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A Review on Nose to Brain Drug Delivery Using Nanoparticles

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Abstract: *The organization of drugs to the central apprehensive framework (CNS) is essentially controlled by the blood-brain barrier (BBB), a structure that avoids the section of outside compounds from the blood to the brain extracellular fluid.*

I spite of the fact that right now accessible medication for brain illnesses that influence millions of individuals globally are in part viable, they are related with serious side impacts of systemic medicate conveyance, On the other hand, the capacity of certain drugs to saturate through the BBB is obstructed by their physicochemical properties, achieving sub-therapeutic concentrations in their target tissues.

In this sense, the intranasal course with its unique anatomical highlights gives a promising section for the conveyance of drugs to the brain.

Nanoparticle-based systems, in specific have illustrated an extraordinary capacity to overcome the challenges displayed by the intranasal course and create sedate collection in the brain whereas maintaining a strategic distance from systemic dispersion.

This review covers later advancements in the utilize of polymer, lipid, and inorganic nanoparticles, as well as drug nanocrystals, to convey drugs to the brain by means of intranasal organization. A common discourse including favourable viewpoints and impediments of this approach is moreover given.

Keywords: Nanoparticle, Nose To Brain Delivery, Blood brain barrier, lipid based nanoparticles.

I. INTRODUCTION

Neurological disorders are a leading cause of disability worldwide, significantly increasing the strain on healthcare systems.1 one of the major challenges in treating these disorders is delivering drugs to the brain due to the presence of the Blood-Brain Barrier (BBB), the complexity of brain function, and concerns about safety and toxicity.

An emerging alternative to traditional methods is nose-to-brain drug delivery, which offers several advantages over systemic administration.

These include the avoidance of systemic side effects, a better side effect profile, non-invasiveness, quicker onset of action, and enhanced bioavailability within the Central Nervous System (CNS)Nose-to-brain drug delivery bypasses the BBB by utilizing neural pathways connecting the olfactory epithelium, olfactory bulb, and trigeminal nerve, facilitating direct transport to the brain.

3 This novel approach is gaining attention in pharmaceutical research as it enables the direct delivery of therapeutic agents from the nasal cavity to the brain, overcoming the barrier posed by the BBB4. With its potential to treat a wide range of neurological conditions.

Advantages:

1) The IN route is a non-invasive or minimally invasive route of administration to the CNS, more effective than intravenous (IV) and oral routes.

2) This direct route to the CNS can avoid the BBB besides reducing systemic side effects.

3) In the case of the other parenteralroutes and oral administration, drugs must first cross several barriers to achieve systemic circulation and then cross the BBB to reach the CNS.

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4) Moreover, IN route avoids hepaticfirst-pass metabolism and drug degradation in the gastrointestinal tract, being an alternativeroute for parenteral administration, especially for biopharmaceuticals (like proteins and peptides).

Challenges:

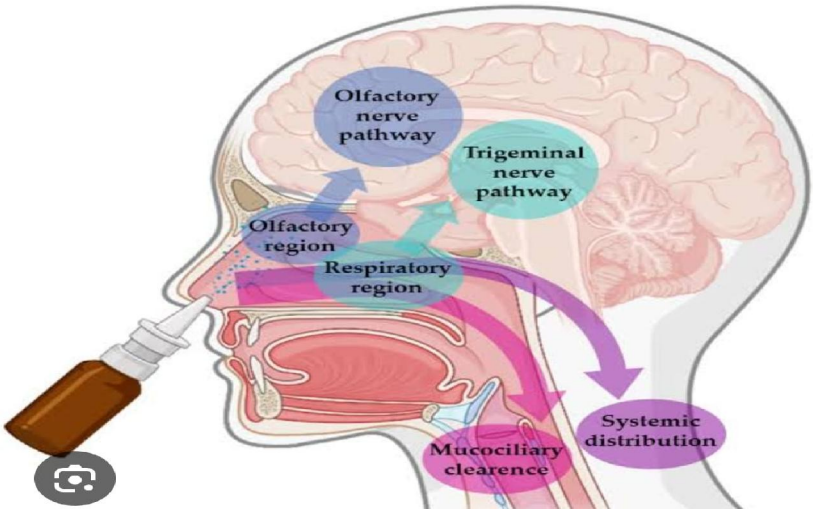
Delivering drugs from the nose to the brain presents several challenges, primarily due to the unique anatomy and physiology of the nasal passages, as well as the protective barriers in the brain. Here are some of the key challenges:

Nasal Mucosa and Drug Absorption: Limited Surface Area: The nasal mucosa, while highly vascularized, offers a relatively small surface area for drug absorption, which limits the amount of drug that can be absorbed at one time. Mucociliary Clearance: The nasal passages have a natural mechanism to clear foreign particles, including drugs, via cilia and mucus. This can reduce thetime drugs stay in contact with the mucosal membranes and decrease absorption efficiency. Enzymatic Degradation: The nasal cavity contains enzymes that can degrade drugs before they have a chance to reach systemic circulation or the brain.

Blood-Brain Barrier (BBB) :

Selective Permeability: The blood-brain barrier is a highly selective membrane that protectsthe brain from harmful substances but also limits the entry of therapeutic drugs. Overcomingthis barrier is one of the most significant challenges in drug delivery to the brain, even withintranasal administration. Need for Specialized Formulations: Drugs need to be specificallydesigned or formulated in a way that allows them to cross the BBB, which often requires the use of carriers or modifications to the drug itself (e.g., nanoparticles, lipid-based formulations, etc.).

Pathways For Nose to Brain Drug Delivery System:



Olfactory Pathway (Transcellular Route):

Direct entry through olfactory neurons: The olfactory region in the nasal cavity is a direct route to the brain. Nanoparticles can be absorbed by olfactory sensory neurons, which are connected to the olfactory bulb in the brain. From there, the nanoparticles can travel via retrograde transport to the brain's deeper structures.

Mechanism:

The olfactory neurons extend from the nasal cavity to the brain without the protective BBB, allowing drugs to bypass the BBB and directly access brain tissue.

Trigeminal Nerve Pathway:(Perineural Route): Transneuronal transport: The trigeminal nerve is another potential pathway for drug delivery to the brain.

Nanoparticles can be absorbed through the nasal mucosa and interact with the trigeminal nerve endings, which areresponsible for sensory information in the face and head.

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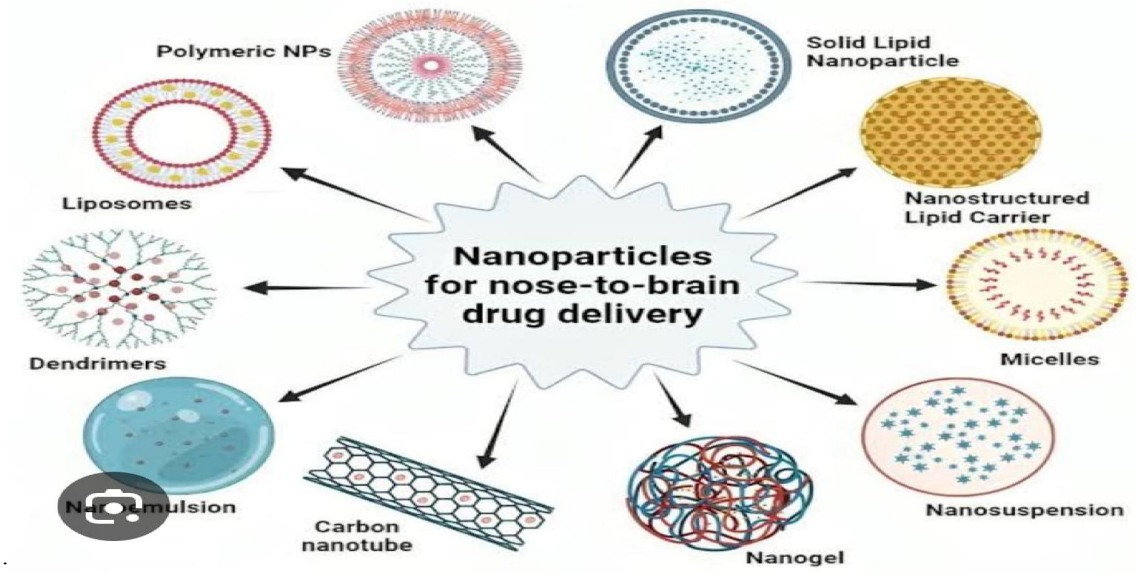
Mechanism: interact with the trigeminal nerve, they can travel along the nerve fibres and reach the brainstem, and then propagate to other areas of the brain.

Nano-Particles Used for Nose To :Brain Drug Delivery.

Nanoparticles offer an advanced and versatile approach to delivering drugs from the nose to the brain, addressing several challenges associated with brain-targeted drug delivery.

These tiny particles, typically ranging from 1 to 100 nanometres in size, holdsignificant promise for enhancing drug stability, controlling drug release, and directingtherapeutic agents to specific areas of the brain.

Nanocarriers smaller than 100 nm often utilize endocytic pathways to facilitate both mucosal and transcellular transport, making them highly effective for nasal drug delivery.



A) Lipid based Nanoparticles:

1) Liposomes for Nose-to-Brain Delivery:

Liposomal formulations have become highly favored due to their biocompatibility, non toxicity, and ability to deliver both hydrophilic and hydrophobic drugs. As versatile lipid based nanoparticles (Figure 1),liposomes hold significant potential for enhancing the delivery of medications from the nose to the brain.

Their compatibility with biological systems, capacity to encapsulate a wide range of drugs, and ability to target specific brain regions make them a promising option for nose-to-brain drug delivery.

Ex vivo studies using sheep nasal membranes to test drugs like tacrine and lamotrigine showed improved nasal permeability when delivered through liposomal formulations, highlighting their potential in brain-targeted drug delivery.

Research by Bender et al. demonstrated that when glial-derived neurotrophic factor was delivered via liposomes, it reached the highest concentration in the olfactory .

2) Solid Lipid Nanoparticles:

Solid lipid nanoparticles (SLNs) represent an advanced class of lipid-based nanocarriers, where a solid lipid replaces the liquid lipid typically used in lipid emulsions.

These nanoparticles typically range from 100 to 300 nm in diameter and form a solid lipid matrix.

SLNs are often made from physiological lipids dispersed in water or aqueous surfactants, which enhance their biocompatibility.

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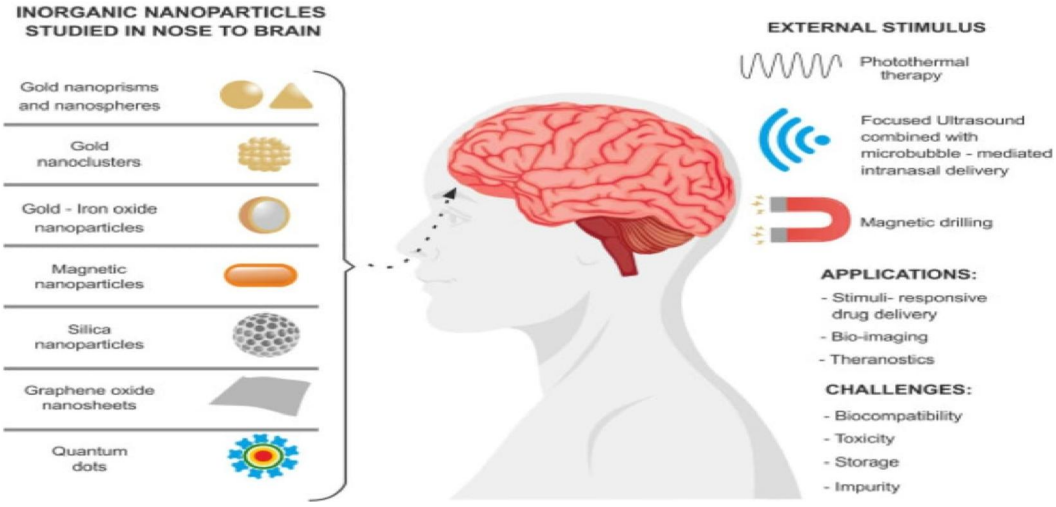
SLNs offer several advantages for drug delivery, such as the ability to be produced without the use of organic solvents, high physical stability, and controlled, sustained release of encapsulated drugs. However, they also

B) Nanoemulsions:

Nasal emulsions (NEs) have been explored as an effective means of delivering various drugs to the brain for treating neurological conditions. NEs are colloidal systems consisting of tiny oil droplets dispersed in a water-based medium. Their small size and stability make them particularly suitable for transporting drugs through the olfactory pathways, enhancing the penetration of active ingredients into the brain. Research has shown that NEs, particularly oil- in-water (o/w) types, can achieve high encapsulation efficiency for lipophilic drugs, improving their solubility, absorption, and bioavailability while reducing the risk of enzymatic degradation.9

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

Nanostructured lipid carriers (NLCs) are a highly advanced type of lipid-based nanoparticle (Figure 1) that have gained significant attention for their enhanced drug loading capacity and stability, particularly in the context of nasal drug delivery to the brain. NLCs are designed to meet various industrial criteria, such as ease of quantification, scalability, cost-effectiveness, and simplicity in production. Additionally, the use of biocompatible and biodegradable lipids and surfactants in NLCs makes them a suitable choice from a regulatory standpoint.1



B) Polymer-Based Nanoparticles:

Polymeric nanocarriers, either natural or synthetic polymers, have been used for N2B delivery to increase stability, control the drug release pattern and modify the surface of nanoparticles.

1) Natural Polymer-Based Nanoparticles: Chitosan (CS) has become a widely used natural polymer for the preparation of various nanoparticles. Chitosan is a polysaccharide derived from the deacetylation of chitin, a natural polymer found in the exoskeletons of insects and crustaceans. The structure of chitosan consists of D-glucosamine and N-acetyl-D-glucosamine. Chitosan has a pKa value of approximately 6.5, meaning that at an acidic pH, it becomes protonated, carrying a positive charge. Since the pH of nasal mucus typically ranges between 5.5 and 6.5, chitosan nanoparticles (NPs) remain positively charged in the nasal environment, which enhances their stability. Due to the negative charge of both the olfactory and respiratory epithelium, chitosan-based nanoparticles can adhere to the nasal mucosa for extended periods, which increases the bioavailability of the drug encapsulated within the nanoparticles, allowing it to be more effectively transported to the brain. Furthermore, chitosan acts as a permeation enhancer

Method of Preparation For Nanoparticles:

Nanoparticles (NPs) are an effective strategy for drug delivery to the brain through the nose due to their ability to bypass the blood-brain barrier (BBB).

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The nose-to-brain delivery route leverages the olfactory and trigeminal nerve pathways for direct delivery to the brain, making it a promising approach for neurological diseases. Several methods have been developed to prepare nanoparticles specifically for this purpose. Below are some of the key methods used for the preparation of nanoparticles for nose-to-brain drug delivery:

A Solvent Evaporation Method :

This is a widely used technique for preparing polymeric nanoparticles. A drug-loaded organic solution is emulsified in an aqueous phase, and the solvent is then evaporated under reduced pressure, leaving behind nanoparticles.

Materials: Polymers like poly(lactic-co-glycolic acid) (PLGA), chitosan, and Dissolve polycaprolactone (PCL) are commonly used.

Procedure:

1) The drug and polymer in an organic solvent (e.g., dichloromethane, acetone).

Emulsify the solution in an aqueous phase containing surfactants.

PLAN OF WORK METHOD OF PREPARATION FOR NANOPARTICLES 23 3)

Evaporate the organic solvent under reduced pressure to form nanoparticles.

Emulsion Solvent Diffusion This method uses an emulsion system where a drug-polymer solution is emulsified in an aqueous phase. The solvent diffuses into the water, leading to nanoparticle formation.

Procedure:

1) The drug and polymer are dissolved in an organic solvent.

2) This solution is emulsified in an aqueous phase (usually with surfactants).

3). The organic solvent diffuses into the aqueous phase, causing the nanoparticles.

II. RESULT AND DISCUSSION

Nose-to-brain (N2B) drug delivery using nanoparticles (NPs) has shown considerable potential as an effective strategy for treating central nervous system (CNS) disorders by bypassing the blood-brain barrier (BBB).

This approach leverages the direct transport of drugs from the nasal cavity to the brain via the olfactory and trigeminal nerve pathways.

Here, wsummarize the key findings from recent studies evaluating the efficacy of N2B drug delivery systems using nanoparticles.

Nose-to-brain drug delivery via nanoparticles (NPs) has emerged as a promising alternative for treating central nervous system (CNS) disorders by bypassing the blood-brain barrier (BBB).

The direct delivery of therapeutic agents to the brain via the olfactory and trigeminal nerve pathways provides distinct advantages, particularly in targeting neurological diseases like Alzheimer's, Parkinson's, and brain cancers.

However, while the results of studies in this area are highly promising, several factors need to be considered to optimize this delivery route and make it viable for clinical use

III. FUTURE SCOPE

1. Nanocarrier Development for Large Biomolecules..
2. Development of nanoparticle-based systems that provide real-time feedback on drug distribution and brain response, allowing for better treatment monitoring and optimization.
3. for developing novel nanoparticle formulations with enhanced brain targeting, reduced toxicity, and improved permeability across the nasal mucosa.
4. Future research may lead to new materials or hybrids that offer better stability, biocompatibility, and targeting efficiency.
5. Research will also need to focus on understanding and minimizing the potential toxicity of nanoparticles.

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