Micro- and Nanosized Carriers for Nose-to-Brain Drug Delivery

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The intranasal route of drug administration offers numerous advantages, such as bypassing the intestine, avoiding first-pass metabolism, and reducing systemic side effects. Moreover, it circumvents the BBB, providing direct entrance to the brain through the olfactory and trigeminal nerve pathways. Micro- and nanotechnological approaches were widely used to overcome these limitations and enhance the availability of drugs in the brain tissue. Micro- and nanoparticulate carriers are composed of natural or synthetic materials that interact with biological structures at the molecular level and lead the treatment of NDs into a new direction. They may induce interaction between target sites, thus minimizing the side effects.

microparticles nanoparticles neurodegenerative disorders Alzheimer's disease Parkinson's disease nose-to-brain

1. The Nasal Route—A Shortcut to Deliver Therapeutics Directly to the Brain

The brain is undoubtedly the most protected organ in the human body from the entry of exogenous substances such as toxins and drug molecules. This protection is provided by different cells at three interfaces: the blood–brain barrier (BBB), the blood–cerebrospinal fluid barrier (BSB), and the arachnoid barrier [1]. To reach the brain, drug molecules must meet certain criteria: they should be non-ionized and lipophilic, with a molecular weight below 400 Da and capable of forming fewer than eight hydrogen bonds [2]. Most drugs used for the treatment of neurodegenerative disorders do not comply with the listed requirements for effective brain delivery. This has led scientists to search for alternative administration routes to bypass the BBB and harness the therapeutic potential of drug molecules. Therapeutics might be administered directly to the central nervous system (CNS) by intrathecal, intraparenchymal, and intracerebroventricular injections/infusions, but these routes are invasive and are not suitable for chronically administered drugs [3][4]. The nasal route has gained attention in recent years as non-invasive and easy-to-self-administer path that allows for rapid absorption and avoids the first-pass metabolism of therapeutics. The number of approved intranasal formulations is constantly growing, e.g., Rivamist® (rivastigmine intranasal spray) (Lachesis Biosciences Ltd, Warrnambool, Australia), and can be used to treat agitation associated with Alzheimer's disease.

Nasal formulations have the potential for self-medication and good patient compliance. The human nasal cavity extends from the nostrils to the nasopharynx (12–14 cm in length) and contains four different types of epithelia and

underneath mucosa: squamous, respiratory, transitional, and olfactory [5][6]. Nasally administered drugs are deposited in the respiratory or olfactory epithelium [7][8]. From the respiratory epithelium, drugs can be absorbed in the systemic circulation, and then can reach the CNS if they can cross the BBB. Regarding nose-to-brain delivery, olfactory mucosa, and the trigeminal nerve, which innervates the olfactory and respiratory mucosa, are of particular interest (**Figure 1**). The nasal route provides two pathways—intracellular and extracellular—that are responsible for the drug being transported directly to the brain [6]. The intracellular pathway involves endocytosis by sensory olfactory cells, axonal transport to their synaptic clefts, and exocytosis into the olfactory bulb, where neurons projecting to brain regions repeat the process [9]. The extracellular pathway directly transports drug molecules into the cerebrospinal fluid (CSF) through the paracellular space of the nasal epithelium and then through the perineural space to the subarachnoid space of the brain [9]. Both mechanisms contribute to the transportation of drug molecules, but the intracellular pathway is quite slow and cannot demonstrate the delivery of intranasal markers to all regions of the brain far beyond the projections of the olfactory bulb. Although reinforced by limited kinetic evidence, the extracellular pathway appears to be the main component of drug transport and should be the primary target [9]. It is reasonable that a combination of these pathways may occur (**Figure 2**), depending on the physicochemical properties of the drugs, characteristics of the formulation, and the type of drug-delivery device. The target region for nose-to-brain delivery is the olfactory epithelium in the upper nasal cavity. Due to the rich vascularization, the nasal mucosa generally serve as an effective absorption surface for therapeutic agents. However, the olfactory region, due to its proximity to the CSF, presents a direct connection to the CNS (nose-to-brain) [10].

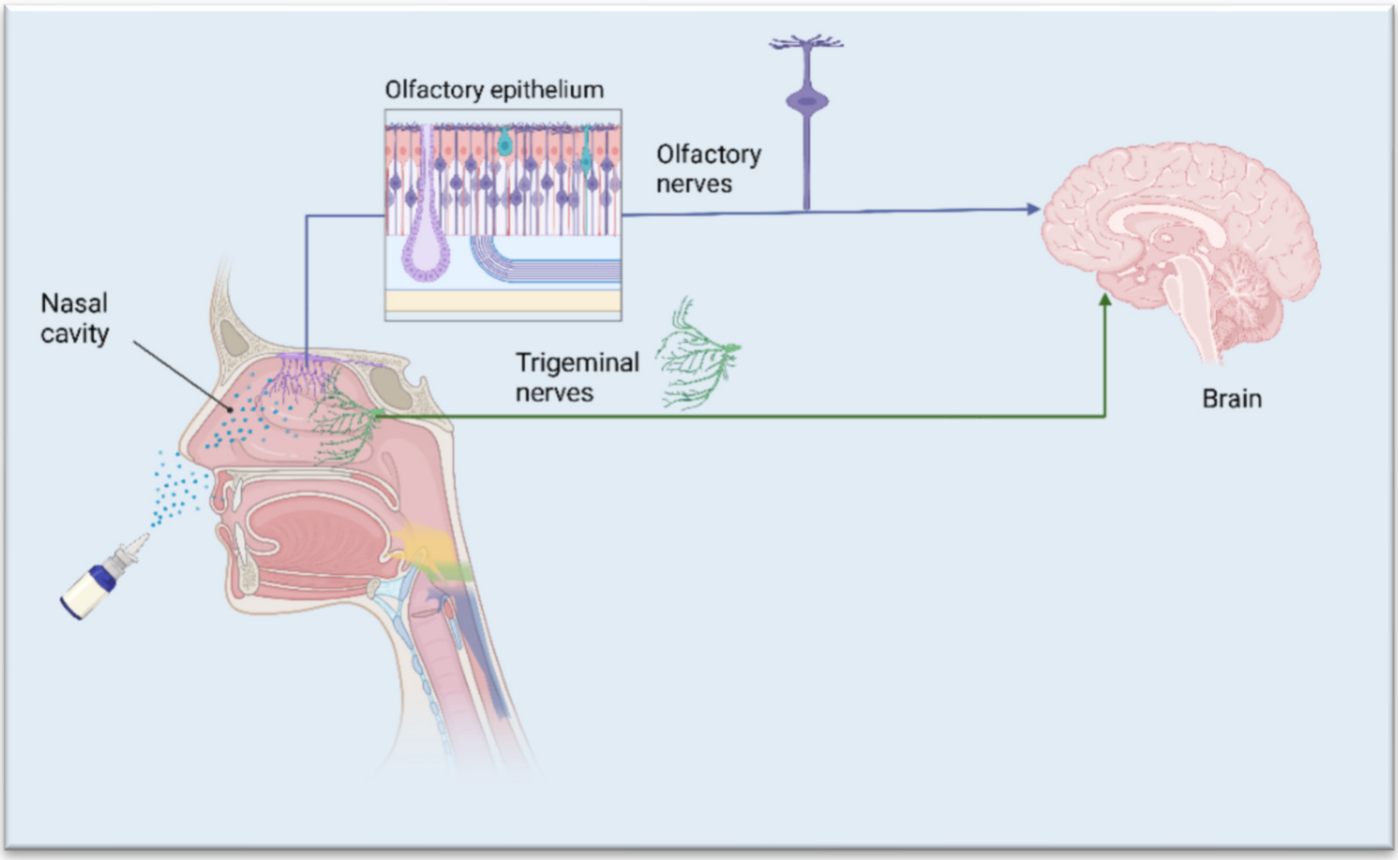

Figure 1. Nose-to-brain drug delivery. Schematic representation of olfactory and trigeminal neurons' position in the nasal cavity; in purple-olfactory pathway, in green-trigeminal pathway. Created with BioRender.com (accessed on 25 June 2022).

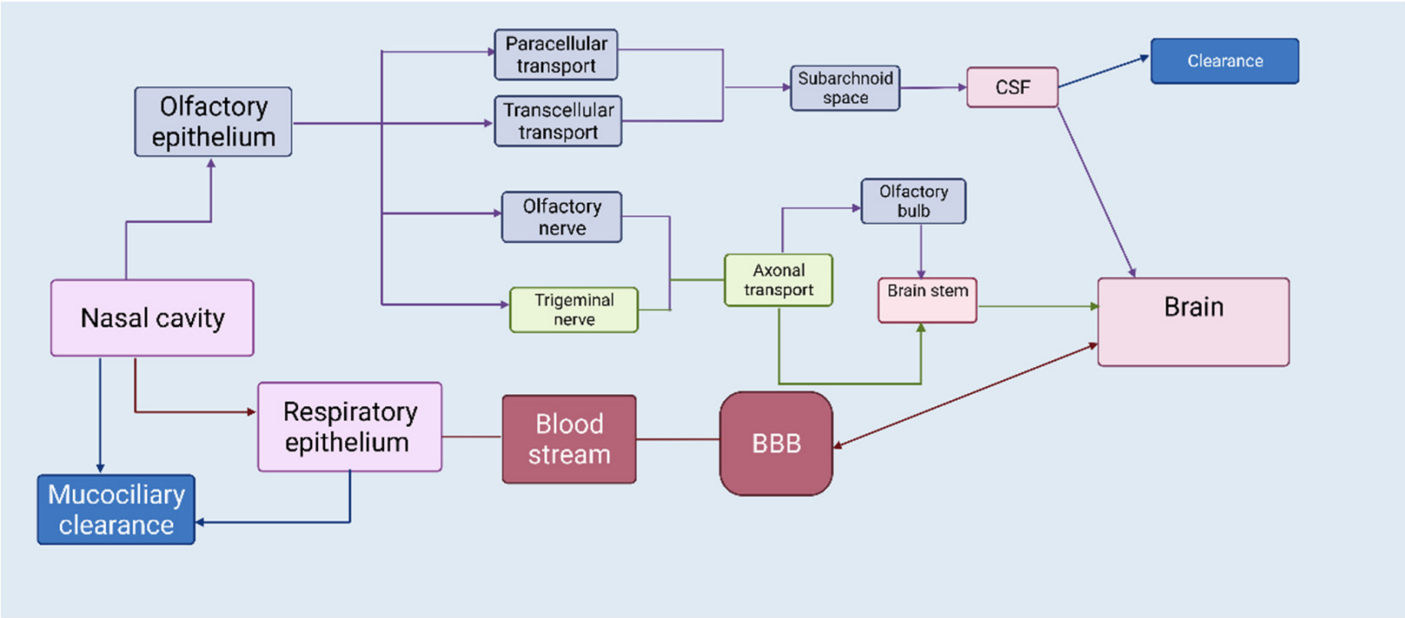

Figure 2. Nose-to-brain drug-transport pathways. After nasal administration drug molecules can reach the brain via olfactory, systemic, and trigeminal pathways. Olfactory and trigeminal pathways avoid first-pass metabolism of drugs and bypass BBB to deliver molecules directly to the brain via transcellular and paracellular transport. Created with BioRender.com (accessed on 25 June 2022).

2. APIs Suited for Nose-to-Brain Drug Delivery

Dosage forms with targeted nose-to-brain delivery include mainly drugs that do not reach therapeutic concentrations in the brain tissue, otherwise administered, e.g., orally, drugs with a pronounced first-pass effect, and drugs with many peripheral side effects [11]. The main properties that affect the rate and extent to which drug molecules will be transported from the nasal cavity to the brain tissue are the molecular weight, lipophilicity, and the degree of dissociation [6].

Dopamine itself, for example, cannot be used for the treatment of Parkinson's disease because it is incapable of crossing the BBB. In an animal study, dopamine levels were investigated in blood and cerebrospinal fluid to find out whether the drug was transferred along the olfactory pathway to the CNS following nasal administration. The drug was given intravenously or nasally. Higher dopamine levels in the brain were registered 30 min after nasal administration compared to those after intravenous administration. These results indicate that unchanged dopamine is transferred into the olfactory bulb via the olfactory pathway in rats [12]. Studies in humans have demonstrated that peptides such as melanocortin, vasopressin, and insulin, which have been shown to affect brain functions, including learning, memory, and cognition, accumulate in the brain tissue after intranasal administration

[13]. Intranasal insulin was found to improve cognitive functions in patients with Alzheimer's disease with no increase in peripheral blood levels [14].

3. Micro- and Nanoparticles for Nose-to-Brain Delivery

Various dosage forms (solutions [13][14], suspensions [15], microemulsions [16][17], gels [18]) have been prepared for nose-to-brain delivery. Conventional forms usually do not provide a controlled release of drug molecules and are not capable of targeted delivery [19]. There is usually a rapid release and absorption of the active molecules soon after administration, and a sharp increase in plasma concentration, which can lead to toxic effects. After a relatively short period of time, this concentration falls below therapeutic levels, and this may lead to more frequent use of the dosage form [19]. Particulate formulations can offer advantages over conventional forms, such as greater stability, convenience [20] and a long residence time in the nasal cavity [21]. Another important aspect to consider when looking at nose-to-brain drug delivery is to ensure that the formulation is deposited in the olfactory region, which can be achieved with the help of appropriate devices for both liquid and solid systems [22]. Furthermore, the nasal dosage form should be designed to provide an extended residence time and maintain a high local concentration for drug diffusion [23]. Particle size is another important feature in the development of an optimized delivery system for nose-to-brain administration. Nanoparticles, for example, permeate phospholipid membranes more easily than microparticles due to their smaller size, since the tight junctions of the nasal epithelium are smaller than 15 nm. Larger particles cannot permeate the epithelium; they release the drug in the mucosal tissue, where it is usually absorbed by passive diffusion. The surface charge of the carrier plays a crucial role in prolonging the contact time between the carrier and the mucosa. Microparticles with a positive charge may adhere to the mucosa due to the net-negative charge of the mucin.

4. Microparticles

Microparticles are drug-delivery systems, in the 1–1000 µm size range. They have both therapeutic and technological advantages based on their structural and functional abilities, such as modified and targeted drug delivery and release, protection of the encapsulated active agent against degradation, protection of the body from systemic side effects, dose titration and less dose dumping, more homogeneous distribution, and more predictable pharmacokinetics with reduced variables [24][25][26]. Microparticles can be considered as homogeneous or heterogeneous systems depending on the formulation and preparation process [27]. They can be incorporated in different dosage forms—liquids (solutions, emulsions, suspensions), semisolids (gels, creams, pastes), and solids (powders, granules, tablets) [25].

The deposition of particles in the human nasal cavity depends on the geometry of the nasal cavity on the one hand, and on the particles' properties, such as size, shape, and density, on the other. Evidence in the literature suggests that particles larger than 20 µm show a preferential deposition in the anterior part of the nasal cavity on inhalation due to high inertial impaction [28], while particles smaller than 5 µm follow the airways and exit the nasal cavity [28]. Research data suggest that particles of around 10 µm in size may show a preferential deposition in the olfactory

region when intranasally administered at normal inhalation rates [29]. This suggests that tailoring the carrier drug particle size (into micron-sized particles) can be a potential strategy to enhance the preferential deposition of drug particles in the olfactory region of the nasal cavity (**Table 1**). Since the mucoadhesive capacity is crucial for the increased residence time of drug-loaded particles in the nasal cavity, a common approach to prolonged deposition on the olfactory epithelium has been to use mucoadhesive polymers for the formulation of drug carriers [30].

Table 1. Polymeric and lipid microparticles developed for nose-to-brain delivery in the treatment of NDs.

Active Ingredient	Polymer/Lipid	Preparation Method	Ref.
	Polymeric microparticles		
β-cyclodextrin, Hydroxypropyl-β-cyclodextrin	Chitosan, Alginate	Spray-drying	[31]
Deferoxamine mesylate	Chitosan, Methyl-β-cyclodextrin	Spray-drying, Freeze-drying	[32]
Ropinirole	Alginate, Chitosan	Spray-drying	[33]
Ropinirole	Carbopol 974P, Guar gum	Solvent evaporation	[34]
Quercetin	Methyl-β-cyclodextrin, Hydroxypropyl-β-cyclodextrin	Freeze-drying	[35]
Rivastigmine	Ethylcellulose, Chitosan	Emulsion solvent evaporation	[36]
FITC-dextrans	Tamarind seed polysaccharide	Spray-drying	[37]
	Lipid microparticles		
Resveratrol	Tristearin, Glyceryl behenate, Stearic acid	Melt oil/water emulsification	[38]

5. Nanoparticles

The great interest in nanoparticles as drug delivery systems is due to numerous advantages such as targeted delivery of drug molecules, greater bioavailability, reduced risk of side effects, etc. [39]. Nanoparticles can incorporate both hydrophilic and hydrophobic drugs and can be used for a variety of administration routes. Inside the nasal cavity, particulates can undertake different pathways according to their size. If the size ranges between 10 and 300 nm, nanoparticles can deliver therapeutic agents through the olfactory pathway directly to the brain; if the size is less than 200 nm, the delivery will occur through clathrin-dependent endocytosis, and if it is in the range from 100 to 200 nm, the transport will occur by caveolae-mediated endocytosis [40]. Certainly, the particle size of the nanocarriers will play a crucial role in achieving brain targeting via the nasal route. However, many other

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factors, such as carrier type, drug properties, mucoadhesion and swelling capacity, would also be of great importance (Table 2).

Table 2. Polymeric and lipid nanoparticles developed for nose-to-brain delivery in the treatment of NDs.

Active Ingredient	Polymer/Lipid	Preparation Method	Ref.
	Polymeric nanoparticles		
Bromocriptine	Chitosan	Ionic gelation	[41]
Ropinirole	Chitosan	Ionic gelation	[42]
Rivastigmine	Chitosan	Ionic gelation	[43]
Galantamine	Poly (lactic acid), Poly (lactide-co-glycolide)	Double emulsification of solid-oil-water (s/o/w)	[44]
Huperzine A	Poly (lactide-co-glycolide)	Emulsion solvent evaporation	[45]
Genistein	Chitosan	Ionic gelation	[46]
	Lipid nanoparticles		
Paenol	Soyabean lecithin	High temperature emulsification/ low-temperature curing	[47]
BACE1 (siRNA)	Solid triglycerides	Emulsion solvent evaporation	[48]
Dopamine	Gelucire® 50/13	Melt emulsification	[49]
Pueraria flavones	Borneol, stearic acid	Emulsion solvent evaporation	[50]
Pioglitazone	Tripalmitin, MCM, Stearyl amine	Microemulsification	[51]

6. Composites

Polymer nanocomposites (PNCs) are a new class of reinforced materials that are formed by the dispersion of nanoscale particles throughout a polymer matrix. Nanocomposites consist of a polymer matrix embedded with nanoparticles to improve a particular property of the material [52]. Researchers span the range from the synthesis of basic structures (such as micro- and nanoparticles functionalized with molecules, simple biomolecules, or polymers) to more complex structures. The main approach initially focused on the control of shape, size, and surface charges, and then on modulating the topology of their chemical composition. At present, many biocompatible and biodegradable polymers have been experimentally and/or clinically investigated for the preparation of polymer-based composites as drug carriers [53]. By designing a composite structure, specific

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physicochemical and mechanical properties may be obtained. The resulting material may show a combination of its components' best properties, as well as interesting features that single constituents often do not possess [54]. Examples of polymer micro- and nanoparticulate carriers' applications for drug delivery in Alzheimer's and Parkinson's disease models are quite numerous, and they can take advantage of a relatively large number of materials that are biodegradable and suitable for particulate synthesis, including polylactide-co-glycolide (PLGA), polylactic acid (PLA), chitosan (CS), gelatin, polycaprolactone, and polyalkyl cyanoacrylates [55]. Polymeric composites might help to ameliorate the quantity and kinetic release profile of potential and existing Alzheimer's and Parkinson's disease drugs. The composite structure should be able, after intranasal application, to stably adhere to outer-nasal olfactory epithelium to promote the release of nanoparticles loaded with active molecules. Nanoparticles should then be able to cross the epithelium and migrate to the nervous cells that comprise the olfactory nerve and project to the olfactory bulbs [5][6][7][8]. It is worth noting that the polymeric composite, after residing for a sufficient time to release its nanoparticles, should be degraded and eliminated without discomfort for the patient [56]. At present, composite structures seem to be promising drug-carriers, with numerous advantages over conventional forms, but scholars still need to deepen our knowledge of their properties and the peculiar features that the resulting nanoparticles are able to gain upon their carefully arranged mixture.

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