A Review on Nose to Brain drug delivery using Nanoparticle

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Abstract: The delivery of medications to the central nervous system (CNS) is primarily regulated by the blood-brain barrier (BBB), a structure that prevents the passage of external substances from the bloodstream to the brain's extracellular fluid. Despite the current availability of drugs for neurological disorders affecting millions worldwide that are somewhat effective, they are linked with significant side effects from systemic drug delivery. Conversely, the ability of some medications to penetrate the BBB is hindered by their physicochemical characteristics, resulting in sub-therapeutic levels in their target tissues In this regard, the intranasal route, with its distinctive anatomical features, offers a promising avenue for delivering drugs to the brain. Nanoparticle based systems, in particular, have demonstrated remarkable ability to tackle the obstacles posed by the intranasal route and enable drug delivery to the brain while avoiding systemic distribution. This review addresses recent developments in the use of polymer, lipid, and inorganic nanoparticle les, along with drug nanocrystals, for delivering medications to the brain through intranasal administration. A typical discussion featuring positive perspectives and challenges of this method is also presented.

Keywords: Nanoparticle, Delivery from Nose to Brain, Blood-Brain Barrier, lipid based nanoparticles

I. INTRODUCTION

Neurological disorders rank among the primary causes of disability globally, greatly enhancing the pressure on healthcare systems. (1) One significant obstacle in managing these disorders is the administration of medications to the brain, resulting from the existence of the Blood Brain Barrier (BBB), the intricacies of brain activities, and issues regarding safety and toxicity. developing option to conventional techniques is nose-to-brain drug delivery, which presents various benefits compared to systemic administration.

These consist of minimizing systemic side effects, an improved side effect profile, noninvasive methods, faster onset of effects, and increased bioavailability in the Central Nervous System

Nose-to brain drug delivery circumvents the BBB by using neural pathways linking the olfactory epithelium, olfactory bulb, and trigeminal nerve, enabling direct transport to the brain. (3) This innovative method is attracting interest in drug research since it allows for the direct transfer of therapeutic substances from the nasal cavity to the brain, bypassing the obstacle created by the BBB. (4)(5)

Benefits:

1) The IN route offers a non-invasive or minimally invasive way to deliver medication to the CNS, proving more effective than both intravenous (IV) and oral methods.

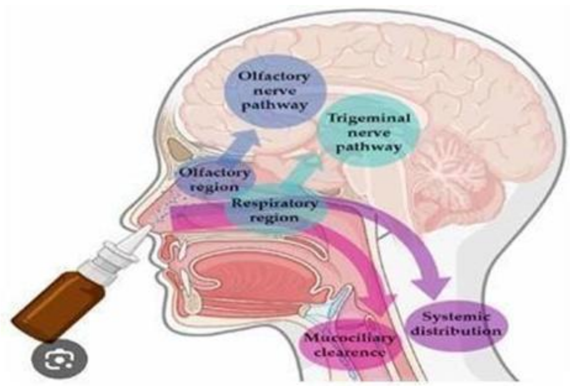
This straightforward pathway to the CNS can bypass the BBB while minimizing systemic side effects.

For other parenteral routes and oral administration, medications must first overcome multiple barriers to enter systemic circulation and subsequently penetrate the BBB to access the CNS.

Additionally, the IN route bypasses hepatic first-pass metabolism and the breakdown of drugs in the gastrointestinal tract, serving as an alternative method for parenteral administration, particularly for biopharmaceuticals (such as proteins and peptides).

Challenges:

Administering drugs from the nose to the brain poses various difficulties, mainly because of the specific structure and function of the nasal passages, along with the brain's protective barriers. Some of the main challenges include:



Nasal Mucosa and Drug Uptake: Restricted Surface Area: Although the nasal mucosa is well supplied with blood vessels, it has a relatively small surface area for drug uptake, restricting the quantity of drug that can be absorbed simultaneously.

Mucociliary Clearance: The nasal cavities possess an inherent system to eliminate foreign substances, including medications, through cilia and mucus. This can lessen the duration drugs are in contact with the mucosal membranes and lower absorption efficiency.

Degradation by Enzymes: The nasal cavity houses enzymes that can break down drugs prior to their entry into systemic circulation or the brain.

Blood-Brain Barrier (BBB):

Selective Permeability: The blood-brain barrier is an extremely selective barrier that safeguards the brain from harmful agents while also restricting the access of therapeutic medications. Surmounting this obstacle is among the primary difficulties in delivering drugs to the brain, even with intranasal administration. Requirement for Tailored Formulations: Medications must be uniquely created or modified to facilitate their passage across the BBB,

Necessitates employing carriers or altering the drug itself (e.g., Routes for Nasal to Brain Drug Delivery System:

Pathways for Nose to Brain Drug Delivery System:

Olfactory Pathway (Transcellular Route):

Direct access via olfactory neurons: The olfactory area in the nasal cavity serves as a direct pathway to the brain. Olfactory sensory neurons can absorb nanoparticles, which are linked to the brain's olfactory bulb. From that point, the nanoparticles can move through retrograde transport to the brain's inner regions.

Mechanism:

The olfactory neurons stretch from the nasal cavity to the brain, lacking the protective BBB, enabling drugs to circumvent the BBB and directly reach brain tissue.

Trigeminal Nerve Pathway (Perineural Route):

Trans neuronal transport: The trigeminal nerve serves as an additional possible route for drug delivery to the brain.

Nanoparticles may enter through the nasal mucosa and engage with the trigeminal nerve endings, which handle sensory input in the head and face.

Mechanism:

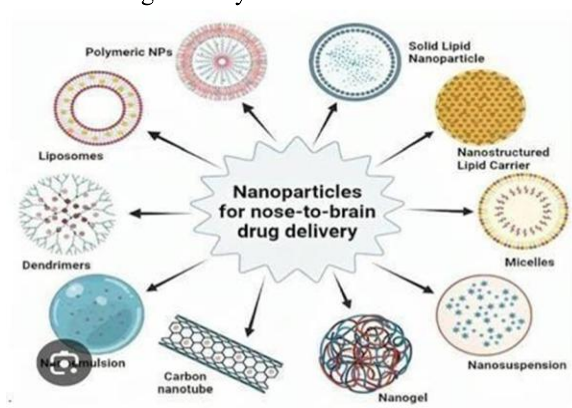
They interact with the trigeminal nerve, travel through the nerve fibers to the brainstem, and subsequently spread to other brain regions. [6]

Nano-Particles Utilized for Drug Delivery from Nose to Brain:

Nanoparticles provide a sophisticated and flexible method for transporting medications from the nose to the brain, tackling various issues linked to drug delivery aimed at the brain.

These minuscule particles, generally between 1 and 100 nanometers in size, offer considerable potential for improving drug stability, regulating drug release, and targeting therapeutic agents to particular regions of the brain.

Nanocarriers measuring less than 100 nm frequently employ endocytic pathways to aid in mucosal and transcellular transport, rendering them very efficient for nasal drug delivery.[7]



A) Nanoparticles Based on Lipids:

1) Liposomes for Delivery from Nose to Brain:

Solid based Nanoparticles:

Lipid for Nose to Brain Delivery:

Liposomal formulations are increasingly preferred because of their biocompatibility, nontoxicity, and capacity to transport both hydrophilic and hydrophobic medications. Lipid based nanoparticles, such as liposomes (Figure 1), offer considerable promise for improving the transport of drugs from the nasal cavity to the brain.

Their suitability for biological systems, ability to encapsulate various drugs, and potential to target particular areas of the brain position them as a promising choice for delivering drugs from the nose to the brain.

Ex vivo experiments with sheep nasal membranes assessing drugs such as tacrine and lamotrigine demonstrated enhanced nasal permeability via liposomal formulations, underscoring their promise in targeted drug delivery to the brain.

A study by Bender et al. showed that when glial-derived neurotrophic factor
was administered using liposomes, it achieved the greatest concentration in the olfactory.(8)

Solid Lipid Nanoparticles:

Solid lipid nanoparticles (SLNs) are an advanced type of lipid-based nanocarriers, in which a solid lipid substitutes the liquid lipid commonly found in lipid emulsions.

These nanoparticles generally have a diameter between 100 and 300 nm and create a solid lipid framework.

SLNs are frequently composed of natural lipids dispersed in water or aqueous surfactants, which improve their biocompatibility.

SLNs provide various benefits for drug delivery, including the capability being manufactured without organic solvents, exceptional physical stability, and controlled, prolonged release of encapsulated medications.

Nanoemulsiones:

Nasal emulsions (NEs) have been investigated as a successful method for administering different medications to the brain for managing neurological disorders. NEs are colloidal systems made up of small oil droplets suspended in a water-based medium. Their limited size and stability render them especially apt for navigating drugs via the oil factory routes, improving the delivery of active compounds into the brain. Studies indicate that NEs, especially oil-in-water (o/w) varieties, can reach high encapsulation efficiency for lipophilic drugs, enhancing their solubility, absorption, and bioavailability while minimizing the risk of enzymatic degradation [9], [10].

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

Nanostructured lipid carriers (NLCs) represent an advanced form of lipid based nanoparticles (Figure 1) that have attracted considerable interest due to their improved drug loading ability and stability, especially regarding nasal drug delivery to the brain. NLCs are created to satisfy multiple industrial requirements, including quantification ease, scalability, affordability, and straightforward production. Furthermore, the incorporation of biocompatible and biodegradable lipids and surfactants in NLCs renders them an appropriate option from a regulatory perspective. [11]

B) Nanoparticles Derived from Polymers:

Polymeric nanocarriers, comprising natural or synthetic polymers, have been utilized for N2B delivery to enhance stability, regulate the drug release profile, and alter the nanoparticles' surface.

Nanoparticles Based on Natural Polymers: Chitosan (CS) is increasingly utilized as a natural polymer for creating different types of nanoparticles. Chitosan is a polysaccharide obtained through the deacetylation of chitin, a natural polymer present in the exoskeletons of insects and crustaceans. Chitosan's composition comprises D-glucosamine and N-acetyl-D-glucosamine. (11)Chitosan exhibits a pKa value around 6.5, indicating that at an acidic pH, it gets protonated and acquires a positive charge. As the pH of nasal mucus usually falls between 5.5 and 6.5, chitosan nanoparticles (NPs) retain a positive charge in the nasal setting, improving their stability. Because of the negative charge present in both the olfactory and respiratory epithelium, nanoparticles made from chitosan can stick to the nasal mucosa for longer durations, enhancing the bioavailability of the drug contained in the nanoparticles and enabling more efficient transport to the brain. Additionally, chitosan serves as a permeation enhancer [12].

Procedure Preparation of Nanoparticle’s:

Nanoparticles (NPs) represent a viable approach for delivering drugs to the brain via the nasal route, as they can effectively navigate past the blood-brain barrier (BBB) [13].

The delivery route from nose to brain utilizes the olfactory and trigeminal nerve pathways for direct brain access, positioning it as an encouraging method for neurological disorders. Various strategies have been created to synthesize nanoparticles aimed at this objective.(14) Here are several important techniques employed in the fabrication of nanoparticles for drug delivery from the nose to the brain [15].

A Method for Evaporating Solvents:

This technique is commonly utilized for the preparation of polymeric nanoparticles. An organic solution containing drugs is emulsified in water, and the solvent is evaporated under reduced pressure, resulting in the formation of nanoparticles.

Materials: Commonly used polymers include poly(lactic-co-glycolic acid) (PLGA), chitosan, and polycaprolactone (PCL) in its dissolved [16].

Procedure:

The medication and polymer in an organic solvent (e.g., dichloromethane, acetone). Blend the solution in a water phase that includes surfactants.

Plan of Work Procedure for Preparing Nanoparticles

Remove the organic solvent by evaporation under reduced pressure to create nanoparticles.

Emulsion Solvent Diffusion This technique employs an emulsion system in which a drug polymer solution is dispersed in an aqueous phase. The solvent penetrates the water, resulting in the creation of nanoparticles.

The polymer and drug are dissolved in an organic solvent.

This solution is dispersed in a water phase (commonly with surfactants).

II. OUTCOME AND ANALYSIS

Nose-to-brain (N2B) drug delivery via nanoparticles (NPs) has demonstrated significant promise as an efficient approach for addressing central nervous system (CNS) conditions by circumventing the blood-brain barrier (BBB).

This method utilizes the direct transport of medications from the nasal cavity to the brain through the olfactory and trigeminal nerve pathways.

We summarize the main results from recent research assessing the effectiveness of N2B drug delivery systems that utilize nanoparticles.

Nose-to-brain medication delivery through nanoparticles (NPs) has developed into a promising option for addressing central nervous system (CNS) conditions by circumventing the blood- brain barrier (BBB).

Directly delivering therapeutic agents to the brain through the olfactory and trigeminal nerve pathways offers significant benefits, especially in addressing neurological conditions such as Alzheimer's, Parkinson's, and brain tumors.

Nonetheless, although the outcomes of research in this field are very encouraging, multiple factors must be taken into account to enhance this delivery method and make it practical for clinical application. [17].

III. PROSPECTIVE OUTLOOK

For creating innovative nanoparticle formulations that have improved brain targeting, lower toxicity, and better permeability through the nasal mucosa Sure! However, it seems there is no text included for me to paraphrase. Please provide the text you would like me to work on. Ongoing research might result in innovative materials or hybrids that provide improved stability, biocompatibility, and targeting effectiveness

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