closely observes the CNS microenvironment, interacts with & adjusts to the behavior of CNS cell as brain illnesses evolve. These characteristics of the BBB make it difficult for bioactive or therapeutic substances to penetrate the brain tissues, making it difficult to treat CNS disorders. Disorders of the central nervous system, including autoimmune Parkinson's, Alzheimer's, and schizophrenia, affect an estimated 1.5 million people according to a WHO healthcare statistics report.[3] There are still problems that need to be resolved before the majority of CNS illnesses may be fully cured or treated, despite the fact that current drug delivery techniques have shown a promising picture of successful CNS treatments with rising survival rates. A sophisticated treatment approach that permits the potential penetration of the blood-brain barrier at a sufficient level to achieve the intended pharmacological activity is unquestionably needed. The BBB significantly lowers bioavailability by preventing 98% of low molecular weight compounds from entering. Only 5% of treatments out of 7000 with a molecular weight of 357 Dalton and a partition coefficient of 2.57 Log P have the capacity to cross the blood-brain barrier and demonstrate strong effects for treating schizophrenia, depression, and insomnia, according to a report taken from the comprehensive medicinal chemistry database.[4-5] For direct medication administration to the brain, invasive techniques such as intra-parenchyma, intracranial, and intra-cerebro-ventricular injections are used. These local tactics, which highlight the use of ultrasound and electromagnetic field techniques, are connected. These are hazardous and uncomfortable, yet they are the primary treatment for neurological and psychological conditions. Therefore, a non-invasive method that avoids the BBB, lowers toxicity, and delivers the medications to the intended location—like the nose-to-brain delivery passageway—is recommended. The medicine can be directly delivered into the cerebrospinal fluid via the intranasal route, which follows the olfactory path.[6-7]

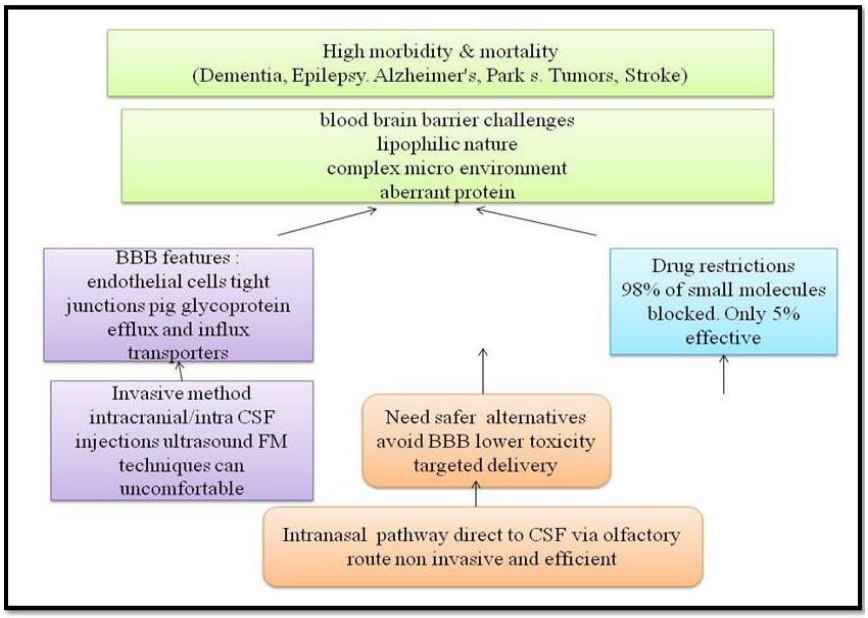

Figure 1: Nasal to Brain Drug Delivery Pathway

ROUTES FOR THE INTRA-NASAL BRAIN DELIVERY

The effectiveness of nasal drug delivery devices greatly depends on an understanding of the architecture and physiology of the nasal cavity. The respiratory region, olfactory region, and vestibule are the three divisions of the nasal cavity. Drug absorption is negligible through the vestibule region because to its tiny surface area. Contrarily, the respiratory region has a large number of blood capillaries, which allows for systemic drug absorption &, following intranasal administration, medication delivery to the brain indirectly. Drugs may also be delivered directly to the brain through the respiratory region's trigeminal neurons. As an illustration, it has been noted that the respiratory system is most suited for intranasal vaccination delivery. Direct drugs transport to the brain and cerebrospinal fluid (CSF) is another key function of the olfactory area. Drugs may not reach this permeation area as much because the area that detects smell is located in the upper portion of the nasal cavity. Delivering the appropriate medication concentrations to the site of action is the main goal of various drug delivery mechanisms. Furthermore, it is possible to reduce both physical clearance and the breakdown of medications through metabolism; Figure 2 provides an overview of drug transport. Because of its high total blood flow, porous endothelium membrane, vast surface area, and ability to evade first-pass metabolism, the highly permeable nasal epithelium enables quick drug absorption to the brain. A large range of therapeutic medicines, including tiny and large molecules, can be administered to the central nervous system via the intranasal route. A number of drugs have been demonstrated to work better in the central nervous system when administered via nasal administration and to have their therapeutic benefits at lower dosages. Furthermore, the

therapeutic agent does not need to be altered for nasal medication delivery, nor does the drug need to be paired with a carrier. With its strong benefits over alternative drug delivery techniques, nasal drug delivery with multiple channels has long been a major research focus for pharmaceutical and medical device firms. Below is an explanation of the routes for delivering from nose to the brain. [8-9]

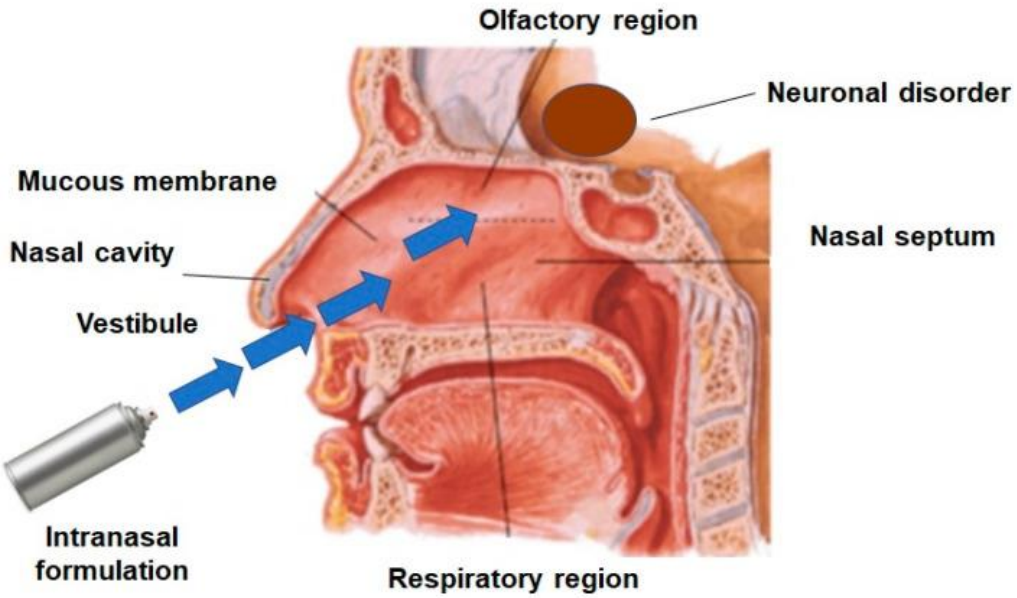

Figure 2: **Routes of Drug Transport for Nose-To-Brain Delivery**

Olfactory Pathways:

According to certain research, the olfactory nerve pathway is how the majority of neurophilic viruses—including rabies, and horse encephalomyelitis viruses—steroid hormones, herpes stomatitis metal-ions, including nickel & cadmium, and proteins reach brain. Pinocytosis is how these substances are taken up at the olfactory neurons' axon terminals. endocytosis, or simple diffusion after passing through the olfactory mucosa. They then pass through the neurons' axonal plasma before being sent straight to the olfactory bulb via the sieve plates, where they eventually arrive at the rhinencephalon. The most direct approach to get beyond the blood-brain barrier is through the olfactory nerve pathway, which is thought to be the most significant route for medicines to enter the brain from the nose. Axonal transport, on the other hand, is rather slow; depending on the characteristics of the medication being given, its rate might vary around 0.1 and 4 mm/d - 20 and 400 mm/d. Because of this, this route is characterized by delayed absorption, which hinders a drug's rapid entry into the brain. Some

medications may not enter the brain for up to 24 hours at slower rates, which limits their therapeutic applicability. One to two hours is the quickest time for drugs to enter the brain.[10-11]

The pathway via the mucosal lining of the nose:

Drugs enter the central nervous system (CNS) directly through the mucosal epithelial channel, also known as the nose–brain pathway, which involves cytosolic action or diffusion from the olfactory mucosal epithelium. This system allows the brain to absorb the majority of small-molecule medications, including insulin, lidocaine, dopamine, 5-fluorouracil, and dihydroergotamine. This pathway can be further separated into two parts: two types of transport pathways: paracellular and transcellular. In the former, drug molecules are transported to the glandular and supporting cells that surround the olfactory nerve by means of cytosolic diffusion, carrier transport, or passive diffusion across mucosal epithelium that is not olfactory neuron receptor cells. Drug molecules enter the intercellular fluid through the latter route through the interstitial space of the supporting cells or the peripheral gap between the olfactory nerve and the cells. The drug molecules that are carried to the basement membrane will be carried to the CSF within the cells that encircle the neuron if they are near the axons in lamina propria. Drugs might concurrently enter the systemic & lymphatic circulations through the lamina propria. Before being transferred into the CSF, the drug molecules that are carried to the basement membrane will penetrate the area around the olfactory nerve bundle if they manage to get past the lamina propria. The anatomical relationships between the subarachnoid space and the olfactory submucosa are necessary for this system to function. The olfactory mucosal epithelial channel enables faster drug absorption than the olfactory nerve system, allowing the drugs to enter brain tissues & cerebrospinal fluid within a few minutes of nasal delivery.[12-13]

Trigeminal Nerve Transmission:

It is possible for the opposite ends of the trigeminal nerve's ophthalmic and maxillary branches to either enter the central nervous system through the pons and end at the spinal nucleus of the brainstem or to pass through the ethmoid plate and end at the area of the olfactory bulb. These branches can extend to epithelial cells in the olfactory and respiratory areas of the nasal cavity. In a study by Thorne et al. (2004), iodine-125-conjugated insulin-like growth factor 1 was given intranasally to the olfactory bulb, trigeminal branch ganglia, and trigeminal nerve. The trigeminal nerve had a concentration ten times higher than the olfactory bulb, indicating that

the trigeminal nerve may occasionally act as a conduit for drugs to enter the brain after intranasal administration.

However, it has been noted that the transit time of the trigeminal nerve is 17–56 hours longer than that of the olfactory nerve.[14]

Pathway for Blood Circulation:

The dense capillary arrangement in the respiratory region's lamina propria allows low-molecular-weight lipophilic medications to primarily penetrate the brain after being absorbed into the general circulation. Drugs must, however, pass across the blood-brain barrier after entering the general circulation in order to reach the central nervous system as a result, this pathway restricts the therapeutic use of many medications. The dominant pathway of a DDS is determined by variations in drug characteristics, formulations, and routes of administration. After nasal administration, a drug will ultimately enter the central nervous system by one or more of the previously described pathways.[15]

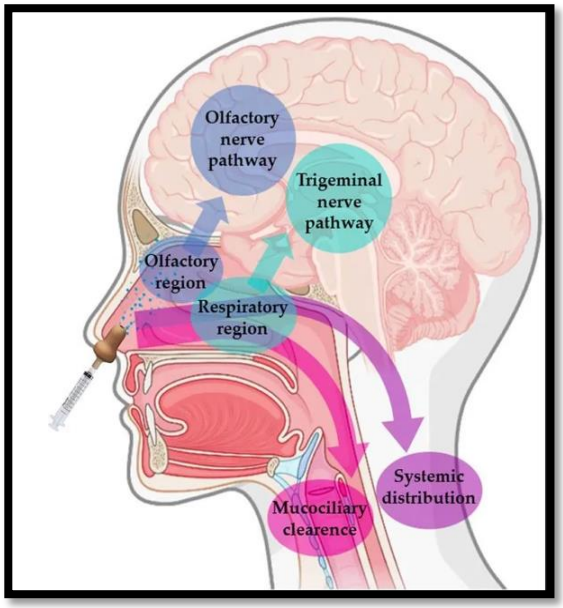

Figure 3: Pathway for Blood Circulation

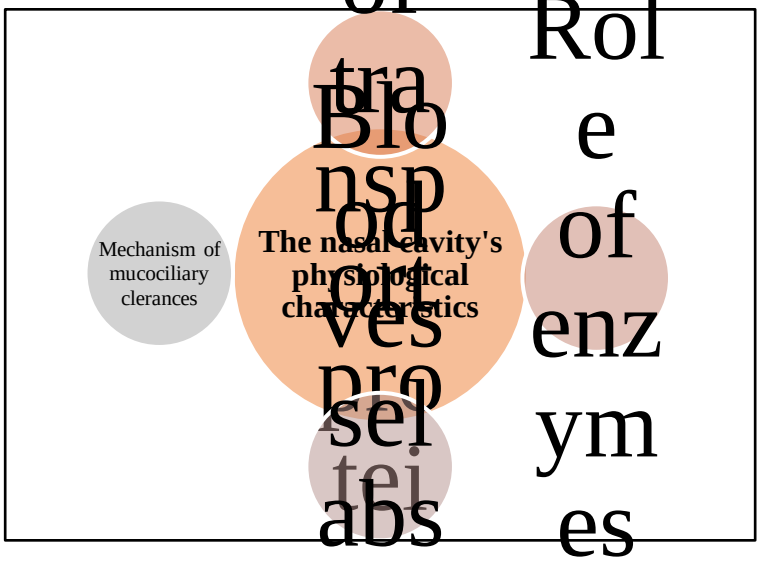

Figure 4: The nasal cavity's physiological characteristics [16-19]

FACTORS INFLUENCING DRUG DISTRIBUTION FROM THE N2B PROPERTIES OF DRUGS

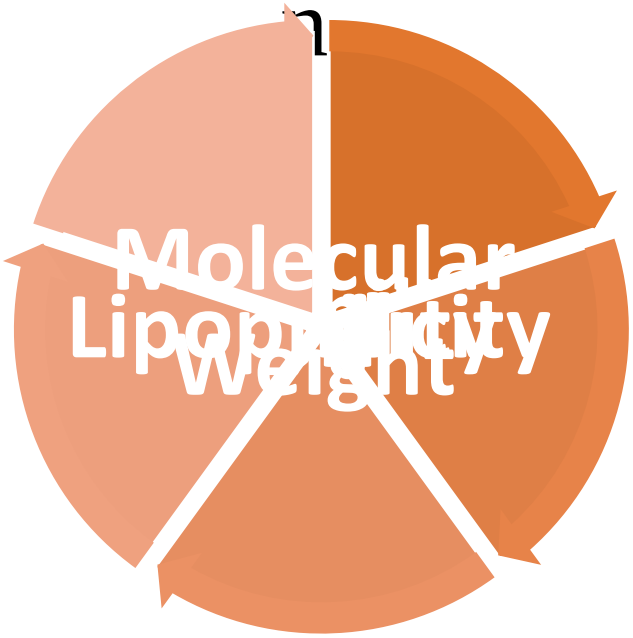

Figure 5: Factors influencing Drug Distribution from Nasal to Brain Drug Delivery

Molecular Weight:

Drug distribution from the nose to the brain depends critically on a drug's permeability via the nasal mucosa, which is mostly determined by its molecular weight. More effective absorption into the central nervous system is made possible by compounds with molecular weights less than 1000 Da, which can typically diffuse through the nasal epithelial cells' tight connections.

Peptides, proteins, and biologics are examples of high-molecular-weight medications that, because of their size, frequently face substantial obstacles that restrict their capacity to pass through the nasal epithelium. Their therapeutic efficacy when taken intranasally may be jeopardized by this decreased permeability. In order to overcome this obstacle, sophisticated formulation techniques include the use of carrier systems and permeation enhancers accelerate the passage of bigger molecules over the nasal barrier.[20-22]

Solubility:

One important aspect affecting a drug's bioavailability is how soluble it is in the nasal cavity's aqueous environment. Drugs that are poorly soluble in nasal secretions may not dissolve completely, resulting in less than ideal concentrations at the site of absorption and decreased therapeutic efficacy. To improve dissolution in the nasal environment, poorly water-soluble medications may need solubilizing agents or specific delivery systems. The drug's availability for absorption can be greatly increased by improving solubility by formulation techniques, such as the use of co-solvents or surfactants, guaranteeing that adequate amounts reach the target site, whether it be the central nervous system or the systemic circulation.[23]

Lipophilicity:

The nasal absorption profile of a medication is significantly influenced by its lipophilicity. Transcellular diffusion allows lipophilic medications, which are attracted to lipid-rich environments, to easily penetrate the nasal mucosa and dissolve into and flow across the lipid bilayers of cell membranes. They are therefore excellent candidates for nose-to-brain delivery systems because of this feature, which increases their penetration rate. However, the lipid-rich nasal membrane makes it difficult for highly hydrophilic medications, which prefer watery conditions, to pass through, leading to decreased absorption rates. To get around this, formulation techniques include adding lipophilic excipients or encapsulating hydrophilic medications in lipid-based NPs can improve their distribution.[24]

Stability:

A drug's physical and chemical stability in a nasal formulation is essential to guaranteeing its therapeutic effectiveness while being administered. Drugs that are susceptible to degradation—whether from oxidative processes in the nasal environment, pH fluctuations, or enzymatic activity—may lose their effectiveness before they reach their intended location. For example, peptide-based medications, such as insulin, are vulnerable to enzymatic degradation in the

nasal cavity, requiring the use of stabilizing excipients or enzyme inhibitors as preventative measures. By ensuring that the active pharmaceutical ingredient stays intact and effective during the delivery process, stable formulations—achieved by encapsulation in protective matrices—maximize therapeutic effects.[25-26]

pH:

The stability of the medicine and the effectiveness of absorption are both greatly impacted by the pH of a nasal formulation. The physiological pH range that the nasal mucosa maintains is roughly 4.5 to 6.5, which is quite acidic. Formulations should be created to fall within this range in order to maximize drug absorption and reduce irritation to the delicate nasal tissues. Variations from this pH range may result in mucosal irritation, which may cause discomfort or tissue injury, or drug instability (such as the hydrolysis of specific chemicals). A formulation with a pH much lower than 4.5, for instance, can hurt or induce irritation, whereas one with a pH much higher than 4.5 might damage the mucosal barrier. In order to maintain pH compatibility and guarantee patient comfort as well as efficient drug delivery, buffering agents are frequently included.[27-28]

TECHNIQUES FOR APPLYING RELEVANT BIOMATERIALS TO ENHANCE BRAIN-TARGETED NASAL MUCOSAL MEDICATION DELIVERY

Table 1: List of Biomaterials to enhance Brain to Nasal Drug Delivery

Sr. No	Biomaterials	Explanation	References
A. Penetration Enhancers			
1.	Cyclodextrin	Cyclodextrins are non-reducing, water-soluble compounds that have the appearance of white, crystalline powders. These are cyclic substances composed of 1,4-glycosidic bonds connecting D-glucose molecules.Glucose molecules make up six, seven, and eight of the commonly used cyclodextrins, respectively. Because of their distinct spatial structure, cyclodextrins can combine with a wide range of molecules, particularly lipophilic ones, to form	29-30

		inclusion complexes. Therefore, cyclodextrins can be utilized either directly or indirectly to improve medication absorption by serving as stabilizers, solubilizers, or enhancers of nasal mucosal absorption	
2.	Cell-penetrating peptides	Short peptides known as cell-penetrating peptides have the ability to pass through the nuclear membrane and/or cell to direct proteins, other bioactive compounds, or other linked peptides into cells. The effects of cell penetrating peptides are probably mediated by signal transduction pathways and endocytosis, even though the exact transmembrane process is not entirely understood.	31
3.	Pz peptidase	It has been shown that Pz-peptidase increases medication permeability to quickly and reversibly cause tight junctions to open.	32-33
B. Adhesives for mucosa			
1.	Ligand-receptor interactions	By selecting appropriate ligands to modify the formulation's surface,the DDS affinity for the mucosa can be increased, resulting in improved mucosal adsorption and increased nose-to-brain distribution of nanoscale pharmaceuticals. The most widely employed targeted ligands are proteins, such as lactoferrin or specific glycoproteins, whose receptors are expressed in the olfactory area. A number of lectins, including solanum tuberosum lectin and wheat germ agglutinin, have also been employed to facilitate medication delivery from the nose to the brain.	34-36
C. Novel medication delivery methods			

1.	Nanoparticles	By shielding encapsulated medications from deterioration, preventing their accidental removal from the nasal cavity, extending the time the drugs are present in the nasal mucosa, and enabling the direct transport of certain drugs from the nasal cavity to the brain, nanoparticles can aid in brain-targeted drug delivery without increasing drug concentrations in the general circulation. The exact process by which nanoparticles enter the brain is yet understood, however it might entail endocytosis via receptors into cerebral capillary endothelial cells.	37-38
2.	In-situ gel preparations	At the drug delivery location, In-situ gel may change phases and become either liquid or semi-solid. These preparations have the ability to raise drug concentrations in brain tissue and prolong the duration that medications remain in the nasal cavity. In situ gels can be categorized as tempe, pH, or ionic-type gels based on the agent that causes the phase shift. By enhancing the water permeability, the extremely hydrophilic three-dimensional network structure of these gels improves medication absorption via the nasal mucosa. Because the medications are carried through the para-cellular channel together with the water flow, the gels can produce their effect without causing harm to the mucosal surface. Consequently, throughout the last few decades, scientists have been working to improve these gels' characteristics and our knowledge of the mechanisms by which they work.	39-40
3.	Liposomes	Liposomes are innovative drug delivery devices with specific dose forms. Enclosed bilayer membranes made of phospholipids,	41

		liposomes have hydrophilic centers and share traits and capabilities with biofilms. Liposomes can transport both lipid & water-soluble medications because lipid-soluble substances can incorporate in phospholipid bilayer membranes while water-soluble substances can be contained in hydrophilic sections. Because of their surface charge, liposomes prolong their interaction with the mucosa, enhancing drug bioavailability and shielding encapsulated biomolecules from the nasal mucosa's enzymes. Liposomes are safe for long-term usage and just slightly or not at all harm the nasal mucosa. They also don't produce ciliary toxicity or irritation.	
4.	Microsphere	A novel dosage form known as microspheres was created recently and uses a particle dispersion system created by medication absorption and dispersion in a polymer matrix. Albumin, gelatin, polylactides, and starches are just a few of the ingredients that make up microspheres, a spherical drug delivery system. Microspheres can prolong the duration of medication retention in the nasal cavity by up to four hours and function as potent bio adhesives. They can also shield medications from enzymatic metabolism, which significantly increases their bioavailability.	42-43

TYPICAL EXPERIMENTAL TECHNIQUES IN STUDIES ON INTRANASAL DRUG DELIVERY [44-49]

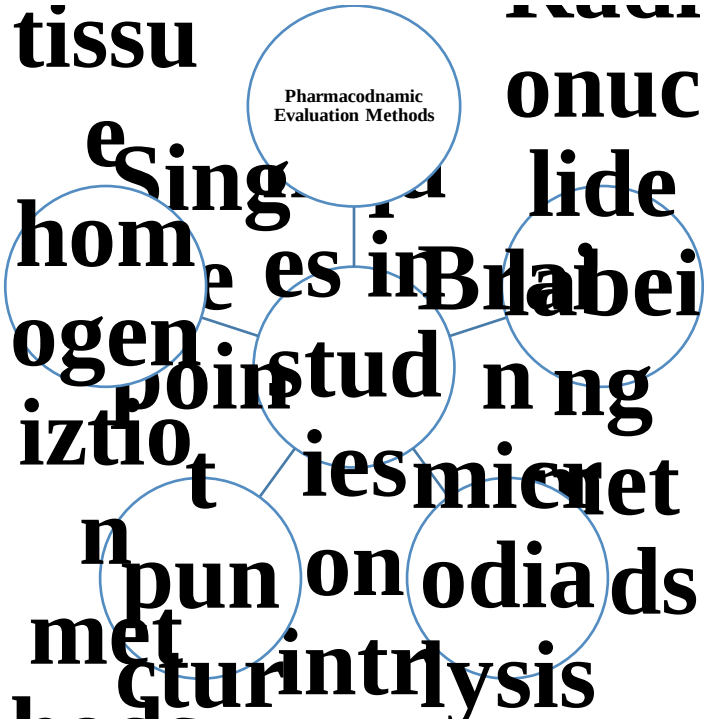

Figure 6: Experimental Techniques used in Nasal to Brain Drug Delivery

CONVENTIONAL FORMULATIONS FOR N2B DELIVERY

Utilizing the nasal cavity's anatomical and physiological links to the central nervous system, a number of items have been created and authorized for therapeutic purposes that profit from nose-to-brain transfer. The authorized formulations with clinical indications that correspond with the nose-to-brain route are summarized in Table 1. These include therapies for mental and neurological disorders such opoid overdose, depression, epilepsy, and migraine. For instance, sumatriptan nasal sprays, which have a quick start of action, were authorized for the treatment of acute migraine attacks. Naloxone nasal spray, which reverses opioid overdose, is another noteworthy example. For depression, esketamine nasal spray was authorized. A major improvement in treatment, nose-to-brain administration enables quick brain access and quick-acting antidepressant effects.[50-51]

Table 2: List of Nasal-to-brain formulations approved by the FDA

Dosage Form	Approval Year	Brand Name	Company	Active Ingredient	Indication
Nasal spray	2023	Zavzpret	Pfizer	Zavegepant	Migraine
Nasal spray	2023	Zomig	Amneal	Zolmitriptan	Migraine
Nasal spray	2023	Naloxone hydrochloride	Amphastar pharms	Naloxone hydrochloride	Opioid overdose
POD system	2021	Trudhesa	Impel	Dihydroergotamine mesylate	Migraine
Nasal spray	2021	Kloxxado	Hikma	Naloxone hydrochloride	Opioid overdose
Nasal spray	2020	Valtoco	Neurelis	Diazepam	Epilepsy
Nasal spray	2019	Nayzilam	UcbInc.	Midazolam	Epilepsy
Nasal spray	2019	Spravato	Janssen	Esketamine hydrochloride	Depression
Xsail system	2016	OnzetraXsail	Currax	Sumatriptan	Migraine

Delivery via intranasal (nose-to-brain) nanoemulgel systems

Nanoemulgels are made up of a lipid nanoemulsion (small particles of oily and surfactants drops) and a gel-like network. With the objective boost the amount of the drug that reaches the

trigeminal/olfactory routes as well as the cerebrospinal fluid (CSF) despite decreasing systemic loss, this novel approach is aimed at

(1) solubilize and defend lipid-based central nervous system drugs,

(2) improve mucosal penetration, and

(3) extend nasal residence time for intranasal brain targeting.[52]

EXPLORED ANATOMICAL AND MECHANISTIC MECHANISM

Important formulation elements and design concepts

1. **Core of Nanoemulgel**: Middle-chain triglycerides (such Capmul and Labrafac) and oleic acid are examples of typical oils; surfactants and co-surfactants may include Tween group, Cremophor, Labrasol, PEG 400, or Transcutol as a cosolvent. The ideal droplet size for stability and penetration is usually less than 200 nm.[53]
2. **Mucoadhesive layer/gel matrix:** Cargopol/carbomer, xanthan, carrageenan (ion-triggered), chitosan (mucoadhesive + permeability enhancer), and poloxamer 407 (thermoreversible). Often, in-situ gelation (ion- or thermo-triggered) is employed: Gel in the nasal cavity to improve retention → liquid for dosing.[15]
3. **Additives:** PEG 400,mucoadesive enhancers,enzyme inhibitors.[54]

VARIOUS KINDS OF NANOEMULGEL SYSTEMS [55-57]

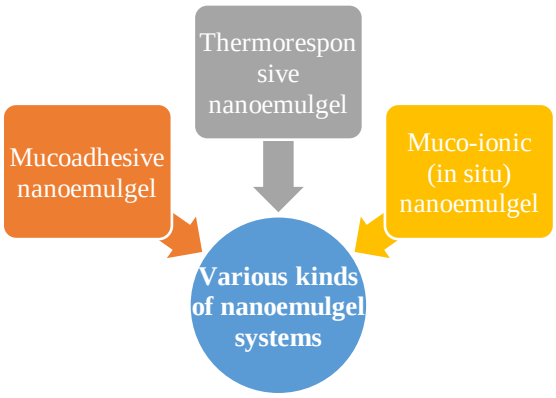

Fig 7: Various nanoemulgel systems

Nanoemulgel Nasal Benefits for Brain Systems [56, 57]

1. Increase brain bioavailability

2. Faster onset of action
3. Support for poorly soluble drugs
4. Bypass of BBB
5. Reduce systemic side effects
6. Extend retention via gelation
7. Reduce dosing frequency

Nanoemulgel Nasal Limitations for Brain Systems [57]

1. Restricted long-term safety information for long-term intranasal usage.
2. For regular dosing, device compatibility (droppers, sprays) is essential.
3. Nanoemulgels' hybrid nature presents regulatory hurdles.

Table 3: List of Essential Requirements for Nanoemulgel

Parameter	Property	Outcomes	Reference
Particle Size	Usually less than 200 nm	Droplets that are too big might not pass through well or be absorbed by brain circuits. Large size may prevent entry into paracellular or neural pathways.	52
Zeta potential	Slightly positive or neutral	Cationic surfaces can interact with negatively charged mucin,but excessive positive charge may cause irritation or toxicity	53
Rheology	Lower viscosity for administration	To low means fast clearance	15

Permeation enhancer	Modification of epithelial permeability by the use of safe penetration enhancers	Non-irritant to tissue	55

STUDIES OF NOSE-TO-BRAIN NANOEMULGEL

Table 4: List of studies done for Nose-to-Brain nanoemulgel

Drug & Year	Formulation / Gel system	Key excipients / gelling agents	In-vitro / Ex-vivo	In-vivo outcomes	Drug & Year
Carbamazepine (2011)	Mucoadhesive nanoemulgel	Oleic acid, Labrasol, Cremophor RH40, Xanthan gum	Droplet size ~130 nm; strong mucoadhesion; ex vivo goat nasal mucosa permeation	Enhanced brain uptake; improved anticonvulsant effect vs oral	Carbamazepine (2011)
Naringin (2021)	Ion-triggered in situ gelling nanoemulgel	Capmul MCM, Cremophor EL, Poloxamer 407 + ion-	Droplet size ~152 nm; mucoadhesive strength; ex vivo sheep	Rapid brain delivery; higher drug concentration in hippocampus	Naringin (2021)

		sensitive polymer	mucosa permeation		
Quetiapine hemifumarate (2023)	QbD-based nanoemulgel	Capmul MCM, Tween 80, PEG 400, Poloxamer 407, Chitosan	Optimized size <200 nm; sustained release; mucoadhesive strength	Improved nose-to-brain transport; potential for schizophrenia	Quetiapine hemifumarate (2023)
Sorafenib (2024)	Poloxamer-carrageenan nanoemulgel	Labrafac oil, Tween 80, PEG 400, Poloxamer 407, Carrageenan	Good viscosity, sustained release; ex vivo rat nasal mucosa transport	Significant tumour reduction in glioblastoma rat model	Sorafenib (2024)
Azilsartan medoxomil (2025)	Thermoresponsive in situ nanoemulgel	Capmul MCM, Tween 80, Poloxamer 407, Carbopol 934	Optimized BBD; droplet size ~160 nm; rapid gelation at 33°C	Improved cognition, reduced oxidative stress & neuroinflammation in dementia model	Azilsartan medoxomil (2025)
Other reports (2019–2022)	Experimental nanoemulgel (various drugs:	Poloxamer 407, Carbopol,	Mostly lab-scale, small animal studies	Showed faster onset, higher brain bioavailability	Other reports (2019–2022)

	Rivastigmin, Donepezil, Fluoxetine)	chitosan derivatives		compared to oral/IV	

CONCLUSION AND FUTURE PERSPECTIVES

By lowering circulatory responses and enhancing medication solubility, mucosal penetration, and brain-targeted intranasal nanoemulgels, the blood–brain barrier can be crossed in a non-invasive, practical, and efficient manner. Clinical translation is currently lacking, despite the promising results of early-phase research involving several medications. More effort must be made in clinical evaluation, device optimization, large-scale production, and regulatory standardization before nanoemulgels can be considered a feasible pharmacological substrate Additional study might concentrate on personalized preparations and integration with state-of-the-art nanocarriers to increase applicability in neurological disorders and brain cancers. Intranasal nanoemulgels have the potential to revolutionize the delivery of central nervous system drugs and greatly enhance patient outcomes with sustained interdisciplinary efforts.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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