JOURNAL OF PHARMA INSIGHTS AND RESEARCH ISSN NO. 3048-5428

REVIEW ARTICLE

A Comprehensive Review on the Nanotechnology-based Intranasal Drug Delivery Systems for Brain Targeting

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Publication history: Received on 1st June; Revised on 14th June; Accepted on 2nd July 2024

Article DOI: 10.69613/fjsep132

Abstract: Intranasal drug delivery has emerged as a promising non-invasive route for targeting the central nervous system, bypassing the blood-brain barrier and minimizing systemic side effects. 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. Various nanocarrier systems, including liposomes, solid lipid nanoparticles, polymeric nanoparticles, and dendrimers, possess unique properties applicable to nose-to-brain drug delivery. The anatomical and physiological considerations of the nasal cavity, particularly the olfactory and trigeminal nerve pathways, provide direct routes to the brain. Biocorona formation on nanoparticles significantly impacts drug pharmacokinetics and distribution. Different nanocarrier systems offer distinct advantages and limitations, particularly in enhancing drug solubility, mucoadhesion, and cellular uptake. Stimuli-responsive and targeted nanocarriers have shown promise for improved spatiotemporal control of drug release. However, challenges remain in translating these nanotechnology-based approaches from bench to bedside, including toxicity concerns, scalability, and regulatory considerations. The current state of nanotechnology in intranasal drug delivery presents exciting opportunities for advancing CNS therapeutics through this innovative route.

Keywords: Nanotechnology; Nasal drug delivery system; Bioavailability; Blood brain barrier, Mucoadhesion

1. Introduction

Nowadays, nasal drug delivery has drawn a lot of attention due to its practical, promising, and dependable method of systemic drug administration, particularly for oral medications that are ineffective and injectable medications [1]. This pathway circumvents the first-pass metabolism, has a large surface area, a porous endothelium membrane, high total blood flow, and is easily accessible. Furthermore, due to the lack of pancreatic and stomach enzymatic activity as well as interference from the gastrointestinal tract, the nasal mucosa is permeable to more chemicals than that of the gastrointestinal tract [2]. Lipophilic medications are typically effectively absorbed via the nasal canal, and their pharmacokinetic profiles are often the same as those obtained after intravenous injection. In many situations, their bioavailability is close to 100%.[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]

Nasal mucus is necessary for the administration and absorption of drugs.Mucin, a protein found in mucus, can bond with solutes, altering the diffusion process. Nasal administration and absorption across the mucosa utilize a variety of methods, including paracellular and transcellular pathways [5]. Intranasal medication administration in neurological illnesses has received a lot of interest. However, attaining targeted drug delivery to specific areas of interest remains difficult due to various parameters, including the drug's physicochemical qualities, experimental circumstances, and anatomical and structural characteristics [6]. The volume to be delivered is the most critical factor to consider for achieving optimum bioavailability. Illum et al. found that the brain had very low bioavailability (0.1-1%), relative to the amount of medication supplied orally or through other routes.[7]

The development of DDS based on nanotechnology is a promising alternative for distributing medications through the NR, including macromolecules and even cleavage-prone pharmaceuticals.[8] 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 human diseases through target-oriented delivery-specific therapy. [9-11] Nanocarriers such as nanoparticles, nanoemulsions, liposomes, and solid lipid nanoparticles have been studied for delivering a wide range of therapeutic agents via the intranasal route because they provide benefits such as stability, increased drug solubility, improved drug bioavailability, targeted delivery, and controlled release. Drug distribution to the brain through the nose route's trigeminal and olfactory pathways can be significantly

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enhanced by nanocarriers. These carriers can pass the nasal mucosa and enter the cerebrospinal fluid. This review attempts to provide light on the role of nanocarriers in nose-to-brain medication delivery[12].

2. Background

2.1. Anatomy of nasopharyngeal tract

Understanding the architecture and physiology of the nasal canal is critical for designing an IN drug delivery formulation based on nanotechnology and determining the channels through which molecules must pass through the mucosal membrane.[13] The nasal cavity is lined with epithelial mucosa, separated into two symmetrical halves by the septum (Figure 1), and extends posteriorly to the nasopharynx.[14]

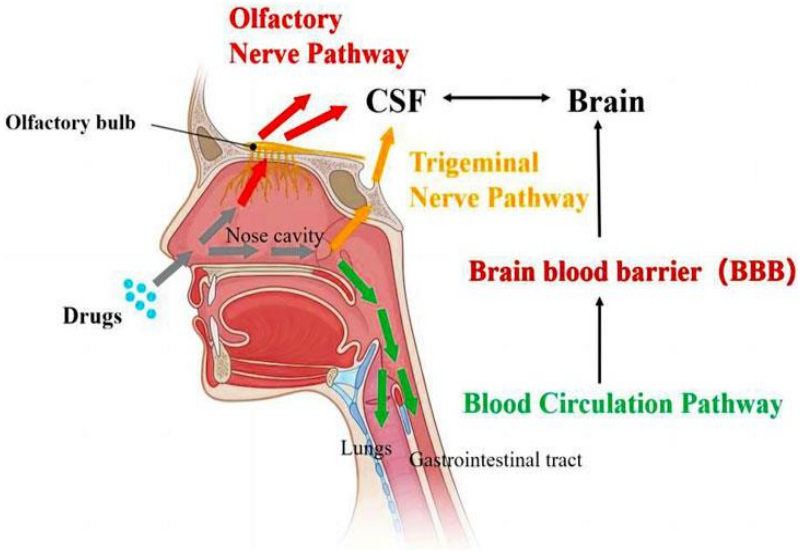

Figure 1. Intranasal drug delivery

2.2. Pathways in the intranasal route of drug administration

The variability in nasal shape across individuals poses significant challenges to the development of reliable medicine delivery systems from the nose to the brain. The nasal cavity's complicated structure, which includes changes in the thickness of the mucosal lining, surface area, and airflow patterns, influences the dependability and effectiveness of medicine absorption and delivery to the brain [15]. There are three probable avenues for drugs to enter the brain via the nasal cavity: (i) indirect or systemic pathways via the respiratory portion of the nasal cavity; (ii) olfactory pathway via olfactory neurons; and (iii) trigeminal pathway. The indirect pathway involves medication absorption from the pulmonary epithelial area directly into the bloodstream. From here, the medicine can be delivered to the site of action, and it may even enter the brain.

2.3. Nasal route for drug delivery

The limited distribution of therapeutic drugs significantly impairs the systemic therapy of many central nervous system (CNS) illnesses, including depression, epilepsy, schizophrenia, and migraine. Deprived CNS access is mostly connected with discriminatory barricades that separate the CNS from the circulatory system. By using nasal delivery methods based on nanotechnology and the olfactory area, this barrier is removed. The olfactory section, which can be located in the upper remote divisions of the nasal channels, indicates the potential for specific medication molecules to cross the blood-brain barrier and permeate into the brain. [16] Following nasal administration, peptides and proteins can enter the brain via the olfactory bulb and trigeminal pathways, bypassing the blood-brain barrier [17,18].

The marketed nasal treatments containing CNS drugs have the potential for direct delivery to the brain and cerebrospinal fluid. In light of this, the combination of systemic absorption and direct transfer to the CNS via the olfactory area or trigeminal neurons is responsible for the increased bioavailability of CNS drugs following nasal delivery. Figure 2 shows the many possibilities for medication absorption following nasal delivery.

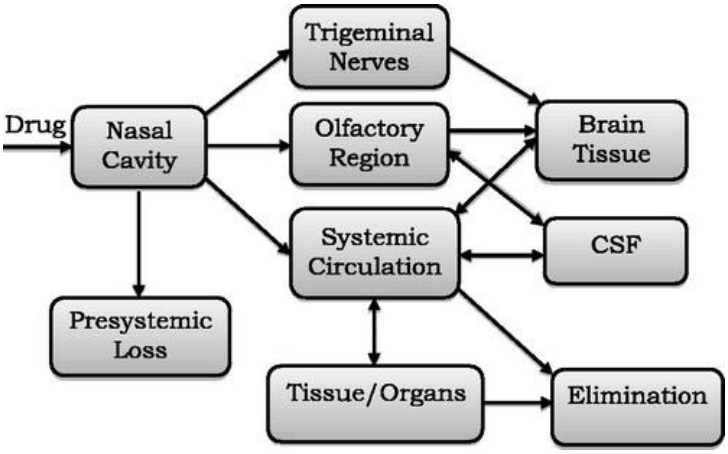

Figure 2. Absorption of medication following nasal delivery

2.4. Advantages and disadvantages of nasal drug delivery

The respiratory and olfactory regions of the nasal cavity present distinct advantages and limitations for drug delivery. The respiratory region offers a highly porous, vast surface area for non-surgical drug administration, allowing rapid absorption and direct brain delivery while bypassing the blood-brain barrier.[19] However, limitations include particle size constraints and limited space for high-concentration 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.

2.5. 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. In neurodegenerative disorders such as Parkinson's Disease, nose-to-brain delivery systems can facilitate the transport of dopaminergic agents directly to affected brain regions. Moreover, this approach holds promise for various other CNS and neurological disorders, offering a non-invasive method to bypass the blood-brain barrier and deliver therapeutic agents more effectively to the central nervous system.[1,4,9]

3. 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 [20]. 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. Various types of nanotechnology that are delivered from the nose to the brain are shown in Table 1.

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.

3.1. Lipid based nanoparticles

They are solid structures called lipid nanoparticles, which offer a cool alternative to other types of nanoparticles—like polymeric ones, nanogels, & nanoemulsions. The size of these lipid nanoparticles is super tiny too! They can be anywhere from 1 to 1000 nanometers in size[29].Since the surface of these solid lipid nanoparticles is made from safe lipids and surfactants, people generally say they're okay for our bodies. Common lipids include things like triglycerides, monoglycerides, diglycerides, fatty acids, & waxes[30]. These lipid nanoparticles are really useful—like special delivery systems! They help get past some issues we see with polymeric nanoparticle systems. We have two generations to consider here! Solid lipid nanoparticles, also known as SLNs, are the first generation. Then comes the second generation with nanostructured lipid carriers (NLC)[31] The NLCs are great because they solve some problems found in the first generation. Their lipid matrix is really good at stopping breakdown after delivery and keeping proteins stable too.[32]

Drug delivery systems utilizing lipid-based nanoparticles have been the subject of extensive research. Because these NPs are amphiphilic, they can transmit components that are hydrophilic and hydrophobic inside a single particle [33]. Similar to the lipids found in the cell membrane, lipids used in lipid-based carriers are biocompatible and biodegradable. These characteristics lessen their toxicity and enable them to enter cells with efficiency. These lipid-based NPs are frequently altered using polymers like poloxamers or polyethylene glycol (PEG). PEG is a biocompatible, hydrophilic polymer that stabilizes nanoparticles [34]

3.2. 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 [35-39]

3.3. Solid Lipid nanoparticles

The more recent class of lipid-based nanocarriers are known as solid lipid nanoparticles (SLNs), which are lipid emulsions in which a solid lipid has taken the place of a liquid lipid. Their diameter ranges from 100 to 300 nm, and they form a solid lipid matrix. They usually consist of physiological lipids in water or aqueous surfactants [40].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 [41,42]

3.4. Nanostructured lipid carriers

A more modern class of lipid-based NPs designed to address the drawbacks of SLNs are called nanostructured lipid carriers, or NLCs. Because NLCs contain a blend of liquid and solid lipids, they increase drug loading and inhibit the drug's burst release [40]. The twofold emulsion method (w/o/w) and high-pressure homogenization are commonly used to create NLCs [43]. Higher

encapsulation efficiency can be attained with hydrophobic compounds because they are more soluble in liquid lipids than in solid lipids. Reduced encapsulation efficiency for a combination of two or more therapeutic agents and comparatively limited drug loading capacity for hydrophilic pharmaceuticals are some of NLC's drawbacks [44]

3.5. Nanoemulsions

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. [45]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 [46]. It can, however, result in poor stability and the release of the encapsulated molecules during storage since it is thermodynamically unstable [47]

3.6. Polymeric nanoparticles

3.6.1. Natural Polymer-Based Nanoparticles

Numerous nanoparticles have been created using chitosan (CS). Insects and crustaceans are made of chitin, which is deacetylated to produce N-acetyl-D-glucosamine, which is the polysaccharide known as chitosan [48]. With a pKa of roughly 6.5, chitosan gets protonated in situations with an acidic pH.Because mucus has a pH of 5.5 to 6.5, chitosan is positively charged, which promotes its stability [49,50]. Chitosan-based NPs extend the bioavailability of the encapsulated medication for the brain by remaining longer in the olfactory and respiratory mucosa since both the respiratory and olfactory epitheliums are negatively charged. Furthermore, it functions as an enhancer of permeation, aiding in the opening of tight junctions between epithelial cells and facilitating the paracellular transfer of materials.

3.6.2. Synthetic Polymer-Based Nanoparticles

Drug delivery methods have been developed using synthetic polymers on a large scale. Numerous of these polymers are biocompatible and biodegradable, which makes them excellent N2B delivery vehicles. Poly(L-lactide-co-glycolide) (PLGA), poly(lactic acid) (PLA), and poly(glycolic acid) (PGA) are the most commonly utilized polymers. Because of their hydrophobicity, they are utilized to promote hydrophobic drug loading and stop medications from degrading in the nasal cavity [51,52]. These polymer-based nanoparticles use single or double-emulsion methods to encapsulate pharmaceuticals [53]. Similar to lipid-based liposomes, PEG or poloxamers are frequently used to modify the surface of polymeric nanoparticles to improve their stability, drug loading, and capacity to pass through nasal mucus [54].)

3.7. 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, three-dimensional molecules with a structure made up of nuclei, repeating units, and different functional groups like COONa, COOH, and NH2. [56] Different forms of 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.[57] 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 and an efficient way to administer hydrophobic and insoluble medications.[58,59]

3.8. 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.[60] An external magnetic field can guide MNPs to specific areas, increasing medication concentration at the target region and boosting therapeutic efficacy[61].

4. 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. While challenges such as enzymatic degradation, limited absorption of certain molecules, and formulation constraints persist, ongoing research continues to address these issues. The

development of advanced nanocarriers, coupled with a deeper understanding of nasal physiology and drug transport mechanisms, paves the way for more effective treatments of neurological disorders.

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