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Original Article

Innovative Nanoformulations for Intranasal Therapy in Neurodegenerative Disease Management

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ABSTRACT

Neurodegenerative disorders pose a significant global health challenge, driving the need for innovative therapeutic strategies to improve drug delivery efficacy and patient outcomes. Nose-to-brain delivery, facilitated by advanced nanoformulations, offers a promising solution to overcome the blood-brain barrier (BBB) and optimize drug targeting for central nervous system (CNS) treatments. This review explores recent advancements in nanoformulation technologies tailored for nose-to-brain delivery, particularly in insomnia and other CNS disorders. Key topics include nanocarrier design strategies, pharmacokinetics, therapeutic efficacy, and clinical implications. Nanoformulations enhance drug bioavailability, minimize systemic side effects, and improve patient compliance, marking a transformative shift in neurodegenerative disorder treatments. The olfactory region and hypothalamic microvasculature bypass the BBB, enabling direct and efficient drug delivery to the brain. This is particularly critical for proteins and peptides, which often exhibit short plasma half-lives and limited natural brain interaction. Emerging formulation strategies, such as surface modifications, incorporation of cutting-edge materials, and particle property optimization, address challenges like drug stability, release kinetics, and targeting specificity. These approaches aim to maximize therapeutic absorption while minimizing nanoformulation-induced toxicity in the nasal mucosa. Such advancements reduce side effects, improving the safety and efficacy of nose-to-brain drug delivery systems. This review serves as an invaluable resource for researchers, clinicians, and pharmaceutical professionals focused on developing innovative, safe, and efficient treatments for neurodegenerative diseases, potentially revolutionizing CNS therapy through nanotechnology-driven approaches.

Keywords: Neurodegenerative disorders , Nasal cavity, nano formulation, Nasal mucosa, NB System

INTRODUCTION

A novel approach for delivering medicinal compounds straight from the nasal cavity to the brain, the nose-to-brain drug delivery device is a game-changer in research on drugs.[1] This new approach makes use of the nasal canal's specific and intricate structure, as well as its special connection to the brain through the olfactory and trigeminal nerve pathways.[2] By overcoming the difficult blood–brain barrier (BBB), this delivery method makes it possible to directly distribute medications to certain brain regions, which is a significant challenge for conventional drug administration. [3]

Numerous neurological conditions, including brain tumors, Parkinson's disease, and Alzheimer's, could be effectively treated with this approach. A major development in the field of neuropharmacology is the non-invasive feature and the capacity to precisely and locally distribute medications. [4]This method has the potential to improve therapeutic outcomes, lessen systemic side effects, and meet unmet medical requirements in the realm of neurological therapeutics in addition to improving drug delivery.[5] The nose-to-brain method of delivery has a chance to significantly revolutionize the field of neurological treatments, as evidenced by the convergence of anatomical knowledge, pharmaceutical developments, and precision treatment procedures. [6]

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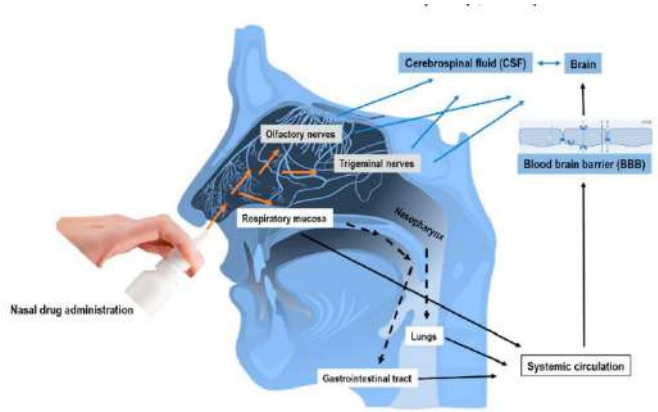

Figure no 1.1. mechanism of nose to brain delivery

Advantage:

Improved the bioavailability

In order to overcome biological barriers to improve the delivery of drugs into their nervous system (CNS), it is essential to carefully use tiny carriers for delivering drugs via the nasal cavity (nose) to the brain.[7] In terms of drug encapsulation, stability, and targeted distribution, nanocarriers—including nano formulation—offer a number of advantages. Because of their small size, they may be transported across the nasal mucosa with more effectiveness, increasing surface area contact and maximizing medicine absorption. By protecting drugs from enzymatic degradation, decreasing drug breakdown or elimination, maintaining drug stability, and enhancing drug solubility, nano formulations help address[8] challenges brought on by the physicochemical properties of specific pharmaceutical actives. Furthermore, it is possible that these carriers are engineered to possess mucoadhesive properties, which boost their capacity to adhere to the nasal mucosa for an extended duration and enable the continuous release of medication with an enhanced therapeutic response[9]. By directly absorbing the nanocarriers into the bloodstream from the nasal respiratory epithelium, via the trigeminal nerve's route, or via lamina propria adsorption from perivascular & lymphatic regions, the circulatory pathway serves as an indirect way of nose-to-brain distribution.[10] Vascular paths require the nanocarriers to first reach the nasal cavity and then endure enzyme-mediated and mucociliary clearance-mediated removal processes. The carriers then traverse the blood-brain barrier to enter the systemic circulation and the brain parenchyma. But being able to cross the blood-brain barrier does not imply a carrier must be directed to the[11] BBB immediately entering the systemic circulation. Generally speaking, concentration, particle size, surface potential, surface functionalization, and other surface characteristics like lipophilicity are thought to affect how well nanoparticles are absorbed by cells.[12] Based on electrostatic interactions, mucoadhesion, permeation augmentation, and brain targeting through a particular absorption process, the efficacy for nano formulation at the bio border may be distinguished. These variables affect nose-to-brain transport by guiding the drug via intricate and constrained routes of transport via the nasal cavity into the bloodstream to the central nervous system.[13] Therefore, choosing the best nanocarriers is crucial to overcoming formulation and transport of drugs problems in systemically nasal or nose-to-brain medication delivery. Generally speaking, the physical properties[14] When choosing a nanocarrier, consider the drug's potency, stability, pharmacodynamics, and mode of action. According to descriptions, the form of the nanoparticles is important for their absorption into the bloodstream after being administered intranasally.[15] In nose-to-brain administration, nanoparticles less than 200 nm are thought to be appropriate. Furthermore, the degree of drug transportation from the nasal cavity to the circulatory system can differ significantly, mostly depending on the availability of effective formulations & carriers, ranging from nearly full absorption to less than 1% of the targeted dose.[16] The enhanced drug delivery mechanism has the ability to improve drug absorption by the brain and reduce systemic side effects by lowering the dose. This focused strategy demonstrates how nose-to-brain medication delivery systems based on nanoparticle formulations can transform the treatment of neurological disorders by increasing bioavailability and reducing systemic effects[17].

Decrease the side effect of systemic:

Imagine administering a novel medication through the nasal route to the central nervous system (CNS) using an enhanced nose-to-brain delivery device. Because systemic medications can permeate the entire body,[18] they can cause serious side effects. But this new method targets the brain exclusively, avoiding systemic circulation and minimizing drug exposure to other tissues and organs. Applied in nose-to-brain drug delivery systems using nanocarrier technology[19], the customized delivery approach offers an advanced method to reduce systemic drug exposure to a large degree and to lessen negative effects on peripheral tissues and organs[20]. Using the special qualities of nanocarriers, like liposomes and nanoparticles, this method allows for targeted drug delivery to the nasal mucosa. In doing so, it avoids both the BBB & the circulatory system, which lowers the drug's maximum overall exposure. With less chance of adverse reactions for peripheral organs and tissues,[21] therapeutic efficacy with lower dosages becomes possible by the targeted & localised transfer to the central nervous system. Nanocarriers' small size facilitates their effective passage through the nasal mucosa, and their regulated release mechanisms help maintain drug levels in the brain over time. As a result, this customized delivery method significantly reduces the possibility of unfavorable side effects in peripheral tissues[22], that not just improves effectiveness in neuro pharmaceutical treatments yet also solves a crucial problem. As a result, patients might experience fewer systemic side effects, such as digestive disorders, liver damage, and cardiovascular problems. By lowering off-target effects & system exposure,[23] this method enhances the acceptance and security of medications. Nose-to-brain delivery devices increase the security of treating brain diseases by maximizing therapeutic efficacy and minimizing systemic side effects.[24]

Quick action of onset:

The goal of nose-to-brain delivery of drugs devices' quick start of action is critical for treating acute neurological disorders. Nano-formulations like liposomes, which take advantage of the direct nasal route to the central nervous system, are essential for obtaining rapid therapeutic effects[25]. Drugs can reach the brain faster due for the nostril mucosa's natural rapid absorption, which also avoids the blood-brain barrier and systemic circulation. This accelerated delivery enables a more rapid commencement of pharmacological activity, that is crucial in curing illnesses where rapid action is required.[26] The nanocarriers' small size and unique formulations make them more adept at navigating the nasal passages, guaranteeing a quick and focused drug delivery for better patient outcomes in acute neurological circumstances.[27]

Non-Invasive Route:

Patients in the early stages of Parkinson's disease and require non-invasive, patient-friendly therapy are best served by a focused nose-to-brain delivery device. The non-invasive nasal route is used in this innovative technique to provide the medication. The drug enclosed in nanoparticles successfully penetrates the nasal mucosa and reaches the brain.[29] This non-invasive method is practical and offers patients a more comfortable and easy administration route. This approach increases patient approval and compliance via doing deal of injections & surgeries, particularly in the case of chronic conditions where long-term treatment adherence is critical.[30] The non-invasive nature of the nasal delivery system eases patients' concerns and discomforts, making therapy more enjoyable. This non-invasive nose-to-brain delivery device, which delivers medicinal substances directly to the brain in an easy, pleasant, and patient-centred way, has the potential to change therapy for neurological diseases.[31]

Targeted Administration

By addressing the brain through the nasal cavity, nose-to-brain medicine administration avoids the BBB. Targeted administration delivers medications to the cerebral cortex via liposomes or nanoparticle base nano formulation. To attach to receptors or transporters on nasal mucosa, nano formulation can be surface-modified using ligands.[32] This targeting enhances the uptake and distribution of drug-loaded nanoparticles via the nasal epithelium to target brain regions. Nanoparticles can be coated by researchers with ligands that bind to receptor on the nasal epithelium. Through receptor-mediated endocytosis, nanoparticles can penetrate cells and pass through the nasal epithelium into the brain.[33]

Challenges:

Drug Attributes

The characteristics of medications present significant challenges to nose-to-brain drug delivery systems' effectiveness. The size of molecules is important

because molecules with high molecular weights usually have trouble passing through the nasal mucosa, which prevents them from being absorbed and then transported to the brain. [34]Furthermore, a drug's ability to pass through the epithelium of the nose relies on a balance of its desire to water and lipids. Strong water-affinity drugs may have trouble getting through lipid-rich barriers, while lipid-affinity drugs may have trouble because of their low water solubility, which may affect how well they are absorbed. There are additional difficulties related to the chemical stability of medications in the nasal environment. When medications come into touch with nasal enzymes or the acidic pH of the nasal cavity,[35] they may break down, which decreases their effectiveness during brain transportation. The amount of active medication that is available for the brain to absorb may also be reduced by the metabolism taking place in the nasal mucosa. The problem is made worse by the nasal mucosa's efflux transporters, which vehemently expels medications, limiting their absorption and decreasing the possibility that they will reach the brain[36] in sufficient quantities. Moreover, the amount of medicine that can be effectively supplied by the dosage limitations based on the size of the nasal cavity or formula limits may affect the route through the nose. Physicochemical properties and stability are considered while developing ways to address these problems[37]. Additionally, limitations imposed by nasal architecture and physiology are addressed. Advances in nanotechnology, carrier systems, and chemical modifications are being studied by researchers to boost drugs delivery systems that use noses to target the brain. Optimizing medication absorption, stability, and transport is the aim of this strategy in order to achieve more successful brain targeting.[38][39]

Nasal Architecture

One of the biggest challenges in developing reliable medicine delivery systems from the nose to the brain is the variation in nasal shape among individuals. The intricate structure of the nasal canal, encompassing variations in mucosal lining thickness, surface area, and airflow patterns, impacts the dependability and efficiency of medication uptake and cerebral distribution.[40] Nasal architectural variations may significantly affect how medications are distributed and retained in the nasal cavity. Variations in the mucosal lining thickness and shape in various regions of the nasal cavity may affect the rate at which medications are absorbed, potentially affecting the drugs'[41] accessibility within the body or their ability to reach the brain. Also, anatomical differences such nasal septum deviations, nasal polyps—soft growths on the inside that line the nose—or other abnormalities may also make it more difficult for drugs to be distributed and absorbed. These structural variations could lead to an unequal drugs dispersion or impede the process drug formulas interact with the tissue in the nose, which may impact the way a medication is absorbed and then delivered to the brain. Developing drug delivery devices that can adapt to the numerous anatomical variations in each person's nasal tube is essential to overcoming this challenge. Customized formulations or systems are necessary to improve medication deposition and absorption while accounting for these anatomical differences. [42]

Formulation Stability

The stability of the formulation plays a significant role in nose-to-brain pharmaceutical delivery systems' efficacy. The nasal environment presents difficulties in maintaining the stability of drug formulations intended to targeting the brain due to changes in pH, activity of enzymes, & mucosal turnover.[43] Epoxide hydrolase, aldehyde hydrogenase, carboxylesterase, glutathione S-transferase, and other enzymes present in the nasal mucosa may break down nose drug formulations enzymatically, potentially leading to the metabolism of the active ingredients in the drug.[44] Furthermore, formulations that are sensitive to pH changes may not be as stable due to the nasal cavity's pH shifts, which can vary from slightly acidic to neutral.[45] This could potentially compromise their efficacy throughout their journey to the brain. The mucosal turnover rate creates more complexities because the nasal canal's quick clearing mechanisms might shorten the time that formulations absorb. The formulation's ability to adhere to the nasal mucosa may be hampered by the rapid turnover rate[46], which could have an impact on the medication's retention and absorption. Formulations must be particularly designed to withstand the ever-changing conditions of the nasal environment in order to ensure that medications remain stable and intact throughout the duration of their journey through the nasal cavity. By strengthening the formulation's

stability,[47] the drug's availability and efficacy for a smooth journey from the nose to the brain remain intact. It is done through applying of protecting additives, encapsulation methods, or chemical changes.[48] Nanoparticles larger than 100 nm are inappropriate to intraneuronal pathway absorption due the size of them is bigger that the size of the axons present within filia olfactoria. In summary, compositions based on nanotechnology are most suited for preserving the medication.[49]

Delivery to Target Sites

Drug delivery systems focusing on the nose-to-brain route face substantial challenges when it comes to delivering therapeutic chemicals to specific brain regions. Drugs must be administered precisely and selectively to treat neurological illnesses because of the complex structure of the brain,[50] which is made up of several locations and barriers. Due to the intricate structure of brain tissues and problems related to the blood-brain barrier, medicines cannot be delivered to specific parts of the brain by the nasal route. The blood-brain barrier (BBB) is crucial for protecting the brain[51], but it also poses a serious challenge since it restricts things, including medications, from entering the brain. The barrier that prevents many medications from efficiently reaching particular parts of the brain at therapeutic doses is quite tough for them to penetrate.[52] Additionally, the effective delivery of medications for certain neurological disorders in the brain requires surmounting barriers that transcend the blood-brain barrier. Further layers of intricacy arise from the occurrence of variations in brain design, an array of neuronal routes[53], or the need for reaching regions located deep in the brain. Getting medications to the right places in sufficient amounts to produce therapeutic effects is the main challenge. In order to address these problems, delivery systems that can precisely target particular regions of the brain while avoiding or surpassing the BBB's barriers must be[54] developed. Because of their small size, nanoparticles can interact with the nasal epithelium more effectively, which improves medicine penetration across mucosal barriers. Drug absorption is improved and drug transportation to the brain is accelerated by his enhanced touch[55]. To increase a drug's capacity to penetrate the brain and interact with certain targets, scientists employ strategies including surface modifications, nanocarriers with specific ligands, or innovative formulations. These modifications enhance the nanoparticles' apprehension of receptors or transporters in the nasal mucosa, hence optimizing their absorption and subsequent conveyance to targeted brain regions. The challenges of precisely delivering medications to the intended brain regions must be addressed and solved in order to fully realize the potential of nose-to-brain drug delivery systems in the treatment of neurological diseases.[56]

Direct Transport of Drugs in Solution from Nose to Brain

Drug molecules are transported via the nasal mucosa to get to the brain through the nasal passages, bypassing the blood-brain barrier and being absorbed into the circulation. By avoiding the systemic circulation process, this channel allows medications to enter the nose & enter the cerebral cortex right away. Drugs that are administered via the nose as suspensions and liquids might readily come into touch the delicate mucosa of the nose.[57] Because the nasal epithelium is a permeable barrier, certain medications can pass directly through it and into the bloodstream. Such physical properties as molecular weight, lipophilicity, and solubility affect the drug's capacity to pass through the epithelium of the nose and enter the brain. Additionally, the presence of transporters or receptors in the nasal mucosa may facilitate the direct delivery of certain medications to the brain.[58]

By delivering the medication exclusively to the brain, enhancing site-specificity, and preventing systemic adverse effects, the intranasal mode of administration increases the medication's effectiveness[59]. However, due to the nasal epithelium or the requirement to bypass the blood-brain barrier, certain medications may face challenges when attempting to utilize this channel. Optimizing this direct transport channel for optimal medication administration from the nose to the brain is the goal of efforts that include formulation modifications or customized drug designs.[60]

Nano formulations for Nose-to-Brain Delivery

Nanogels for Nose-To-Brain Delivery

A versatile and effective drug delivery method for administering drugs through the nose to the brain is nanogels. They have a unique set of properties, such as being highly water-soluble, biocompatible, and able to contain a wide variety of medications. The production of the nanoscale hydrogel structures, which typically have diameters between 10 and 200

nm, involves chemically joining polymer chains. Through this procedure, pharmaceutical chemicals are efficiently captured by a three-dimensional network. Nanogels provide a number of advantages[61] when it comes to the transportation of materials and the nose into the head, including extended release, preventing the drugs inside of deterioration, or the ability to move things directly to the central nervous system. When creating nanogels to carry drug via a nose to our brain, a number of important factors need to be carefully considered. It is crucial to select the appropriate polymers, preferably biocompatible and mucoadhesive ones that can lengthen[62] the time in contact with the nasal mucosa. Furthermore, the incorporation of both hydrophilic and hydrophobic monomers allows for the trapping of a diverse range of drugs, catering to different therapeutic needs. It is possible to modify a nanogel's size, charge, or surface attributes to improve how well it interacts with the nasal mucosa, which would make medication delivery more effective. Biocompatible and mucoadhesive polymers like chitosan and polyethylene glycol (PEG) are frequently used to create nanogels[63]. Because of its cationic properties, chitosan may interact with the nasal mucosa, which is negatively charged, allowing it to stay in the nose for a longer amount of time. PEG increases the nanogel's resilience and water-attracting qualities. The networked structure of the nanogel protects the fragile nerve-growth factor, preventing degradation during transportation. Its mucoadhesive properties enhance the nanogel's interaction with the mucosal surface, as its small size facilitates efficient absorption into the nasal canal. When taken by nasal, this nerve-growth factor-containing nanogel may successfully penetrate the BBB[64] and reach the brain parenchyma. Because of its sustained release properties, the nanogel is a good option for conditions including brain diseases that benefit from continuous medication delivery. Numerous medication classes have been developed as nanogels and tested for their effectiveness in treating a variety of illnesses, such as cancer, Alzheimer's, schizophrenia, migraines, hypertension, and migraines.[65]

Mesoporous Silica Nanoparticles (MSNs) for Nose-to-Brain Delivery:

Mesopores, a large number of pore channels with the capacity to absorb molecules, exist across the pores of MSNs, which resembles a honeycomb. MSNs' vast size, adaptable pore sizes, & tolerance to organisms caused attention to the realm of medication delivery. Targeted distribution[66] of medicinal medicines to different organs has been accomplished through the use of MSNs. It was shown that ponatinib-loaded molecular-gated mesoporous nanoparticles may improve brain delivery in glioblastoma patients by intranasal administration. The created formulation was found to be safe for BBB cells and to effectively transport a higher concentration of the medication into the brain.[67] CNS inflammation is a hallmark of multiple sclerosis. It is challenging to get anti-inflammatory medications straight to the affected areas of the brain. MSNs may serve as drug carriers for medications intended to reduce inflammation in MS patients. Their unique qualities allow for controlled drug release, which may make it easier for the therapy to reach parts of the brain affected by inflammation in multiple sclerosis. MSNs have the capacity to enhance the nasal path for hydrophobic phytochemical move to the brain. Corticosteroids may be better targeted to the brain by using MSNs to transport them through the nose.[68] By lowering CNS inflammation, this may have a focused anti-inflammatory effect while minimizing systemic side effects. To validate the safety, efficacy, and precise mechanisms of MSNs in medicine delivery systems from the nose to the brain for neurological illnesses, however, a great deal of research is needed.[69]

Carbon Nanotubes (CNTs) for Nose-to-Brain Delivery:

Because of their unique structure and properties, CNTs hold promise for the administration of medications. Their precise use in nose-to-brain delivery systems is still being researched, though. By diffusing across the glial cytoplasmic membrane or by going via the nasal cavity and nerve terminals, these fibers can get beyond the blood-brain barrier. CNTs may be able to pass through the BBB or help with transportation via olfactory pathways because of their unique structure and huge surface area. After a stroke, targeted delivery of neuroprotective peptide-loaded functionalized carbon nanotubes (CNTs) may be made easier to the afflicted regions of the brain**.**[70] Neuroprotective peptides can lessen brain damage and speed up the recovery process following a stroke. However, the BBB makes it difficult for getting drugs to the brain. Owing to their special properties, CNTs may be employed to transport the peptides to boost

their delivery to the brain following a stroke. Research conducted on fish & rats has demonstrated the nose's sensory neurons have a capacity to absorb and transfer tiny carbon atoms to the brain.[71] To deliver neuroprotective peptides, scientists have adapted carbon nanotubes (CNTs) and created a nasal drug delivery apparatus. A study has shown that CNTs have the ability to penetrate the brain by intranasal administration, primarily targeting the limbic region. Furthermore, they demonstrated that electroconductive multiwalled carbon nanotubes might possibly alter a critical neurotrophic factor to have neuroprotective effects and reduce gliosis associated with neurodegeneration. Improved targeting of neuroprotective peptides to the brain by the use of CNTs as nasal delivery may help maintain neurons following a stroke and reduce brain damage, which would speed up recovery and lessen neurological deficits. This theoretical situation highlights the potential application of CNTs as delivery systems for neuroprotective peptides in the management of stroke. [72]

Nanosuspensions (NSs) for Nose-to-Brain Delivery

NSs, or colloidal fragments for drug-like parts, stabilize with the use of polymers or surfactants. Stabilized medication particles distributed in a liquid carrier make up the nervous system (NS). By doing this, medications become more stable and soluble, which keeps them from degrading in the nasal cavity. Through improved drug solubility and dissolution rate, the NS facilitates absorption of medicines through the nasal mucosa, thus boosting brain targeting. Drug transmission is aided via the small size of particles and the stability provided by surfactants or polymers. enhancing the way that medications are delivered to the brain. When NSs are used for nasal administration, the brain's concentration of clozapine is increased.[73] This might potentially enhance the medication's therapeutic advantages when it comes to treating symptoms associated with schizophrenia. To treat Neuro-AIDS, NSs were created using a mix of antiretroviral drugs, and their intranasal delivery capability was assessed. Based on a recent study, the optimal strategy of neuro-AIDS treatment could mean giving efavirenz NS via the nose to the brain. An NS-based in situ gel that was the result of another experiment proved to be a useful and effective nasal preparation for the administration of breviscapine. Additionally, research has demonstrated that ruby NS-containing ionic-sensitive to gel form increases nostril mucosal porosity & cavity residency duration.[74]

Nanoemulsions (NEs) for Nose-to-Brain Delivery

NEs have been studied as a way to deliver various medications to the brain through the nasal route for a range of neurological therapies. NEs are water-based solutions containing microscopic oil droplets dispersed throughout them, which form a colloidal system. They have demonstrated a great deal of promise as efficient medication delivery systems from the nose to the brain.[75] Since NEs are durable and small, they make it easier for medications to go via the olfactory pathways, which increases the amount of active ingredients that enter the brain. Increased solubility, absorption, and bioavailability are reported when lipophilic medicines are highly encapsulated in o/w-type NEs, while enzymatic degradation is minimized[76].

A careful choice of elements is required to the formulation processes of NEs. These components include cosurfactants as ethanol or propylene glycol (PG), biodegradable oil such medium-chain fatty acids, or surfactant like polysorbates or sorbitan ester. The proportions of these elements are adjusted to achieve stability and nanoscale droplets. To improve droplet size accuracy, high-energy methods including homogenizing at high pressure and ultrasonication are employed. Parkinson's disease is mostly treated with levodopa; nevertheless, its usefulness is limited by its capacity to reach neurons or its pace or metabolism. An approach was developed to encapsulate levodopa in NEs so as to offer a nasal dosage form with strong thermal & antioxidant stability. The researchers examined lecithin and Cremophor EL levels, as well as key parameters related to them, using response surface technique study. They found that lecithin and Cremophor EL stabilize the levodopa-loaded NE, while RSM is an effective tool to enhance it NE formulations.[77]

Polymeric Micelles for Nose-to-Brain Delivery

Amphiphilic molecules, which possess both hydrophobic and hydrophilic areas, create micelles when they assemble in a solution. They are created when amphiphilic molecules spontaneously arrange themselves into core-shell configurations in fluids containing water. Due to their many advantages, including as improved penetration across biological

barriers, thermodynamic stability, simplicity in formulation, & Newtonian flow characteristics, micellar formulations have particular appeal for administration of drugs.[78] These advantages make micellar nano systems versatile while under investigation for non-invasive medication delivery techniques such as nose-to-brain administration. Polymeric micelles have demonstrated potential in aiding the passage of medications from the nose to the brain. Sipos et al. investigated the potential of utilizing mix polymer micelles for treating Neurological illnesses by delivering dexamethasone via the nose-to-brain route. [79] A 14-fold improvement in water solubility and good dissolving profiles under nasal and axonal circumstances resulted from the developed formulation's low Z-average and strong surface polarity. Permeability on polarized brain lipids extraction has been shown in vitro, and diffusion experiments verified effective transit across the nasal mucosa because of the substance's potent mucoadhesive qualities. Similarly, a polymer micelle composition filled via meloxicam has been shown for administration by nose to brain tissue for the treatment of neuroinflammation. With nose-to-brain administration, the proposed formulation demonstrated a considerable improvement in drug dissolution rate and nasal permeability, suggesting potential for successful treatment of neuroinflammation. Lurasidone's development into mixed polymeric micelles for intranasal administration was the subject of [80] another investigation. In comparison to pure lurasidone, the produced formulation exhibited desirable properties and enhanced drug-targeting efficiency, suggesting the potential of micelles for efficient nasal delivery of medication to the brain. Utilizing polymeric micelles, a thermosensitive gel delivery method of rotigotine was created to increase brain-tissue concentration[81]. When as opposed to iv therapy, the new formula exhibited higher means residency time & better product variation in brain zones. Through the creation of nano-micelles modified with peptides that penetrate cells, the possible use of micelles as a delivery system for siRNA was examined. The intriguing findings show that the produced micelles boosted brain delivery, most likely as a result of better transport via several channels. [82]

Dendrimers for Nose-to-Brain Delivery

Dental dendrimers are intricate polymers with unique structures in which medicinal active ingredients are physically or chemically bonded to the end functional units found in dendritic molecule. Dendrimers have unique surface functionalities that allow surface modifications to improve brain targeting by delivering drugs in a focused manner. due to their unique characteristics, it can help in the flow of drugs via the nose to the brain. The effects of varying generation & concentrations of polyamidoamine dendrimers[83] on the nasal absorption of fluorescein isothiocyanate-labelled dextran, which, calcitonin, & glucose were investigated in rat studies. Researchers looked at the potential therapeutic benefits of intranasal delivery of siRNA that targets high-mobility group box-1 in the brains of postischemic rats. This biodegradable polyamidoamine dendrimer was administered nasally to rats who had brain ischemia. It considerably decreased the amount of the brain infarct by as much as 43%, allowing the animals to recover from their neurological and behavioral impairments.[84] This demonstrates the great potential of nasal dendrimer-based gene delivery to the brain. In a further investigation, researchers looked at the efficacy of an intranasal delivery system based on dendrimers to target the brain. It was discovered that the created in situ gel significantly improved the nasal transport efficiency of the nanotechnology and generated more of the drug within the brain, suggesting its potential for nose-to-brain administration. Additionally, investigations have been conducted to evaluate the in vivo impacts of nasal polyamidoamine dendrimer intake on neurological biomarkers in the mouse brain. The findings suggest that, after being delivered intranasally, the dendrimers may enter the brain via systemic circulation or the olfactory nerve[85]. In addition, they propose that dendrimers could influence neuronal functions via altering the gene expression of the brain-derived neurotrophic-factor signalling pathway after just one intranasal dose.[86]

Nanostructured Lipid Carriers (NLCs) for Nose-to-Brain Delivery

When it comes to nose-to-brain medication delivery, NLCs—a complex class of lipid-based nanoparticles—have attracted attention due to their improved stability and drug-loading effectiveness. All industrial needs, such as quantification, scalability, affordability, and fundamental technology,[87] are

satisfied by NLCs. Regulation-wise, NLCs are also suitable as they involve biocompatible and recyclable lipid & surfactants. Because of the lipophilic features, NLCs are better likely to dissolve in a lipid bilayer of nasal epithelial cell membranes than free medicines.

Moreover, intercellular gaps between olfactory cells are rapidly traversed by nanoparticles possessing abundant lipophilicity. Surfactants are added for NLCs so as to facilitate the opening of tight junctions between epithelial cells, which increases drug permeability. Studies have shown that an outer layer of polyethylene glycol 25 stearate stops P-glycoprotein efflux at the membranes of cerebrovascular endothelial cells by increasing the concentration of drugs in the brain. Substance retention in the nasal cavity can be improved by dispersing pharmaceuticals in hydrogel systems or covering them with mucoadhesive polymers like chitosan. These methods further improve medication retention when combined with NLCs. When it comes to reducing the digestive process of drugs in nasal mucus, NLCs outperform conventional solution-based dosing forms[88]. Crucially, the safety profile of NLCs amply validates their viability for transport from the nose to the brain. There have been reports on the probable toxicity of NLCs & the potential in inhalation of diazepam-loaded NLCs. In essence, a perfect NLC formulation for efficient brain delivery was produced by using a QbD method to carrier development. According to the study's findings, nose-to-brain administration worked best with the negatively charged NLCs it created. In a different investigation, NLCs carrying the antiviral drug efavirenz were created and tested for nose-to-brain transport to the brain. Based on their results, it was proposed that the best way for directing the drug to the brain is using the right lipid carriers and employ additives strategically.[89] Additionally, the potential of NLC-containing in situ gel was reported. With greater systemic and cerebral bioavailability than asenapine solution, the intranasal administration of asenapine via glycol chitosan-coated NLCs demonstrated encouraging outcomes. Good biocompatibility was shown by the produced NLCs, which may have better pharmacokinetics and safety if utilized as an intranasal delivery route. Rats served to evaluate the efficacy of NLCs in providing neurons has astaxanthin, an antioxidant has neuroprotective and anti-inflammatory qualities. It was shown that the created NLCs improved cholinergic neurotransmission and greatly decreased oxidative stress,[90] neuroinflammation, and apoptosis if administered intranasally. Similar investigations were also published by other researchers, showing that NLCs have the ability to carry several active ingredients to the brain through nose-to-brain delivery.[91]

Solid Lipid Nanoparticles (SLNs) for Nose-to-Brain Delivery

Because of their potential to distribute medications via a variety of pathways, including the nose-to-brain route, SLNs are being researched more and more. This is so because SLNs have a reputation for being stable, biocompatible, and capable of encapsulating a variety of medications.[92] Sumatriptan was utilized to show the possibility of using SLNs to deliver activities to the brain. through the nose-to-brain pathway. The synthesized SLNs showed a spherical shape and twelve hours of continuous drug release. Histopathology investigations verified the nasal mucosal's stability following treatment, whereas ex vivo experiments showed rapid penetration throughout the mucosa. A solution to the problem of drug delivery for the treatment of Alzheimer's disease is offered by SLNs, which improves the way that medications reach the brain.[93] Asiatic acid-loaded solid lipid nanoparticles (SLN) were created in one research with the intention of increasing the bioavailability via the intranasal route. The intranasal administration of drug-loaded SLNs proved to boost memory and learning deficits caused by amyloid-β1-42. Asiatic acid also decreased oxidative stress and inflammatory marker levels across the brain, plus stimulation of microglial and astrocyte reactivity. Researchers have used SLNs containing antidepressant it to create a nasal drug delivery technique. When compared to oral delivery, modified particles showed notable benefits to greatly improved relative accessibility, AUC, or plasma level. They also successfully showed brain targeting, suggesting that this strategy may be used to increase agomelatine's therapeutic efficacy. [94]

Likewise, SLNs were studied as a medication delivery method to improve rosmarinic acid's brain-targeting efficacy when administered intranasally. The SLN therapy was found to considerably alleviate behavioral impairments and decrease oxidative damage in the rat model of Huntington's disease. With

a brain drug concentration of 5.69 µg and acceptable kinetic real estate, nose delivery of SLN did, in fact, provide substantial therapeutic benefits as compared with intravenous treatment.[95] The oral route was used to administer haloperidol, another medication, to the brain. When pharmacokinetic tests in rats were conducted, the results showed that the brain concentrations of haloperidol with SLNs were much greater than those via various administration ways. Meanwhile, in vitro emission experiments showed sustained release. The ability of SLNs to generate high local concentrations in the brain when the levofloxacin/doxycycline combination is administered intranasally was investigated.[96] Pharmacokinetic analyses demonstrated that the SLN-based combination significantly raised brain levels & AUC for rats as compared with nasal free solutions. The enhanced formulation showed a high percentage of drug-targeting & direct transport efficiency, indicating that this method may be used to deliver medications to the brain. Another attempt was made to enhance brain delivery by intranasal dosage, so n-propyl gallate was added to the hydrogel-based SLN formulation.[97] According to the study, hydrogel-based SLNs can improve mucosal residence duration and security, that can enhance nasal intake and present a viable method for intranasal administration. A SLN in in situ gel filled with piribedil was created and assessed using the nose-to-brain route. Pharmacokinetic analyses showed that, in comparison to intranasal solution, the prepared gel significantly reduced plasma levels at 2.3 times or increased concentrations of drugs in brain tissue at around 4-fold. Additionally, with a direct-transport % value of 27%, this gel method demonstrated effective direct nose-to-brain [98] absorption, underscoring its potential for improved medication delivery to the brain. It was revealed that BACE1siRNA could be effectively transported from the nose to the brain using an SLN-based delivery method, which might be used to treat Alzheimer's disease. According to the study's findings, siRNA released from SLNs was more effectively transported across a Caco-2 monolayer, indicating the system's possible effectiveness.[99]

Liposomes for Nose-to-Brain Delivery

Because liposomal formulations are non-toxic, biocompatible, and capable of delivering both hydrophilic and hydrophobic compounds, they have become more popular. As flexible lipid-based nanoparticles, liposomes may improve the delivery of drugs from the nose to the brain. This is explained by their ability to target certain parts of the brain, include an array for drugs, & interface with other biological processes. Ex vivo studies using sheep nasal membranes for drugs (lactacrine and lamotrigine) showed increased nasal permeability from liposomal formulations, suggesting their usefulness in nose-to-brain drug delivery. They also showed that, when delivered through liposomal preparations, glial-derived neurotrophic factors reached its maximum levels in the brain's olfactory bulb region within one hour of administration.[100] The H102 liposomal formulation delivered intranasally showed slower systemic absorption than when supplied intravenously because it couldn't penetrate the blood-brain barrier. When liposomal drugs arrived through the nose, brain levels of each of hydrophilic & lipophilic drugs was significantly less compared to that for hydrophobic molecule[101]. Their effective absorption via direct and indirect cerebral transport channels is responsible for this. Conversely, hydrophilic therapeutic molecules with molecular weights under 1000 Da can be easily injected intraperitoneally into the brain using liposomal formulations. For example, when pyridine-2-aldoxime methochloride was given to killed rats using intranasal liposomal preparations higher values in acetylcholine ester activation were seen. Rats given liposomal versions of donepezil showed longer half-lives, increased AUC and Cmax levels in the brain and plasma, and improved brain & systemic permeability[102]. When delivered intranasally via liposomal formulations, quetiapine fumarate showed noticeably greater brain levels for a longer duration than when the drug was free; this difference may have been caused by enhanced brain absorption by endocytosis. All of these experiments demonstrate how well liposomal formulations, which include hydrophilic & hydrophobic substances, can carry molecules of medicine through the nasal cavity to the brain. However, while choosing materials in the liposome analysis, it's important to keep in mind physical features including length & area charges. These elements may affect nasal residence duration and mucoadhesion, which may have an effect on the method by which the drug molecules are subsequently absorbed by the brain. As nano formulation,[103] liposomes can be utilized in nose-to-brain drug

delivery systems to improve the accuracy, potency, and security of medications for neurological conditions including schizophrenia. Olanzapine is a medication used to treat schizophrenia, a mental illness marked by irrational beliefs and actions. Olanzapine may be difficult to take orally due to factors such poor absorption in the blood and systemic adverse effects. But the liposomal formulation that was created offered promising possibilities for olanzapine's nose-to-brain transfer during the treatment of schizophrenia[104]. Liposomal formulations are the most effective way to transport BBB-impermeable medications to the brain, according to one study on brain distribution. Combining the benefits of polymeric & liposomal particles, scientists developed gelatin nanoparticle encapsulating beta-fibroblast growth factor. After a week of through the nose of liposomal formulation containing bFGF, the results showed enhanced neurological in origin degree achieve or unplanned locomotor tasks, showing greater levels in growth factors in the hippocampus, cortex, and pallium parts of the cerebral cortex versus the infusion of remedies or liposomes of bFGF. Both polymeric nanoparticles and liposomes have benefits that these studies indicate.[105]

Innovative Drug Delivery Strategies

Nanostructured Lipid Carriers (NLCs): The benefits of solid nanoparticles of lipid (SLNs) & liposomes combine in nanostructured lipids carriers. They are made up of a lipid core with a nanostructured surface that can hold hydrophilic & hydrophobic drugs. NLCs show promise in nose-to-brain administration due to their enhanced stability, slow-release characteristics, or drug loading capacity.[106]

Polymeric Nanoparticles: Nasal to brain distribution of polymeric nanoparticles has been the subject of much research, especially those derived from biocompatible and biodegradable polymers like poly (lactic-co-glycolic acid) (PLGA). By encapsulating a variety of medications, preventing their breakdown, and promoting prolonged release kinetics, these nanoparticles can maximize therapeutic effectiveness.[107]

Intranasal Hydrogels: Large volumes of water or biological fluids may be absorbed and retained by hydrogels, which are three-dimensional networks made of hydrophilic polymers. With their extended duration of residency in the nasal mucosa, intranasal hydrogels improve medication absorption and enable sustained release. They can be designed to deliver medications in a regulated way, enhancing therapeutic results and bioavailability.[108]

Inorganic Nanoparticles: The distinct characteristics of inorganic nanoparticles, such as quantum dots or particles of silica, are being investigated for their potential in medication delivery. In order to increase their stability, biocompatibility, and precise targeting to brain areas through the nasal route, these nanoparticles can have their surfaces altered. Their durability and capacity to conjugate or encapsulate drugs provide innovative prospects for medicinal uses.[109]

Exosomes: The Exosomes are naturally occurring extracellular vesicles secreted by cells that have the ability to transfer biomolecules—including medications—between different tissues and cells. Targeting certain cell types or tissues, such as brain cells, engineered exosomes can be loaded with therapeutic cargo and altered. Therapeutic drugs can be delivered across the blood-brain barrier and focused brain delivery can be achieved with less immunogenicity when exosomes are injected intravenously.[110]

Combination Therapy Approaches: Nose-to-brain delivery can be improved by combining several the delivery of drugs methods, to as using hydrogels & nanoparticle and exosomes with surface-modified nanoparticles. In order to maximize drug release, target specificity, and treatment results for complicated neurological diseases, such combinations make use of the benefits for every form of technology.[111][112]

Novel Nanoparticle Formulations

- **Magnetic Nanoparticles**: By using external magnetic fields to direct and improve their passage through the mucosa of the nasal cavity to the brain, metallic nanoparticles (MNPs) give a unique benefit in nose-to-brain administration. To enhance brain intake, such nanoparticles may be surface-modified using aimed ligand & modified with therapeutic payloads. Using magnetic fields to deliver drugs more effectively allows for fine-grained control over the location and motion of nanoparticles inside the brain.[113]
- **Dendrimer-Based Nanoparticles:** Their nanoscale size facilitates penetration through the nasal mucosa and enhances transport to the brain;

surface modifications with ligands or peptides further improve targeting specificity and cellular uptake in brain tissues. Dendrimer-based fine particles may contain medicines in the inside or conjugate substances to the covering. These have lots of branch's polymers that have several functions or clear objects, thus being the perfect fit to therapeutic applications.[114]

- **Metal-organic frameworks (MOFs):** Are crystalline materials consisting of metal ions or clusters connected by organic ligands, creating high-surface-area porous structures. These nanoparticles can be designed to have controlled release properties in order to contain drugs in the pores. By preventing drug degradation, improving drug solubility, and enabling tailored delivery to brain tissues by surface modifications or functionalization with targeting ligands, MOFs may be advantageous in nose-to-brain administration.[115]

- **Hybrid Nanoparticles:** Multiple materials or architectures are combined in hybrid nanoparticles to improve drug delivery capabilities in a synergistic way. The benefits of lipid-based systems (biocompatibility, drug encapsulation, etc.) and polymer-based systems (controlled release, stability), for instance, can be combined in hybrid lipid-polymer nanoparticles. These nanoparticles are adaptable to a range of use in medicine and may be designed to optimize drug absorption kinetics, improve brain target precision, and minimize adverse systemic effects.[116]

CONCLUSION:

The field of nose-to-brain drug delivery while illustrating current advancements which highlight the cavity's anatomical characteristics, high permeability, and abundant blood supply, which enable quick drug absorption and onset of action and make this area a promising one for neurological therapeutics. In general, a number of considerations must be taken into account while creating nose-to-brain medication delivery systems. Nasal architecture, cleared mucociliary medication characteristics, formulation stability, targeting efficiency, etc. are some of the main issues with this drug-delivery strategy. In addition to solutions, a variety of alternative dosage forms, such as nanogels and nanocarriers, can be one of the substitute methods for more effective and safer nose-to-brain medication administration. Several studies have demonstrated that the dose that reaches brain tissue may be significantly increased with the appropriate nanocarrier. The future of cns treatments can be changed by improving an drug-distribution efficacy of these complex systems of delivery by targeting specificity. With varying levels of glory, many studies have tried to convert research data towards clinical settings. Still, not much has been done to optimize and improve dosage efficiency due to the freshness for this strategy and route of administration. Important obstacles are the restricted amounts that may be given, differences in the nasal structures of individuals the animals under study, Such can impact therapeutic results, necessitating the development for formulations and appropriate delivery systems for this route of administration in addition to overcoming the toxicity of nanoparticles in brain tissue & nasal mucosa.

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