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Review Article

Current advances in nose to brain drug delivery

Venkatesh Prasad S, Preethi Sudheer*, Kannika Belludi Chandrashekhar Shetty

Department of Pharmaceutics, Krupanidhi College of Pharmacy, Bengaluru, Karnataka, India

ABSTRACT

The systemic treatments are not able to assure adequate drug concentration in the brain tissues in many neurological disorders due to the biological barriers such as the blood-brain barrier. Therefore, drug delivery systems can directly target the brain cells in a noninvasive means and bring about adequate drug in the brain is the focus in many of central nervous system (CNS) diseases. Perhaps the intranasal route and the direct anatomical connection between the nasal cavity and the brain can be supportive in the direct entry of therapeutic agents into the brain. This review paper is an insight into various considerations involved in the nose to brain drug delivery, such as the pros and cons of intranasal delivery, the anatomical and physiological features of the nose, various pathways, mechanisms of drug transport, disease perspectives, approaches to enhance the drug absorption with brief emphasis on types, and examples of agents used and advents in the nose to brain drug delivery.

Keywords:
Nose to brain, Drug delivery, Neurological disorders, Polymers, Nanocarriers

1. INTRODUCTION

Epileptic seizures (convulsions), migraines, Parkinson's disease, schizophrenia, meningitis, and Alzheimer's are CNS diseases requiring drug delivery to the brain for therapy. Nevertheless, owing to the impermeable character of an endothelium barrier that divides the bloodstream from the cerebral interstitial fluid, the blood-brain barrier (BBB), such transport is challenging, particularly for hydrophilic and high-molecular-weight medications. As a result, several treatments have been abandoned because systemic circulation alone cannot generate appropriate drug levels in the brain. Medications enter the body in various ways, including oral and parenteral (intravenous). The drugs generated through these channels are often acid or enzymatically degraded and may undergo first-pass metabolism after administration. Due to these circumstances, effective medication dosages may not always reach the circulatory system, resulting in unsuccessful therapy. Exploring additional routes or specialized delivery technologies that might lead to more sophisticated and effective medication delivery choices[1]. One option is to employ nasal delivery; the channel gives access to a highly vascularized mucosa for local drug administration and controlled and targeted drug delivery.

Several techniques have targeted the brain, including BBB rupture, receptor-mediated transport, peptides entering cells, and targeted administration utilizing prodrugs. Because of their poor distribution in the CNS, the BBB has prevented the development of several prospective CNS medicines for some time. Because of the nose's unique relationship with the CNS, medicinal compounds can enter the brain through the intranasal pathway bypassing the BBB[2].

In recent decades, the capability to investigate the nasal route as non-invasive means of delivery to the brain has gained considerable interest as an additional viable route to oral and parental administration strategy. The brain can access drugs controlled by the nose through several mechanisms, with natural movement through the olfactory neurons and trigeminal nerve endings while avoiding the BBB and drugs that enter the BBB cross-sectional system depending on their molecular structure and lipophilicity[2-3].

Because of their capacity to detect the active component, colloidal carriers with diameters ranging from 10 to 400 nm garner more significant attention than conventional therapy in treating CNS disorders. These new nanocarriers result in an increasing onset of action, better brain identification, and reduced toxicity by lowering

***Corresponding author:**
*Preethi Sudheer Email: preetisudheer@krupanidhi.edu.in, preetisudheer@gmail.com

the medication dose. Because of its favourable features of biodegradability, biocompatibility, and simplicity of production, polymeric systems are now widely used in nasal nanotherapeutics. The nanoparticles (NP) enable simple access to the remainder of the BBB by conveniently mixing drug molecules and enhancing their dispersion in the cellular membrane. They can protect drugs against physiological, pharmacological, and related enzymes, and an extracellular pathway known as the P-glycoprotein efflux system, allowing them to reach more targeted sites[4].

2. ANATOMY AND PHYSIOLOGY OF NOSE

The human nasal region is split into two sides by a septum and has a total capacity of 16 to 19 mL and around 180 cm^2. Each hole has a capacity of around 7.5 mL and a surface area (SA) of more than 75 cm^2. After the drug delivery in the nasal cavity, the solute may pass through one or more distinct areas, such as vestibular, respiratory, and olfactory (Figure 1). In addition to the oral cavity, the nasal cavity houses the external entrance to the respiratory system, serving as a pathway for the airflow before it continues to the lower airways. The nasal cavity plays a crucial role in essential physiological functions such as regulating moisture and air temperature, filtering particles, and facilitating the process of olfaction.

2.1. Vestibular region

The vestibular area is most prominent, located immediately near the nasal apertures. It has a surface area of around 0.6 cm^2 and nasal hairs that help filter inhaled pollutants. Squamous epithelial cells are the most common cell type in this area, with only a few ciliated cells. The small surface area and cell structure limit drug absorption[5].

2.2. The respiratory epithelium

The respiratory region, which includes a large portion of the nasal cavity, (80-90 % of the all-out SA), is

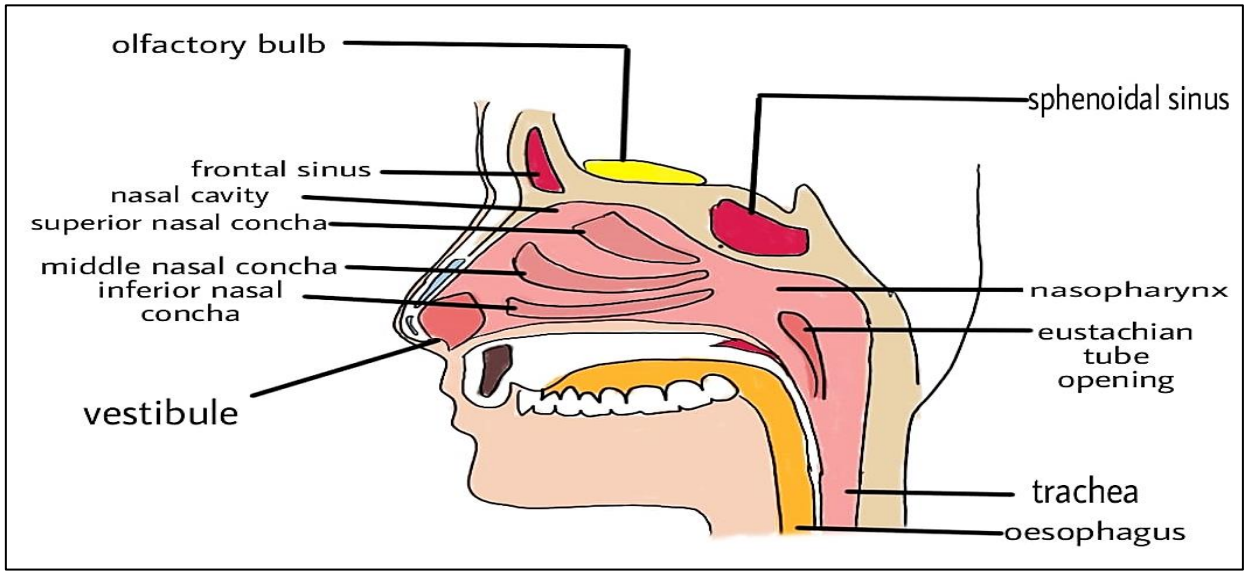

Figure 1. Anatomy of nose.

bordered by a ciliated pseudostratified columnar epithelium called respiratory epithelium or Schneiderian layer. Because of its large area covered with microvilli and evident degree of vascularization, the respiratory epithelium is an excellent guide for the intake of drugs to systemic medicines.

The low viscosity pericilliary layer grows 3-5 m thick and includes the motile cilia (2-4 m long), and the underlying viscous gel layer, which broadens 2-4 m in thickness, is present on the respiratory epithelium.

The pulmonary mucosal fluid is a viscoelastic gel that consists of mucins, water, salts, various proteins, and a small number of lipids. Its viscoelastic and adhesive nature is the defense against nebulized fine particles and allergens. The low viscosity of the thin serous liquid layer allows cilia to move freely within the same, just the cilia tips in touch with the viscoelastic mucous fluid gel layer.

This specific capacity to carry out a planned clearing action with an intensity of approximately 1,000 strokes/min devotees to bodily fluid discharge by a vectorial impetus towards the pharynx. The combined effect with the constant mucous fluid emission results in mucociliary clearance, which has a defensive impact by entrapping and eliminating inhaled fine particles, allergens, and toxins, i.e., the respiratory mucous fluid layer restores every 10-20 minutes[6-7].

2.3. The olfactory epithelium

The olfactory system has drawn its potential among

the other the segments of the brain, due to the capacity of its neurons to identify odorants and give the feeling of smell, also acts as an entrance in brain delivery.

The olfactory mucosa comprises a ciliated chemosensory pseudostratified columnar epithelium arranged on the predominant turbinate and, respectively, on the nasal septum, encircled by respiratory epithelium. The olfactory epithelium is a conduit for chemicals reaching the CNS and peripheral nervous system. The nasal mucosa and the cerebrum are neuronally connected, providing a pathway for direct nasal-to-brain delivery via intraneuronal and extraneuronal routes. The intraneuronal route takes hours to days to deliver medicines to different brain parts via axonal vehicle. The extraneuronal route utilizes perineural channels, which carry medicines directly to the cerebrum parenchymal tissue or cerebrospinal fluid (CSF). The extraneuronal pathway provides a quick means of drug targeting, as it takes only a minute. When the olfactory axon bundle passes through the skull lamina and approaches the subolfatory mucosa in the upper part of the nasal cavity, the cerebrospinal fluid gets redirected to the lymphatic vessels of the nasal cavity. It is not uncommon for experts to inject cerebrospinal fluid intranasally. Passive diffusion occurs by the passage of NPs via the pores in the nasal mucosa or any non-detached conveyance used to transport medicines through the nasal film and into the circulatory system.

The two hurdles in direct drug delivery are the tight endothelial boundary of the cerebrum vessels (the blood-mind hindrance) or the 'leakier' barrier of the choroid plexus into the CSF to reach the neurons. Mucosal drug delivery utilizes the nerve axon (intracellular), paracellular, or transcellular routes. After crossing the mucous membrane, chemicals may migrate into the subarachnoid CSF and reach the cerebrum interstitium via perivascular channels, be consumed into submucosal blood and lymphatic vessels, or travel into the subarachnoid CSF and be consumed into the same blood vessels further. The sensitive areas on the trigeminal nerve do not cross the mucosal membrane. Substances should pass through the mucous layer and follow the transport paths described above. The uppermost nasal segment receives innervation from a division of the ophthalmic branch that has similar projections to the olfactory nerve. The maxillary branch provides sensory and parasympathetic innervation to the majority of the respiratory mucosa and functions in the brainstem[6-7].

3. ADVANTAGES AND LIMITATIONS OF THE NOSE TO BRAIN DELIVERY

It is a method of drug administration that is rapid, safe, non-invasive, and convenient. It increases medication bioavailability by bypassing hepatic first-pass metabolism and gut-wall metabolism. It bypasses the BBB, permits neurotransmitter delivery systems, and reduces systemic drug exposure and side effects. The therapeutic agent must not be altered to deliver through the nose-to-brain platform. The nasal mucosa's high vascularity and permeability help accomplish rapid drug absorption and therapeutic activity. Because this mode of drug delivery allows for self-medication, patient compliance is improved. It can be used as a substitute for parenteral delivery, particularly for protein and peptide medications and stem cells, lest the absorption of substances is affected by nasal secretions. This route can enhance the bioavailability of low-molecular drugs.

The prime most challenge in nasal drug delivery is the small surface area contribution of the nasal cavity. Drug substance elimination occurs rapidly from the nasal cavity due to mucociliary clearance. Absorption enhancers used in formulation may create mucosal toxicity. Significant variability exists in the concentration in the different brain and spinal cord regions. The high molecular weight of drugs may decrease permeability across the nasal mucosa. Some therapeutic agents may irritate nasal mucosa or be susceptible to enzymatic degradation and metabolism in the nasal milieu at the mucosal surface. Nasal congestion due to cold or allergic conditions may interfere with this drug delivery technique. Frequent use of this route may cause mucosal damage or anosmia[6].

4. MECHANISM OF DRUG TRANSPORT

Exchange of medicine through olfactory mucosa, trigeminal nerve route, and respiratory pathway are three primary processes that lead to the brain from the intranasal route the mechanisms involved in CNS delivery.

4.1. Trigeminal pathway

The drug enters the olfactory bulb via the olfactory epithelium in the trigeminal pathway, innervated by the trigeminal nerve, the largest cranial nerve. The trigeminal nerve leads to ganglion to CNS. The nerve enters the cerebrum through the anterior lacerated foramen close to the pons and cribriform plate close to the olfactory bulbs[7].

4.2. Respiratory pathway

This pathway utilizes direct drug absorption from the nostrils to the systemic circulation and subsequently to the brain via BBB. It is a potential route for highly lipophilic and low molecular weight drugs[7].

4.3. Olfactory pathway

The drug enters the brain from olfactory neuronal receptors by exploring extracellular and intracellular pathways. Extracellular is a quick method of drug entry, whereas intracellular is a leisurely method. A receptor-

intervened vesicular mechanism from neuron to axons gets the cribriform plate through holes[7].

5. APPROACHES TO ENHANCE DRUG ABSORPTION TO THE BRAIN VIA THE NASAL CAVITY

Due to the nasal cavity's primary intricacy, the brain delivery of these carriers is limited. The significant reasons are high enzymatic movement, quick physical clearance mechanisms, poor mucosal permeability, and drug deposition. The traditional and nontraditional approaches explored for brain delivery are chemical alterations of the drug molecule, some agents as components of formulations or co-administration agents, and formulation improvement strategies as mentioned below[8].

5.1. Chemical modification of therapeutic agents

Chemical modification methods can enhance the ability of therapeutic agents to BBB, thus potentially increasing brain drug concentrations. This method helps deliver therapeutic agents to specific brain regions or cells and minimizes off-target effects. The stability of drugs can be improved by making them less susceptible to degradation or metabolic processes. This can prolong the agent's half-life and improve its effectiveness. The dose reduction and corresponding adverse effects can be achieved. This method allows versatility of the formulations in terms of altered physicochemical properties, lipophilicity, charge etc. However, some limitations include complex, synthetic processes, safety concerns of the modified compounds due to altered pharmacokinetics, increased uptake of drugs off target within the brain, and limited understanding of the method's regulatory constraints[9].

Increasing stability, regulating protease defenselessness, and improving membrane penetrability and retention by synthetically changing the structure of dynamic mixtures and then modulating their approach in nasal absorption of progesterone and antihistamines were explored and suggested that olfactory CSF is the preferential route to entry into the brain[10-11]. For another example, Yajima et al. has examined nasal absorption of 2′,3′-didehydro-3′-deoxythymidine and its ester prodrugs. The results showed that nasal absorption of 2′,3′-didehydro-3′-deoxythymidine and its acetate prodrug was rapid and almost complete via the olfactory region to the brain. Lipidization; lipid core nanocapsules of indomethacin found to reduce the damage triggered by Aβ1-42 in Alzheimer's disease models; neuroinflammation triggered by Aβ is involved in the neuroprotective effects of IndOH-LNCs. Another approach, amino acid substitutions (L-type amino acid), is studied in brain delivery of the anti-Parkinson drug L Dopa and anticancer drug Melphalan. The study indicated that some valuable specialized traits are modified (or acquired) based on the context to improve such features for the intended goal. Chemical changes and surface functionalization can focus on explicitness, whereas lipidation, PEGylation, or amino acid substitution can impact hydrophilicity/hydrophobicity regulation[12].

5.2. Enzyme inhibitors

The drug delivery to the brain using enzyme inhibitors increases the target concentration by reducing the metabolism, bypassing BBB, and a noninvasive therapy, which can provide rapid drug action with minimized systemic toxicity. Limited specificity is the primary concern in the use of enzyme inhibitors and the inherent toxicity of these agents.

The high mucosal protease and reductase activity in the nasal cavity and olfactory region is due to CYP-450 isomers, oxidative and conjugative chemicals, and exo-and endopeptidases. Moreover, many drug compounds are substrate to it. This enzymatic environment degrades and metabolizes the specific medications (mostly protein therapeutics) that use the NC as a passageway into the body, resulting in a "pseudo" first-pass effect and implying that the penetration barrier is not only causing the restricted retention. Formulation-based therapies and enzyme-inhibiting drugs can achieve enzyme inhibition either as excipients or as co-administrating agents (i.e., micro or nanoparticulate frameworks). Similarly, the pH of the surrounding environment changes by protease movement's strategies. Protein inhibitors, in particular, may increase the stability of labile medications by inhibiting enzyme-induced degradation at the retention site[12]. Some protease inhibitors studied over the last decade in pulmonary/nasal drug administration as absorption enhancers are: nafamostat mesylate, aprotinin, bacitracin, soybean trypsin inhibitor, phosphoramidon, leupeptin, and bestatin. As mentioned earlier, during the study, rats received insulin with protease inhibitors via intratracheal administration[13].

5.3. Permeation enhancers

Permeability enhancers/absorption enhancers are flexible formulation additives for increasing permeability via biological membranes. After everything is said and done, they are low molecular weight specialists who help medications be absorbed in pharmacologically active quantities for a short period. Permeation enhancers temporarily disrupt complex functional constructions between neighboring epithelial cells, linking with the phospholipid layer, increasing viscoelastic properties or changing the properties of the actual medicine (i.e., by altering its thermodynamic moment). Some examples of absorption enhancers are unsaturated fats such as stearic acid, palmitoleic acid, cyclodextrins; beta cyclodextrins, hydrophilic polymers; chitosan derivatives, surfactants;

phosphatidylcholine, soybean lecithin; bile salts such as sodium taurocholate, sodium deoxycholate. A combination of chelating agents, fats, and semi-engineered or naturally determined surfactants are also used as permeation enhancers. By their property to alter the mucosa and gain entry to the brain, these agents facilitate good permeability via nasal mucosa and, therefore, rapid drug action. However, mucosal irritation and toxicity are the primary concerns[14].

5.4. Vasoconstrictors

Vasoconstrictors are usually used with nasal decongestants. A suggested mechanism of action is the constriction of enlarged veins, which raises blood pressure, decreases oedema, and improves nasal congestion symptoms. Vasoconstrictors are used in formulation development or are administered before medication administration to reduce the amount of medication retained in the foundational flow via the respiratory epithelium, allowing for more precise targeting of specificity to the CNS via the olfactory pathway and reducing the unfavourable side effects identified with the olfactory pathway. The enhanced nucleotide delivery in the presence of the vasoconstrictor agent phenylephrine was reported. Vasoconstrictors helps in reducing drug loss to blood, thus results increased brain uptake, increased contact time and thus increased brain bioavailability and reduced systemic clearance, thus longer retention time. The local mucosal tissue damage, systemic side effects and limited duration of drug action and drug interactions are some the side effects associated with this therapy[15].

5.5. Efflux transporters

Efflux transporter's presence in nasal epithelia and BBB helps in pumping out the unwanted toxic substances thus decreases the neurotoxicity. They can help in maintaining optimum drug levels. By overcoming the certain efflux pumps, the brain uptake can be increased considerably. Prolonged drug exposure to efflux system can develop drug resistance. The number and expression of these agents are not uniform in brain. So, there are chances of upper or lower therapeutic effect.

The medication transport through the nasal mucosa addresses the efflux carriers. However, the co-organization of rifampicin (a P-glycoprotein efflux inhibitor) in the cerebrum enhanced drug absorption. P-glycoproteins' effect in the olfactory epithelium help in medication absorption in the CNS. Wang and coworkers conducted a study employing the abcb1a/b knockout mouse model with a functional deficiency in P-gp. By utilizing ATPase activity as a marker for P-gp activity, an *in vitro* study provided evidence that P-gp may effectively efflux various atypical antipsychotic drugs such as risperidone and olanzapine[16].

5.6. Mucoadhesive agents

Mucoadhesive agents are usually employed as formula excipients, co-agents, or permeation enhancers. The mucoadhesives interact with mucous fluid to lengthen the drug residence time in the nasal cavity, thus prolonging the drug action. Mucociliary clearance arises due to gravity forces and the Bowman's organ's continuous outflow of mucous fluid, despite the lack of motile cilia at the olfactory mucosa. The increase in mucosal permeability may be due to the fluidization of the mucosal layer. Some examples that support mucoadhesion and its application in nasal delivery are hyaluronic acids enhance the mental transport of a supportive peptide, carboxymethylcellulose carbopol, and polyacrylic acid, had brought a significant increase in the pharmacokinetics of apomorphine. The bioavailability of the new growth factor was higher in the cerebrum by chitosan.

A mucoadhesive polymer combination of chitosan hydrochloride with hydroxypropyl-cyclodextrin increased the uptake of Buspirone hydrochloride. Dopamine D2 agonist distribution in the cerebrum was improved using *in situ* thermosensitive chitosan and hydroxypropyl methylcellulose gel. However, the efficiency of the mucoadhesive polymers on olfactory epithelium is less than a combination of mucoadhesive with proper ligand concentration in nose-to-brain pharmaceutics delivery. Mucoadhesive system helps in increased contact followed by increased penetration via the nasal epithelium and thus helps in adequate drug concentration in the brain cells. Thus, a targeted drug delivery can be expected. Moreover, a controlled drug action can be achieved. However, the response may vary from m individual to individual. The nasal irritation is another drawback of the same. The limited nasal residence time due to nasolacrimal clearance may be observed. And formulating a nasal mucoadhesive system is challenge in terms of selection of polymers, viscosity, stability etc[17-19].

5.7. Nasal delivery devices

The flexible innovations target and maximize the deposition of the drug in various forms, such as powder, particle, and vaporized form, to the upper region of the nasal cavity employing gadgets such as powder inhalers, nebulizers, splash atomizers, and other nasal devices. Kurve Technology is a Controlled Particle Dispersion® Technology for direct Nose-to-Brain distribution. In clinical studies, NDDs that employ this technology, such as the Via Nose electronic atomizers, were demonstrated to achieve Nose-to-Brain transmission via the olfactory region. Non-invasiveness, direct drug action, non-invasiveness' and dose flexibility are some of pros of administering the therapeutic agents. It encounters the problem of limited payload in a single dose, require multiple administration to achieve therapeutic levels.

Also come across the nasal irritation and discomfort. Variable absorption pattern is observed from nasal cavity. Sometimes nasal side effects are observed. Drug delivery challenges may be an issue if not properly handled[20-21].

6. NANOCARRIERS AND POLYMERS MEDIATED NOSE TO BRAIN DELIVERY

NPS is an exceptionally flexible, multifunctional structure that utilizes remarkable properties such as shape, size, hydrophobicity, surface science, and charge for direct action cerebrum. Moreover, NPs are advantageous due to (i) biocompatibility; (ii) low toxicity; (iii) variable loading capacity; (iv) *In vivo* drug degradation can avoid; (v) regulation of therapies discharge for delayed timeframes; and (vi) exploration of the BBB. A thorough examination of these points can improve the effectiveness of the BBB invasion.

The following are some of the current methods (Figure 2) for gettingg drugs/NPs into the CNS: (i) Non-invasive intranasal administration via drug modification to enhance BBB permeability; (ii) Invasive methods requiring direct intraventricular or intracerebral injection/ implantation, infusion; or (iii) BBB interruption temporarily. The inherent physicochemical characteristics of NPs determine the pathways and methods of the intersection of the BBB and their mechanism of drug uptake to the brain cells are briefed in Figure 3[22].

6.1. Ligand based approach

A suitable ligand-based approach utilizes crossing the BBB without causing injury, which can carry and circulate medicines or possibly hereditary material into the lesioned brain.

In the ligand-based approach, specific ligands are employed to enhance the targeting of therapeutic agents to the brain. Ligands are molecules that have a high affinity and selectivity for a particular receptor or protein. By conjugating these ligands to the therapeutic agent or carrier system, it becomes possible to increase the specificity and efficiency of brain targeting.

The ligands used in nose-to-brain delivery are typically chosen based on their ability to bind to receptors or transporters present on the nasal epithelium or the BBB. These receptors or transporters can recognize and internalize the ligand, allowing the drug or carrier system to be transported across the epithelial cells or endothelial cells of the BBB and reach the brain.

One example of a ligand commonly used in nose-to-brain delivery is the transferrin receptor ligand. The transferrin receptor is expressed on the endothelial cells of the BBB, and by conjugating the therapeutic agent or carrier system with transferrin or its derivative, it can bind to the transferrin receptor and facilitate transport across the BBB.

Other ligands that have been investigated for nose-to-brain delivery include antibodies, peptides, aptamers, and small molecules. These ligands can target various receptors or transporters, such as insulin receptors, low-density lipoprotein receptors, nicotinic acetylcholine receptors, and neuropeptide receptors, among others.

Overall, the ligand-based approach in nose-to-brain delivery holds promise for enhancing the targeted delivery of therapeutic agents to the brain. However, it is important to note that further research is needed to optimize ligand selection, conjugation strategies, and delivery systems to achieve effective and safe brain

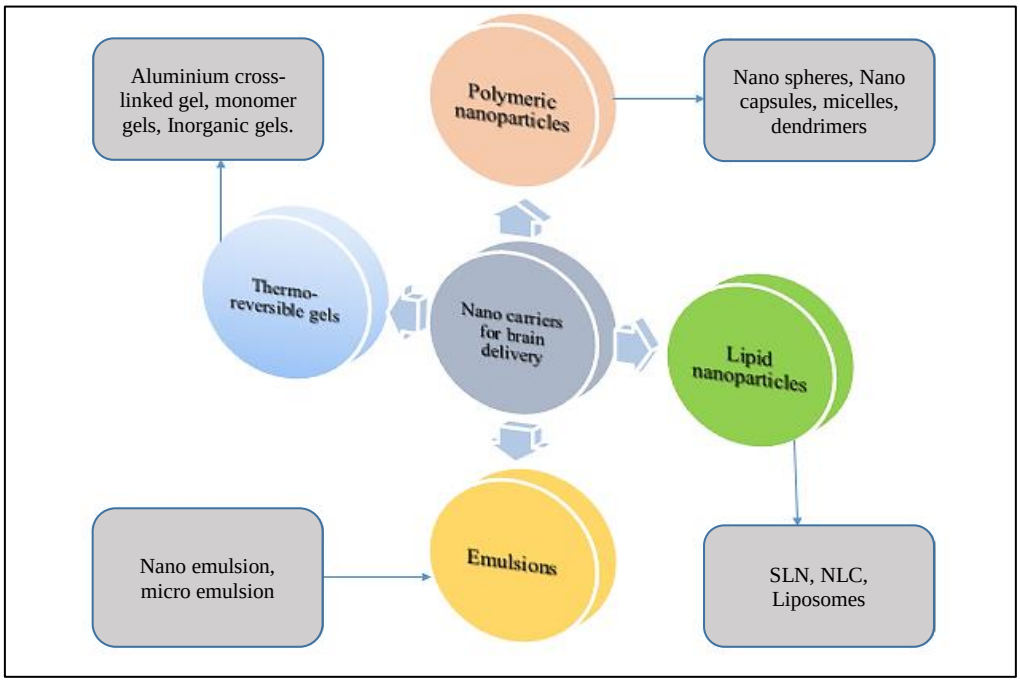

Figure 2. Types of nanocarriers.

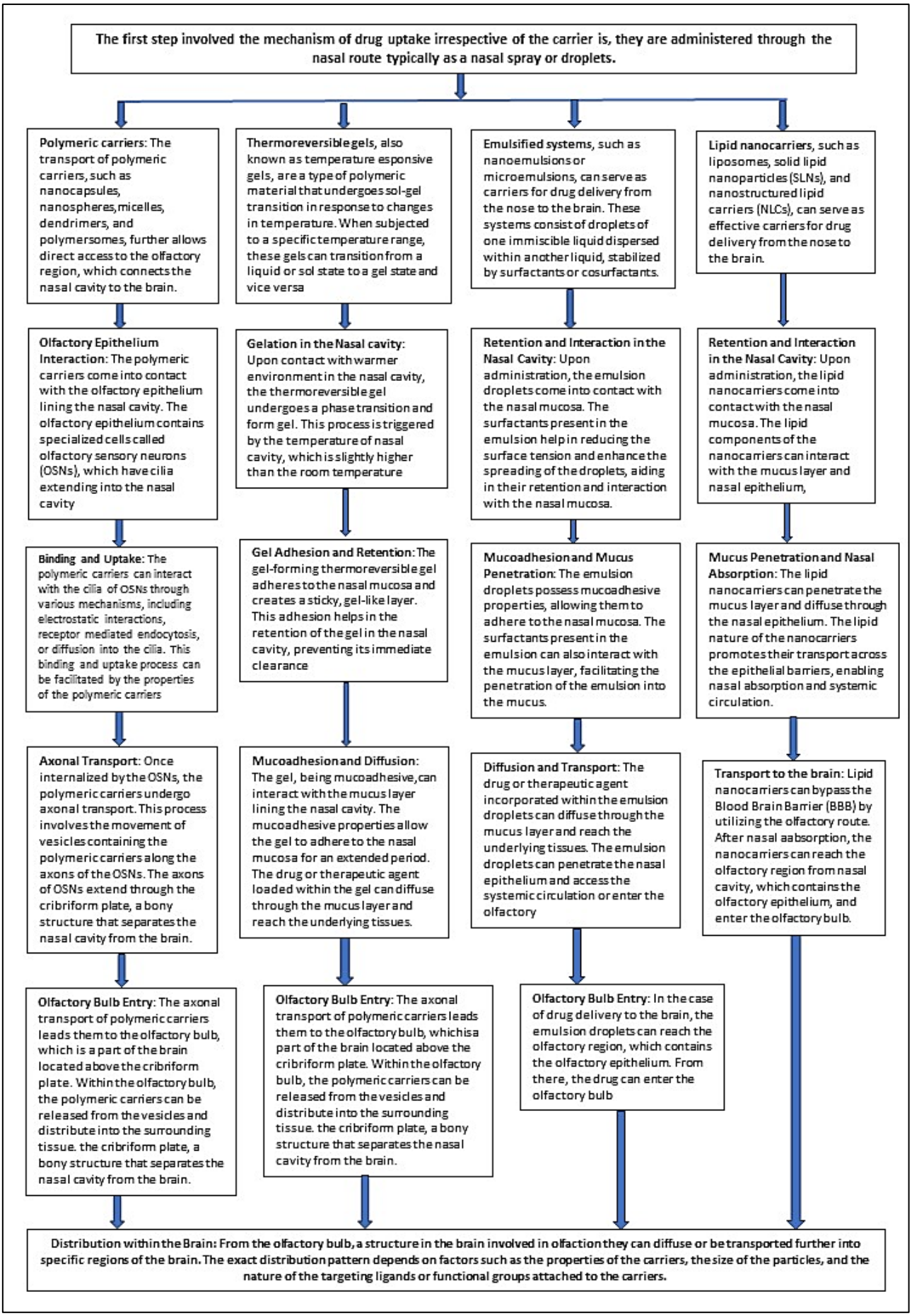

Figure 3. Mechanism of drug uptake from various nanocarriers to brain cells.

Table 1. Nanocarriers for nose to brain delivery.

Carriers	Subtype	Description	Ref.
Polymeric carriers	(NPs) like nanocapsules and nanospheres, micelles, dendrimers, polymersome	-Colloidal solid particles with a size range of 10 to 1000 nm. Spherical, branched, or shell structures made from biodegradable and non-biodegradable polymers. -The drug incorporation NPs through dissolution, entrapment, adsorption, attachment, or encapsulation. -The ability to use a wide variety of polymeric excipients and composite processes aids in fine-tuning. -Nanocarriers based on morphological/sub-molecular structures, drug adequacy, drug extraction methodology, capacity, bioresponsiveness, and other factors	25,26
Lipid carriers	Liposomes, (SLN), nanostructured lipid carriers (NLC), lipid-polymer hybrid NP's, lipoplexes, and phytosomes	-Lipid carrier's capacity to increase the solubility, adsorption, and hence BA of poorly soluble compounds through a selective mechanism gives these systems a unique delivery option for some medication classes. Using NLCs as potential lipid nanocarriers, the drug targeting can be achieved to tissues in lungs, brain anterior and posterior ocular tissues, in various types of malignancies, which improves bioavailability and specificity, and reverses the multidrug resistance.	
Subtypes	**Components**	**Properties**	
Solid lipid nanoparticles (SLN)	**Lipids:** lipids can be fatty acids, acylglycerols, and waxes **Surfactants:** Lipoid S75-3, Lipoid SPC-3, Phospholipon 80 H and Phospholipon 90, polyhydroxy surfactants	-Possess of liposomal and polymeric properties. -Presence of biocompatible solid lipid core. -Used for hydrophobic medications to a lesser extent, hydrophilic macromolecules in the presence of surfactants.	27
Nanostructured lipid carriers (NLC)	**Liquid lipids:** like soya bean oil, oleic acid, isopropyl myristate olive oil, castor oil, glycerides, fatty acids, waxes **Cationic lipids:** cetrimide (tetradecyl trimethyl ammonium bromide) CTAB **Surfactants:** glycolesters, glycerol (and polyglycerol) esters, glucosides (and polyglucosides), sucrose and sorbitan esters	-Colloidal carriers with a lipid core are blended strong and fluid lipids responsible for the lipid grid's specific structures. NLCs can be beneficial to SLNs in terms of drug payload, storage stability, and other factors.	28
Liposomes	**Phospholipids:** Phosphotidylcholine (PC), phosphatidylethanolamine. **Cholesterol**	-They are bilayered vesicles with a fluid core surrounded by several, few, or only one phospholipid bilayer. The vesicular shape permits the incorporation of both hydrophilic and lipophilic drugs either in the interior core or interstitial spaces. Liposomes can also be regarded as safe because they are mostly made up of biodegradable excipients.	29
Emulsions	Nano emulsions, micro emulsions	-Carriers with increased biocompatibility due to their lipid constituents, higher stability to enzymatic degradation, higher permeation profiles via epithelium, controlled drug release.	30
Subcategories	**Components**	**Properties**	**Ref.**
Nano emulsions	**Surfactants:** cremphore, lecithin, Labrasol, Tween 20, Tween 60, and Tween 80 **Oils:** spans (sorbitan fatty acid esters), tweens [polyoxyethylene (POE) derivatives of sorbitan fatty acid ester], Cremophor® EL (polyoxyl-35 castor oil), lauroyl macrogolglycerides (Gelucire® 44/14), polysaccharides **Co-surfactants:** propylene glycol, polysorbate 80, cetylphosphate, hydrogenated castor oil	-Nanoemulsions can be enhanced by combining them with a mucoadhesive excipient to extend their duration on the epithelium. -Nanoemulsions are thermodynamically unstable systems consist of isotropic nano droplets of 20-500 nm. The components such as oil, surfactant, and co-surfactants make the system. They require an enhanced energy contribution to frame.	29,30
Micro emulsions	**Surfactants:** sodium lauryl sulphte (anionic), Quaternary ammonium halide (cationic), polysorbates (non-ionic).	-Micro emulsions, are thermodynamically stable, self-controlled systems that are abruptly formed droplets (1-100 nm), when combining oil and fluid phases with appropriate surfactants.	31

Table 1. Nanocarriers for nose to brain delivery.

Carriers	Subtype	Description	Ref.
Micro emulsions	**Oils:** spans (sorbitan fatty acid esters), tweens [polyoxyethylene (POE) derivatives of sorbitan fatty acid ester], Cremophor® EL (polyoxyl-35 castor oil), lauroyl macro-golglycerides (Gelucire® 44/14), polysac-charides	-Micro emulsions, are thermodynamically stable, self-controlled systems that are abruptly formed droplets (1-100 nm), when combining oil and fluid phases with appropriate surfactants.	31
Thermoreversible gels	Aluminium cross-linked gel, cross-linked with an organic cross-linker biopolymer gel, monomer gels, polymer self-induced gels, Inorganic gels	-Thermoreversible gels are used as components for the DD via nasal route. -Poloxamer 407 or Pluronic F127 (PF127) is a hydrophilic triblock copolymer that undergoes temperature-dependent sol to gel conversion.	32

Table 2. Examples of polymers used in nose to brain delivery systems.

Polymers	Examples	Properties	Ref.
Cellulose derivatives	Hydroxypropyl Methylcellulose (HPMC), Hydroxypropyl Cellulose (HPC), Methylcellulose (MC), and Carboxymethyl Cellulose (CMC), and Ethyl cellulose and Microcrystalline Cellulose (MCC)	-Cellulose substitutes prolong the drug action by their attractive mucoadhesive properties. -Furthermore, after hydration in the nasal depression, celluloses can aid medication delivery because of their high thickness. s a result, employing celluloses as a bioavailability enhancer can boost intranasal intake and BA.	33
Polyacylates	Polyethyl acrylate, polymethyl acrylate	-Polyacrylates with various cross-connecting condi-tions and thicknesses are utilized in mucoadhesive approach. -Polyacrylates get connected to the mucosal surfaces, prolong medication residence duration at absorption sites, and guarantee close contact on the membrane surface. -Polyacrylates in the nasal route can also be used to provide more extended drug release, resulting in a more consistent plasma concentration-time profile.	33,34
Chitosan	Chitin, chitosan ascorbate, deacetylated chitin biopolymer, N-carboxybutyl chitosan, sulfated O-carboxymethyl chitosan	-The biodegradable, biocompatible, and bioadhesive properties and low toxicity make chitosan is exten-sively utilized in intranasal formulations. -Furthermore, it collaborates with the nasal mucous fluid layer to increase drug exchange contact time across the membrane. -Powders, fluids, gels, microparticles, and microspheres include chitosan, among other intranasal medicine forms.	35
Lectins	peanut agglutinin, ulex europaeus agglutinin, and lentil lectin	-Lectins might be utilized in nasal drug delivery, especially when the concealment of medication-type NPs is necessary, such as DNA delivery.	35,36
Poloxamers	Poloxamer 188, poloxamer 182, poloxamer 407 NF, poloxamer 388 NF, poloxamer 124	-Poloxamers are thought to have ther moreversible characteristics, forms. -A gel at body temperature (*in-situ*) prevents the medication from being transported out of the nasal cavity for mucociliary clearance. The drug's BA is greatly improved.	34,36
Alginate-Polyethylene glycol Acrylate		-Possess combined properties of both polymers such as strength and gelation (alginates), acrylic (PEG) *In situ* gelation place when it interacts with multi-valent particles like Ca^{2+} and Fe^{2+}, decreasing its grip on mucosal tissues.	35
Thiomers	**Cationic thiomers:** chitosan cysteine, chitosan-thioglycolic acid, chi-tosan thio-butyl amidine. **Anionic thiomers:** carboxy methyl guar gum, sodium carboxy methyl starch, sodium aliginate.	-The oxidation of thiol bunches at physiological pH levels creates inter and intramolecular disulfide con-nections. The development of disulfide connections with the nasal mucosa increases the coating's consistency while significantly expanding the formulation's resi-dence time.	35

targeting in clinical applications. Nanocarriers and various agents under each carrier system for nose-to-brain delivery are shown in Tables 1 and Table 2[23-24].

6.2. Mechanism of nanocarriers[7,5,9]

The mechanism of various nanocarriers are descripted in Figure 3.

7. CURRENT RESEARCH ADVANCES IN NANOPARTICLES-BASED TREATMENT OF CENTRAL NERVOUS SYSTEM (CNS) DISEASES

7.1. Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative illness caused by beta aggregation of amyloid and intracellular neurofibrillary twists in the cerebrum. There are two types of promotion treatment: non-clinical and clinical. Non-clinical therapy aims to improve patients' pleasure or maintain their psychological and daily movement capacities. There are now six FDA-approved physician-recommended medicines for treating Alzheimer's disease. Regardless, these drugs can only reduce the severity of the illness's adverse effects for a short time; none have proven to affect disease progression. Considering the microenvironment of CNS, and the role of receptors on the surface in communicating with the cerebrum, researchers may develop and use a wide range of nanocarriers[37].

Shengnuo Fan et al., developed curcumin-loaded Polylactic acid-glycolic acid-Polyethylene glycol (PLGA-PEG) NPs linked with B6 peptide to treat Alzheimer's disease. *In vitro* studies using dynamic light scattering (DLS), flow cytometry (FCM), RBC lysis, and thromboelastographic (TEG) indicated that NPs decreased Cur's diameter, improved cellular absorption, and had good blood compatibility. According to Morris's water maze data, the spatial learning and memory capacity of APP/PS1 mice was significantly improved compared to native Cur, the PLGA-PEG-B6/Cur. *Ex vivo* studies revealed that PLGA-PEG-B6/Cur might reduce the hippocampal b-amyloid formation and deposit and tau hyperphosphorylation using Bielschowsky silver staining immunostaining western blotting[18].

7.2. Parkinson's disease

Parkinson's disease (PD) is a severe neurological condition characterized by a progressive loss of neurological function in older people caused by neuronal damage or death. Parkinson's disease degenerates the dopamine-producing cells in the substantia nigra region of the brain. The disease causes symptoms including resting tremors and stiffness, hypokinesia, stiffness, and bradykinesia. Drugs cannot reach the brain due to the BBB, making PD therapy exceedingly challenging. Traditional DD methods cannot cross the BBB, resulting in low BA and substantial toxicity (due to off-site drug release). As a result, new DD techniques for PD treatment, such as NPs, microemulsions, matrix systems, solid dispersions, liposomes, and SLN, must be developed faster[38].

Muthu et al., Risperidone was encapsulated in PLGA NP coupled with a poloxamer 407 thermally sensitive ISG. *In vivo*, investigations after IV administration in mice indicated a lower dose, less dose-dependent extrapyramidal side effects, and a more prolonged antipsychotic effect. On the other hand, the hematopoietic cytokine glycoprotein recombinant human erythropoietin increased the long-term potentiation, memory function, and dopamine and acetylcholine release. Chitosan and PLGA NPs for recombinant human erythropoietin improved pharmacokinetic properties. However, in terms of PD, there are no direct applications to date[39].

7.3. Epileptic disease

Epilepsy is the 4th most frequent global neurological disorder; it describes a set of illnesses that include several comorbidities such as depression, anxiety, learning disabilities, attention-deficit hyperactivity disorder, intellectual disability, and autism[40].

Shanshan Liu studied carboxymethyl chitosan NPs as a carrier for intra-nasal delivery of carbamazepine (CBZ) for direct drug delivery. The produced CBZ-NPs have a tiny particle size (218.762.41 nm), a high drug loading (approximately 35%), and a high EE, according to preliminary findings (around 80%). The *in vivo* results demonstrated that encapsulating CBZ in NPs and administering it via the nasal route improved medication BA and brain targeting properties[19].

7.4. Depression

Depressive disorders are prevalent in children throughout the world. The disease has profound implications for one's quality of life and financial issues owing to lost income and healthcare costs.

Haque et al., prepared venlafaxine-loaded alginate NP's NP's (VLF AG-NPs) and chitosan NP's NPs for antidepressant nose-to-brain transfer and investigated their efficacy in rats. Intranasal administration of VLF AG-NPs significantly improved behavioural and locomotor indicators compared to a VLF solution and an oral VLF tablet. On intravenous and intranasal administration of rhodamine-123 loaded alginate nanoparticles, biodistribution from intranasal administration exhibited a drug greater localization than free drug solution to the intravenous product. These findings also revealed that medicines might be given to the brain through the olfactory system, bypassing the circulatory system[41].

8. CONCLUSION

Transnasal delivery has great potential in targeting drugs to the brain in various disorders due to the exploration of anatomical and physiological advantages, noninvasive and its hierarchy of circumventing the problems associated with oral therapy of drugs. However, much of the research is still preclinical; a proper validation of the system is necessary to ensure these systems' safety. Target-based therapies can provide a future perspective in the nose-to-brain drug delivery studies that should concentrate on understanding mechanisms involved in carrier-mediated drug delivery, toxicodynamic and kinetic studies to accelerate the research in the same direction.

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REFERENCES

1. Giunchedi P, Gavini E, Bonferoni MC. Nose-to-Brain Delivery. Pharmaceutics. 2020;12(2):138.
2. Lee D, Minko T. Nanotherapeutics for nose-to-brain drug delivery: An approach to bypass the blood brain barrier. Pharmaceutics. 2021;13(12):2049.
3. Wang Z, Xiong G, Tsang WC, Schätzlein AG, Uchegbu IF. Nose-to-brain delivery. J Pharmacol Exp Ther. 2019;370(3):593-601.
4. Selvaraj K, Gowthamarajan K, Karri VVSR. Nose to brain transport pathways an overview: Potential of nanostructured lipid carriers in nose to brain targeting. Artif Cells Nanomed Biotechnol. 2017;46(8):2088-95.
5. Formica ML, Real DA, Picchio ML, Catlin E, Donnelly RF, Paredes AJ. On a highway to the brain: A review on nose-to-brain drug delivery using nanoparticles. Appl Mater Today. 2022;29(8): 101631.
6. Jeong SH, Jang JH, Lee YB. Drug delivery to the brain via the nasal route of administration: Exploration of key targets and major consideration factors. J Pharm Investig. 2023;53(1):119-52.
7. Crowe TP, Greenlee MHW, Kanthasamy AG, Hsu WH. Mechanism of intranasal drug delivery directly to the brain. Life Sci. 2018; 195:44-52.
8. Su Y, Sun B, Gao X, Dong X, Fu L, Zhang Y, et al. Intranasal delivery of targeted nanoparticles loaded with miR-132 to brain for the treatment of neurodegenerative diseases. Front Pharmacol. 2020;11:1165.
9. Alabsi W, Eedara BB, Encinas-Basurto D, Polt R, Mansour HM. Nose-to-brain delivery of therapeutic peptides as nasal aerosols. Pharmaceutics. 2022;14(9):1870.
10. Passoni A, Favagrossa M, Colombo L, Bagnati R, Gobbi M, Diomede L, et al. Efficacy of cholesterol nose-to-brain delivery for brain targeting in Huntington's disease. ACS Chem Neurosci. 2020;11(3):367-72.
11. Musumeci T, Bonaccorso A, Puglisi G. Epilepsy disease and nose-to-brain delivery of polymeric nanoparticles: An overview. Pharmaceutics. 2019;11(3):118.
12. Lima PHC de, Butera AP, Cabeça LF, Ribeiro-Viana RM. Liposome surface modification by phospholipid chemical reactions. Chem Phys Lipids. 2021;237:105084.
13. Puris E, Gynther M, Auriola S, Huttunen KM. L-Type amino acid transporter 1 as a target for drug delivery. Pharm Res. 2020;37 (5):88.
14. Ghadiri M, Young PM, Traini D. Strategies to enhance drug absorption via nasal and pulmonary routes. Pharmaceutics. 2019; 11(3):113.
15. Xu J, Tao J, Wang J. Design and application in delivery system of intranasal antidepressants. Front Bioeng Biotechnol. 2020;8: 626882.
16. Bonferoni M, Rossi S, Sandri G, Ferrari F, Gavini E, Rassu G, et al. Nanoemulsions for "Nose-to-Brain" Drug Delivery. Pharmaceutics. 2019;11(2):84.
17. Wong K, Riaz M, Xie Y, Zhang X, Liu Q, Chen H, et al. Review of current strategies for delivering Alzheimer's disease drugs across the blood-brain barrier. Int J Mol Sci. 2019;20(2):381.
18. Fan S, Zheng Y, Liu X, Fang W, Chen X, Liao W, et al. Curcumin-loaded PLGA-PEG nanoparticles conjugated with B6 peptide for potential use in Alzheimer's disease. Drug Deliv. 2018;25(1):1091-102.
19. Liu S, Yang S, Ho PC. Intranasal administration of carbamazepine-loaded carboxymethyl chitosan nanoparticles for drug delivery to the brain. Asian J Pharm Sci. 2018;13(1):72-81.
20. Ganger S, Schindowski K. Tailoring formulations for intranasal nose-to-brain delivery: A review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. Pharmaceutics. 2018;10(3):116.
21. Froelich A, Osmałek T, Jadach B, Puri V, Michniak-Kohn B. Microemulsion-based media in nose-to-brain drug delivery. Pharmaceutics. 2021;13(2):201.
22. Cunha S, Forbes B, Sousa Lobo JM, Silva AC. Improving drug delivery for Alzheimer's disease through nose-to-brain delivery using nanoemulsions, nanostructured lipid carriers (NLC) and *in situ* hydrogels. Int J Nanomedicine. 2021;16:4373-90.
23. Deshkar SS, Jadhav MS, Shirolkar SV. Development of carbamazepine nanostructured lipid carrier loaded Thermosensitive gel for intranasal delivery. Adv Pharm Bull. 2021;11(1):150-62.
24. Ribeiro LNM, Rodrigues da Silva GH, Couto VM, Castro SR, Breitkreitz MC, Martinez CS, et al. Functional hybrid nanoemulsions for sumatriptan intranasal delivery. Front Chem. 2020;8: 589503.
25. Chatterjee B, Gorain B, Mohananaidu K, Sengupta P, Mandal UK, Choudhury H. Targeted drug delivery to the brain via intranasal nanoemulsion: Available proof of concept and existing challenges. Int J Pharm. 2019;565:258-68.
26. Haumann R, Videira JC, Kaspers GJL, van Vuurden DG, Hulleman E. Overview of current drug delivery methods across the blood-brain barrier for the treatment of primary brain tumors. CNS Drugs. 2020;34(11):1121-31.
27. Costa C, Moreira JN, Amaral MH, Sousa Lobo JM, Silva AC. Nose-to-brain delivery of lipid-based nanosystems for epileptic seizures and anxiety crisis. J Control Release. 2019;295:187-200.
28. Alexander A, Agrawal M, Uddin A, Siddique S, Shehata AM, Shaker MA, et al. Recent expansions of novel strategies towards the drug targeting into the brain. Int J Nanomedicine. 2019;14: 5895-909.
29. Antimisiaris SG, Marazioti A, Kannavou M, Natsaridis E,

Gkartziou F, Kogkos G, et al. Overcoming barriers by local drug delivery with liposomes. Adv Drug Deliv Rev. 2021;174:53-86.
30. Bayanati M, Khosroshahi AG, Alvandi M, Mahboobian MM. Fabrication of a Thermosensitive *in situ* gel nanoemulsion for nose to brain delivery of temozolomide. J Nanomater. 2021;2021: 1-11.
31. Lobaina Mato Y. Nasal route for vaccine and drug delivery: Features and current opportunities. Int J Pharm. 2019;572:118813.
32. Abdulla NA, Balata GF, El-Ghamry HA, Gomaa E. Intranasal delivery of Clozapine using nanoemulsion-based *in-situ* gels: An approach for bioavailability enhancement. Saudi Pharm J. 2021; 29(12):1466-85.
33. Ciolacu DE, Nicu R, Ciolacu F. Cellulose-based hydrogels as sustained drug-delivery systems. Materials (Basel). 2020;13(22): 5270.
34. Agrahari V, Burnouf PA, Burnouf T, Agrahari V. Nanoformulation properties, characterization, and behavior in complex biological matrices: Challenges and opportunities for brain-targeted drug delivery applications and enhanced translational potential. Adv Drug Deliv Rev. 2019;148:146-80.
35. Piazzini V, Landucci E, D'Ambrosio M, Tiozzo Fasiolo L, Cinci L, Colombo G, et al. Chitosan coated human serum albumin nanoparticles: A promising strategy for nose-to-brain drug delivery. Int J Biol Macromol. 2019;129:267-80.
36. Li J, Zhao J, Tan T, Liu M, Zeng Z, Zeng Y, et al. Nanoparticle drug delivery system for glioma and its efficacy improvement strategies: A comprehensive review. Int J Nanomedicine. 2020; 15:2563-82.
37. Kaur A, Nigam K, Bhatnagar I, Sukhpal H, Awasthy S, Shankar S, et al. Treatment of Alzheimer's diseases using donepezil nanoemulsion: An intranasal approach. Drug Deliv Transl Res. 2020; 10(6):1862-75.
38. Aderibigbe BA. *In situ*-based gels for nose to brain delivery for the treatment of neurological diseases. Pharmaceutics. 2018;10 (2):40.
39. Tan MS, Parekh HS, Pandey P, Siskind DJ, Falconer JR. Nose-to-brain delivery of antipsychotics using nanotechnology: A review. Expert Opin Drug Deliv. 2020;17(6):839-53.
40. Akhtar A, Andleeb A, Waris TS, Bazzar M, Moradi AR, Awan NR, et al. Neurodegenerative diseases and effective drug delivery: A review of challenges and novel therapeutics. J Control Release. 2021;330:1152-67.
41. Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2022;7(2): e105-25.