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CURRENT METHODS FOR INRANASAL DRUG DELIVERY BASED ON NANOTECHNOLOGY FOR BRAIN TARGETING

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Abstract
Intranasal drug delivery is as a noninvasive and efficient approach extensively utilized for treating the local, central nervous system, and systemic diseases. Recent advancements in nanotechnology-based intranasal delivery systems have shown potential to enhance drug bioavailability, improve brain targeting, and overcome limitations associated with conventional delivery methods. As nanotechnology utilization in drug delivery has rapidly spread out, the nasal delivery has become attractive as a promising approach. The use of lipid-based nanoparticles, including nano/microemulsions, liposomes, solid lipid nanoparticles, and nano structured lipid carriers, has shown promise in enhancing the efficiency of nose-to-brain delivery. These nanoparticles facilitate drug absorption from the nasal membrane. Additionally, the in situgel (ISG) system has gained attention owing to its ability to extend the retention time of administered formulations within the nasal cavity. The anatomical and physiological considerations of the nasal cavity, particularly the olfactory and trigeminal nerve pathways, provide direct routes to the brain. Overall, this review furnishes a perspective aimed at galvanizing future research and development concerning intranasal drug delivery.

Keywords: Nasal drug delivery system, Intranasal route, Nano technology, brain disorder.

Introduction

Intranasal drug delivery, because of its non invasive and efficient nature, has found extensive application in treating local, central nervous system, and systemic diseases [1]. Intranasal delivery serves as an excellent strategy for brain disease therapy, bypassing the BBB and directly targeting drugs to the brain through the nose-to-brain route, involving the olfactory and trigeminal neural pathways [2]. The brain is one of the most intricate and important organs in the body; it processes information received from the sense organs and controls the majority of the body's functions. Movements, both voluntary and involuntary, the release of hormones, the storing of memories, and the operations of many other organs are all under its command [3]. The nasal canal provides a direct route for nose-to-brain medication distribution via the olfactory and trigeminal pathways. The nasal mucosa's strong vascularization facilitates rapid drug absorption and allows for potential dose reduction through better brain

targeting[4]. Nanotechnology-based modified delivery has gained popularity as a solution to problems with compliance and restricted bioavailability from the nasal cavity, depending on the drug's physicochemical qualities and the physiological parameters of the human nose. Furthermore, it has numerous advantages for treating chronic

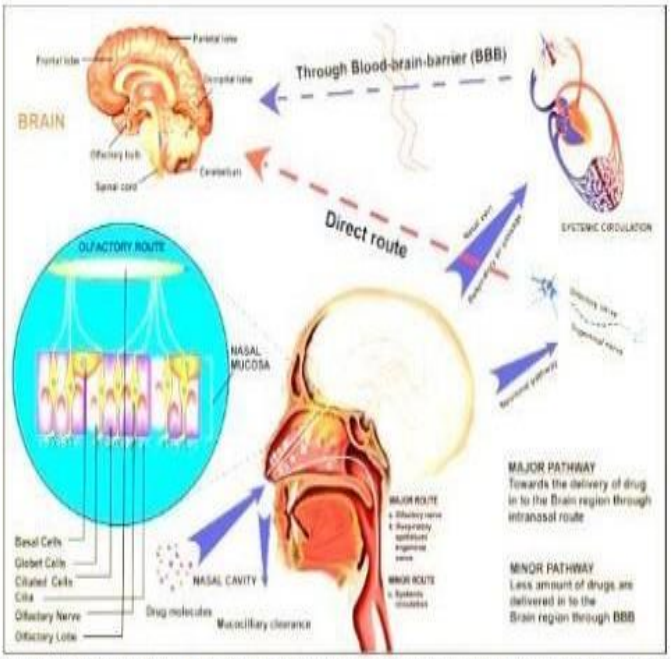

Figure 1: Transport of drugs from the nasal cavity to the brain happens in two ways: first, via the neuronal pathway, which travels through the olfactory and trigeminal sensory neurons; second, via the systemic circulation.

human diseases through target-oriented delivery-specific therapy [5]. Therefore, intranasal administration has attracted considerable research interest as an alternative method to conventional parenteral and oral routes, because it can increase the drug concentrations in the brain by direct nose-to-brain delivery via olfactory and trigeminal nerve pathways. This additionally ensures a rapid onset of action, it circumvents hepatic firstpass effects, and provides a patient-friendly administration route. To increase the efficacy of nose-to brain delivery, nanoparticles have emerged as promising carriers because of their remarkable capacity to facilitate drug transportation. Among the various nanoparticle types, lipid-based nanoparticles, such as nano emulsions, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs), may be suitable to solubilize poorly water-soluble drugs16 due to their rapid uptake and biodegradation, low toxicity, absence of a burst release effect, and easy scale-up process [6]. These carriers can pass the nasal mucosa and enter the cerebrospinal fluid.

Nasal Cavity: Anatomy of the Nasal Cavity

The nasal cavity can be divided into the vestibule, atrium, turbinate (respiratory), and olfactory regions. The upper part of the nasopharynx is connected to the nasal cavity [7]. The outermost nasal cavity is the vestibule (0.6 cm2), which is lined by keratinized and stratified squamous epithelium with embedded vibrissae [8]. The total surface area and volume of the nasal cavity are 150 cm and 15 ml, respectively [9]. The nasal respiratory area is the largest part of the nasal cavity, it is confined between the septal and lateral walls and it contains the superior, middle, and inferior turbinates forming the slit-like area that is responsible for the humidification and temperature regulation of the inspired air [10]. The anatomical aspect plays a crucial role in nasal delivery. To get the benefit of the high surface area of the nasal cavity and its consequences on higher absorption, the formulation must be spread over a large mucosal area.

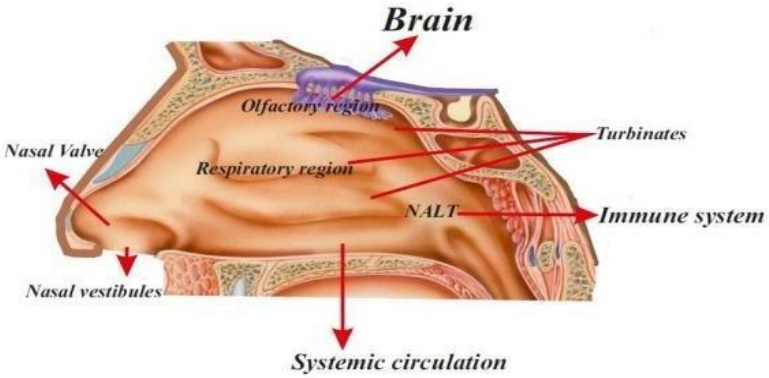

Figure 2: Anatomical structure of the human nasal cavity.

Nanotechnology for nose to brain delivery

Nanocarriers, such as nanoparticles and liposomes, offer significant advantages in improving drug administration from the nose to the brain. These carriers excel in pharmaceutical encapsulation, stability, and precision delivery to specified targets. Their small size facilitates efficient transportation along the nasal mucosa, increasing surface area contact and enhancing drug absorption [11] This enhanced delivery route can improve brain drug absorption while lowering the required dose, consequently reducing systemic side effects. Nanoparticle-based formulations for nose-to-brain drug delivery devices demonstrate potential in improving neurological disorder therapies by enhancing bioavailability and limiting systemic toxicity.

Table 1. Types of nanotechnology used for nose to brain delivery

S.No	Types of Nanoparticles	Characteristics
1)	Liposomes	Phospholipid bilayers are the basis of liposomes, which are lipid-based nanoparticles.
2)	Nanoemulsions	Surfactants stabilize oil-in-water or water-in-oil dispersions, which are known as Nanoemulsions.
3)	Nanostructured Lipid Carriers(NLCs)	Lipid-based carriers, known as NLCs, consist of a liquid lipid matrix and a solid lipid core.
4)	Solid Lipid Nanoparticles (SLNs)	Solid lipids make up SLNs, which stabilize medications inside their matrix.
5)	Polymeric Nanoparticles	The biocompatible polymers used to make these nanoparticles include chitosan and PLGA.
6)	Magnetic Nanoparticles	magnetically-active nanoparticles.
7)	Dendrimers	Proteins with a tree-like branched structure.

Conventional methods of administering drugs for braintargeting systems, such as oral and parenteral routes, involve delivering drugs into the brain through the systemic circulation.

However, the majority of administered drugs often remain in the systemic circulation due to challenges in penetrating physiological barriers, such as the BBB. Specifically, large molecules and more than 98% of lowmolecularweight drugs face difficulties permeating the BBB, resulting in low brain bioavailability. Additionally, oral administration leads to hepatic firstpass metabolism and intestinal enzymatic degradation prior to the arrival of the drug in the brain. Parenteral administration, like intrathecal delivery, can lead to complications, such as cerebrospinal fluid leakage and meningeal issues. On the other hand, the receptormediated approach has gained attention as a potentially safe and effective method for enhancing braintargeting

capability without disrupting the BBB membrane. However, this strategy carries the risk of losing therapeutic effectiveness due to the accumulation of drug carriers in unintended sites, such as the liver.

Pathway of Intranasal Transport to the Brain

The motivation for developing intranasal drug administration stems from the challenge of delivering drugs to the brain while overcoming the BloodBrain Barrier (BBB).Two primary delivery pathways in intranasal administration, the olfactory and trigeminal nerve pathways, provide direct routes to the brain. However, not all drugs administered intranasally are confined to these pathways. Some drugs may enter systemic or lymphatic circulations, where crossing the BBB is necessary to reach the brain. In such cases, the quantity of the drug that successfully penetrates the BBB and reaches the brain is often limited.

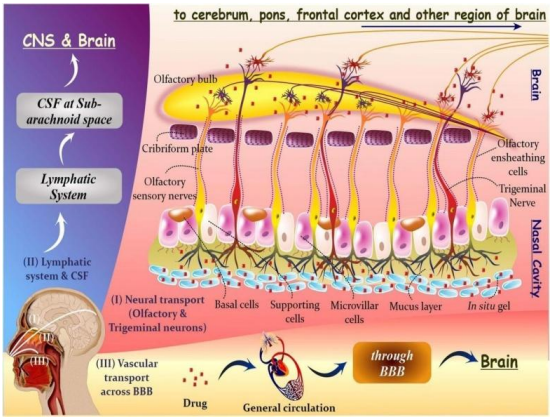

Figure 3 : Intranasal mechanism nose-brain delivery.

Strategies to Improve Drug Delivery via the Intranasal Route

Non-Invasive Methods: Two strategies can be used to overcome the BBB: invasive and non invasive approaches. Invasive techniques involve direct injection into the brain parenchyma or cerebrospinal fluid or the therapeutic opening of the BBB [12]. The direct injection of drugs or implantation into the brain parenchyma has been studied to treat neurological and mental disorders and stroke.

The other invasive approach, temporarily opening the BBB, necessitates collaboration with highly trained neurosurgeons and it may cause potential adverse effects from BBB disruption, such as hemorrhage and brain damage or inflammation.

Intranasal Lipid and Surfactant-Based Nanoparticulate Drug Delivery Systems

Lipid nanoparticles show a promising approach for intranasal delivery. The advantages of active agent protection from enzymatic degradation, capability for hydrophilic as well as lipophilic molecule delivery, low toxicity, good permeability, and the possibility of modifications and adaptations have justified their wide application for the intranasal route. These systems include liposomes, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), niosomes, nanoemulsions (NE) and nanocapsules (NC) [13].

Liposomes

One of the most popular lipid-based NPs for drug delivery applications is liposomes. A liposome normally consists of one or more phospholipid bilayers, frequently combined with additional lipids like phosphatidylcholine or cholesterol. The size and surface charge of liposome membranes can be changed by utilizing different kinds of lipids. For example, hydrophilic (located inside the aqueous core) or hydrophobic (located inside the lipid membrane) active substances can both be included in neutral or slightly negatively charged liposomes. On the other hand, negatively charged nucleic acid and positively charged liposomes can create multiplexes [14].

Solid lipid nanoparticles (SLNs)

Solid lipid nanoparticles are another example of lipid-based systems that have shown promising prospects for intranasal delivery. SLNs offer several benefits for drug delivery, including great physical stability, increased, controlled release of loaded medicines, and the capacity to be manufactured without the need for organic solvents. The main disadvantages of SLNs are their inflexible form, which limits the effectiveness of drug loading (particularly for hydrophilic molecules) and causes unwanted particle growth through agglomeration, which might result in the drug's burst release [15].

Nanostructured lipid carriers [NLCS]

These systems, composed of both solid and liquid lipids as a core, offer the advantages of higher loading capacity than SLNs without undergoing polymorphic transition and drug explosion during storage [16]. Intranasal NLCs have been utilized for the brain targeting of temozolomide -an antitumor agent- in a recent study. In this study, NLC protected the drug from the p-gp system by the effects of Poloxamer 188, which also increased drug mucosal penetration. As a result, the brain concentration of temozolomide was higher than what has been achieved after IV administration with a sustained effect. Thus, it can provide a direct delivery for the treatment of brain tumors [17].

Nano emulsions

Three phases make up the micelles that comprise nanoemulsions: an oily phase, an emulsifier, and an aqueous phase. There are three distinct types of nanoemulsions: bi-continuous (inter-dispersed water and oil domain), water in oil (sometimes called "reversed" micelles), and oil in water.[18]

Particularly for lipophilic medications, nanoemulsions can increase the drug's stability and bioavailability while increasing drug absorption through a larger surface area from nano-sized droplets [19].

Niosomes

Niosomes are structurally similar to liposomes in the concept of bilayer systems that entrap drugs with a chief difference in composition. Unlike liposomes, niosomes are composed of non-ionic surfactants that are responsible for a vesicle-like structure, thus providing more stability over liposomes by removing the inconvenience of oxidation and the purity variation of phospholipids . The main limitations of niosomes include aggregation, fusion, and leakages during storage. These adverse properties of niosomes can be minimized by additives such as cholesterol, fatty alcohols, charge inducers (dicetyl phosphate and stearylamine) or steric groups on the surface of niosomes .

Dendrimers

Dendrimers belong to the class of polymeric NPs, but what sets them apart from other polymers is their altered structure. These are big, single-weight, threedimensional molecules with a structure made up of nuclei, repeating units, and different functional groups like COONa, COOH, and NH2. [20]

Dendrimers, including polyamidoamine (PAMAM), carbosilane, poly-l-lysine (PLL), and polypropylene-imine (PPI), exist because of the chemical makeup of the core and branches. It is possible to manage the form, size, polydispersity, and specified

surface structure (hydrophilic or lipophilic, charged or neutral) in the nanoscale range because of the synthesis procedure.[21]

The most prevalent type of dendrimers, known as PAMAM dendrimers, have applications in regenerative medicine, medication and gene delivery, and many other fields. They are made up of an outer shell with amine branches and an inner core made of alkyl-diamine. Due to the extensive control over dendritic designs, Dendrimers are promising carriers for use in biomedical applications .

Magnetic nanoparticles

In nasal delivery systems, magnetic nanoparticles (MNPs) have demonstrated considerable promise, especially in brain targeting. The nasal route is a useful strategy to provide therapeutic drugs for neurological diseases because it provides a direct pathway to the brain, avoiding the blood-brain barrier.

Through the olfactory and trigeminal nerve pathways, the nasal cavity offers a direct connection to the brain, enabling MNPs to deliver medications to certain brain regions efficiently.[22]

Nano capsules (NCs)

Nano capsules are composed of an oily core surrounded by a polymeric coat (shell) with a general range of particle sizes of 100–500 nm. NCs have been one of the systems in the focus of research due to their promising potential as an effective drug delivery platform for the transmucosal administration of peptides, vaccines, and
hydrophilic and lipophilic drugs. The development of NCs has emerged from the ability to control particle size, surface properties, and composition.
Therefore, control over stability and interaction with the mucosal membranes are attainable
However, the NE with chitosan (NCs) formulations showed a significantly higher Cmax and AUC in addition to higher brain targeting (approximately 2-fold higher DPT%) The same effects have been achieved with olanzapine. A mucoadhesive NE of olanzapine showed a higher brain AUC0-∞ compared to a NE without mucoadhesive polymer and also showed a 2-fold higher brain bioavailability than the IV injected drug Recently, Colombo et al investigated the brain delivery of an intranasal NE containing kaempferol for glioma cell targeting.
This study showed the enhanced delivery effects of the chitosan-based mucoadhesive NE compared to the NE without chitosan. A mucoadhesive NE of zolmitriptan is another example that showed the enhanced brain permeation of zolmitriptan from a chitosan-based mucoadhesive NE. A 2.8-fold higher brain AUC
(08) compared to the IV and brain targeting parameters of 164.77 and 9.61 for DTE% and DTP%, respectively, were attained.

In-Situ Gel System

Recently, ISGs have emerged as a promising approach to address the challenges of nose-to-brain drug delivery through intranasal administration and to enhance drug uptake. Intranasal in situ gel mainly includes environment-responsive gel that transitions from a solution to a gel state in response to ions, temperature, or pH levels specifically within the nasal cavity.
Gellan gum gel, an ion-sensitive in situ gel, relies primarily on the nature of cations, particularly divalent cations over monovalent ones, to effectively facilitate the gelation of the solution. An in situ gel utilizing gellan gum demonstrates potential as a gel system, showcasing an optimal viscosity within the pH range of the nasal cavity. Moreover, it achieves high drug release (97.34%) without causing significant damage to the nasal mucosa. In situ ion-sensitive gelling systems using deacetylated gellan gum also enhance the solubility of drugs such as curcumin and subsequently improve bioavailability through intranasal delivery.

Devices for Nasal Administration

Traditional intranasal devices of liquid formulations, such as droppers and spray pumps, face challenges in delivering drugs to the olfactory epithelium because of their location in the upper part of the nose and the restrictions imposed by the nasal turbinate. For example, less than 3% of the drug reaches the olfactory region using a spray pump, and a dropper requires a precise patient position. Consequently, the drug may be absorbed systemically by blood vessels or cleared via mucociliary clearance. To overcome the disadvantages of conventional devices, researchers have developed devices capable of delivering drugs in different forms (powders or liquids).

Advantages and disadvantages of nasal drug delivery

The respiratory and olfactory regions of the nasal cavity present distinct advantages and limitations for drug delivery.. However, limitations include particle size constraints and limited space for highconcentration medicines, as well as poor CNS penetration for peptides and proteins. The olfactory region provides a minimally invasive method for direct administration to the inflamed brain, enabling the use of minimum therapeutic doses.
Limitations in this region include enzymatic inactivation of drugs by nasal enzymes, necessitating small medication quantities (less than 200 μL), poor protein delivery to the brain, and potential membrane disruption by high surfactant concentrations.

Therapeutic applications of nose to brain drug delivery

Nose-to-brain delivery systems have shown promising potential in treating a wide range of neurological and psychiatric disorders. This innovative approach has been explored for conditions such as epilepsy, where direct brain targeting can enhance anticonvulsant efficacy. In depression and schizophrenia, intranasal delivery of psychotropic medications may offer rapid onset of action and improved therapeutic outcomes. For acute conditions like stroke, this route provides a potential means for quick intervention and neuroprotection.

Conclusion

Nanotechnology-based intranasal drug delivery systems offer a promising approach for enhancing brain targeting and overcoming the limitations of conventional methods. These systems demonstrate improved bioavailability, reduced systemic side effects, and the potential for precise drug delivery to the central nervous system. The primary focus was on two methods: utilizing small lipid-based particles to transport drugs, and employing adaptable gels for controlled drug release within the nasal cavity. These approaches have the potential to revolutionize drug delivery from the nose to the brain. This paper provides a thorough review of the multifaceted nature of this specialized delivery method. Emphasis was been placed on its benefits, such as rapid drug absorption and the circumvention of specific digestive processes. The successful formulations can map the future of intranasal delivery. However, there are still many challenges to face. Increasing knowledge of nanotechnology is the first step towards successful delivery. The two-branch approach of utilizing nanoparticles coupled with intranasal delivery can provide the opportunities for efficient and convenient drug (vaccine) delivery. Accordingly, the future decades will most likely witness the production of intranasal formulations that overcome the current limitations.

Author Contributions
All authors are contributed equally

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