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EDITORIAL

Can nanoparticle-based intranasal delivery systems revolutionize treatment of central nervous system diseases?

Giuseppe Nunziata[a], Fabio Pizzetti[a], Pietro Veglianese[b], Gianluigi Forloni[b], Claudia Balducci[b] and Filippo Rossi[a]

[a]Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano Milan, Italy; [b]Department of Neuroscience, Istituto di Ricerche Farmacologiche Mario Negri IRCCS Milano, Italy

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1. Introduction

Nasal drug [1] delivery is a noninvasive and effortless system of drug administration through the nasal passage that offers an alternative pathway for direct entry into the central nervous system (CNS) by circumventing the blood–brain barrier (BBB) and hepatic first-pass metabolism [2]. Thus, nasal drug delivery can minimize systemic exposure and give rapid-fire onset of action. In comparison to the intravenous and oral routes, the nasal route administration can enhance drug bioavailability due to the largely vascularized nasal mucosa, therefore allowing quick pharmaceutical absorption. Even if recent progresses are very positive, there are still some challenges that should be solved to obtain reliable and consistent intranasal administration of drug molecules. Indeed, the administration dosage, which is very limited due to the fact that nose volume is very small (5–6 cm^3), together with the quick clearance and possible degradation of the active molecules present key points that should be investigated. In this framework, in the last decades, polymeric nanoparticles evidenced to be the ideal candidates as carriers for the delivery of drugs or genes, thanks to their ability to sustain and control the localized release of active principles in situ [3]. Polymeric nanoparticles are defined as colloids in the range of 1 nm and 100 nm that can work as carriers and load active principles within their core absorbing them onto the surface or loading them within their core. They are characterized by high surface to volume ratio, compatibility with biological environment and biodegradability. These properties together with their high versatility in terms of hydrophilic or hydrophobic behaviors, size, shape, and surface charge make them ideal candidates in drug or gene delivery. Another key opportunity is represented by the possibility to modify their structure using responsive polymers that can introduce functionalization on nanoparticles surface. All these features can tune the selectivity of the device and ameliorate their ability as controlled delivery systems over time. Various nasal administration route showed extremely promising results in many human districts, their best performances are recorded in the treatment of diseases related to the CNS. The treatment of CNS diseases is often challenging due to many factors that have a negative impact on the efficient targeting of the brain.

In particular, the low permeability of the BBB is probably the most severe one and almost no nanotools showed the ability to cross it in clinical trials [4]. Intranasal administration is a good alternative to bypass the BBB allowing pharmaceutical treatments to reach the brain directly. Thus, the use of NPs in nasal delivery route can be considered as an extremely attractive possibility to ameliorate the treatments of Alzheimer's disease, Parkinson's disease, brain cancer, multiple sclerosis, epilepsy, and many other CNS related disorders. About the cargo, in Table 1, the drugs already approved for nose-to-brain delivery for the treatment of neurological diseases are presented.

2. Nasal drug delivery requirements

Human nasal cavity represents a very promising route for active principles directed not only to the nose but also to the systemic and brain districts. However, despite encouraging evidence, there are also some significant challenges that might reduce the effectivity of medicine administration through this indispensable route which is related to the nasal environmental condition. These include the specific pH of the nose, its permeability, the extremely small volume of instillation, the epithelial membrane, the mucus layer, and the enzymatic barrier among others. In addition, the proper understanding of the different mechanisms behind the drug transport through the nose is pivotal. In particular, as widely described in literature, both the trigeminal and olfactory nerves are involved in the transport of drug molecules to the CNS (Figure 1) [5,6]. Between them, the olfactory nerve can provide better properties of absorption and transport through the CNS with less systemic dispersion. Thanks to the shorter length of the olfactory nerve, transport is faster respect to the trigeminal one. Then the drug can follow two different routes, or a combination of them, intracellular or extracellular. The *intracellular pathway* involves the interaction between drug molecules and neurons at the epithelium site, thus transport along the axons and exocytosis within the CNS. *Extracellular transport* can involve different mechanisms with the common principle of the movement of the drug molecules in the spaces between neurons without binding with neurons or endocytosis. All these considerations should be taken into account for an efficient design of the formulation where the final aim is to

CONTACT Filippo Rossi filippo.rossi@polimi.it Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Piazza Leonardo da Vinci 32, Milan, 20133, Italy

Table 1. Approved drugs using intranasal delivery in the CNS.

Drug	Approved by European Medicines Agency	Approved by U.S. Food & Drug Administration	Applications
sumatriptan	1996	2019	migraine treatment
zolmitriptan	2002	2002	migraine treatment
midazolam	2022	2019	seizure treatment
diazepam	–	2020	seizure treatment

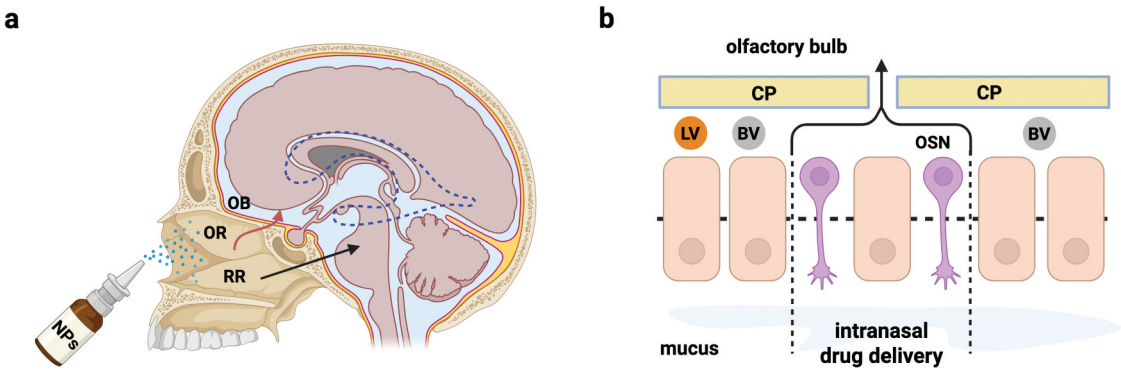

Figure 1. (a) NPs administered intranasally pass through the epithelium using the lateral respiratory region (RR) and the trigeminal nerve (black arrow) or the superior olfactory region (OR) then moving to the olfactory nerve (red arrow) and then the olfactory bulb (OB); (b) NPs are transported to the CNS using olfactory sensory neurons (OSN) across the cribriform place (CP) and similarly considering trigeminal nerve. Drug loss can take place with systemic absorption via vasculature (BV) or lymphatics (LV). Adapted with permission from MDPI [5]. Created in BioRender. Rossi, F. (2025) https://BioRender.com/c3lvzhh.

combine the pharmacological efficacy together with the global safety of the treatment. One of the possible strategies allowing to further optimize nasal drug delivery as well as efficacy and outcomes is through nanodevices, such as nanoparticles, which have shown promises in various contexts [7].

3. Nanoparticles design

Nanoparticles can be prepared starting from a large amount of materials, inorganic, or organic, as visible from Figure 2. In intranasal delivery applications polymeric NPs (neat or functionalized with proteins), liposomes or lipoprotein-based NPs are the carriers most commonly used. All these systems can be synthesized from the physical interactions between polymeric chains, phospholipids, or lipoproteins where the amphiphilic nature of the molecules considered can create the spherical structure through self-assembling [8]. The main advantages or disadvantages of the different systems described are summarized in Table 2.

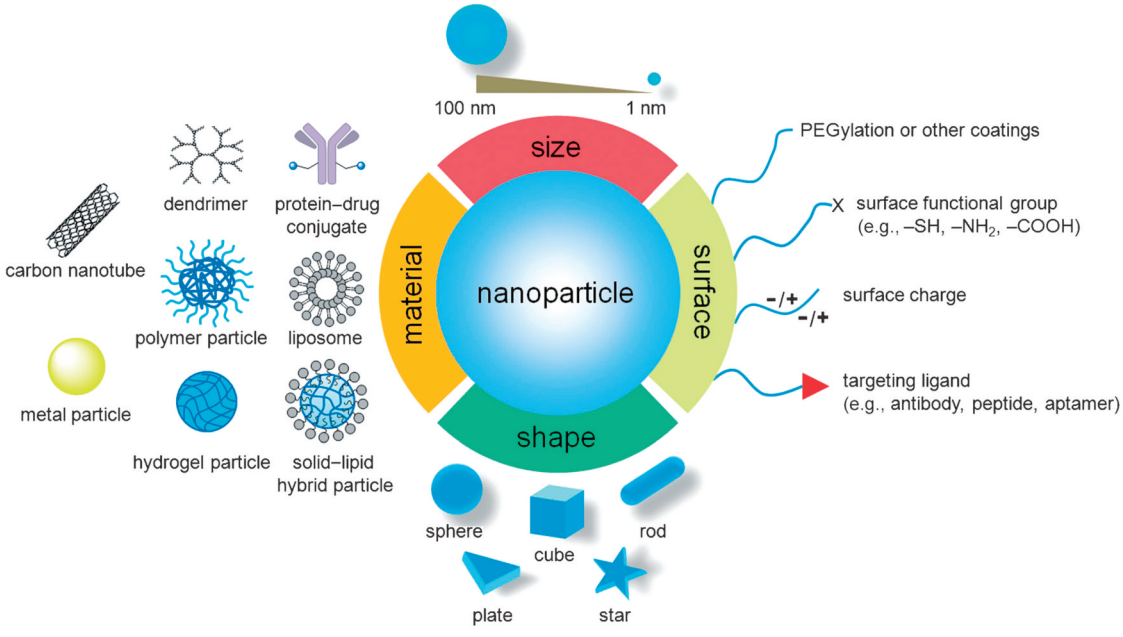

Figure 2. Nanoparticles design process. Reprinted with permission from Elsevier [8].

Table 2. Advantages and disadvantages of NPs for intranasal delivery.

	Advantages	Disadvantages
Polymeric NPs	– Good adhering time – Tailored properties to enhance the absorption and brain targeting	– Difficulty in scaling up – Potential toxicity – Limited biodegradability
Liposomes	– High drug solubility – Good Clinical translation	– Potential instability
Protein-functionalized NPs	– High targeting efficiency – Lack of toxicity – Versatility	– Potential batch-to-batch variability – Drug loading capacity
Lipoprotein-based NPs	– Tailored properties – Low immunogenicity – Drug loading capacity	– Nose-to-brain delivery efficiency

In NPs design process, other parameters that should be taken into account, beyond the materials chosen, are the final size, shape, and surface decoration. The proper choice of all these combinations allow optimized cell-materials interaction and proper delivery kinetics of their cargo in the target tissue.

4. Strategies to enhance intranasal drug delivery with nanotechnology

Different nanocarriers have been considered for their promising use in intranasal drug delivery. The proper formulation strategy for optimizing intranasal delivery depends on drug properties. Indeed, molecules with either high hydrophobicity, high steric hindrance, or high superficial charge will diffuse through the mucus in a more difficult manner [9]. Similar problems are found when the drug used acts as a good substrate for the enzymes it encounters in its way to the target site in the brain. Among the different polymers available very good results were obtained with the natural ones like chitosan and its derivatives. Chitosan-based NPs allow the intranasal release of leucine-5-enkaphilin to the brain, which is not achievable when administered as a liquid thanks to the high targeting ability to the brain with no peripheral exposure [10]. Quetiapine, pramipexole, and rivastigmine efficient transport to the brain through NPs further corroborates the validity of NP-based intranasal delivery underlining that the better targeting performance of NPs can optimize drug administration [11,12]. Promising results were also obtained using an siRNA targeting the chemotherapy-resistant gene for galectin-1, which improved survival of a pharmacological therapy based on temozolamide carried by chitosan NPs [13]. These NPs can silence galectin-1 with a remarkable switch of macrophages from M1 (pro-inflammatory) to M2 (anti-inflammatory) phenotype. Chitosan-based NPs can also carry lipid particles loaded with resveratrol which showed improved efficacy (sixfold higher cerebrospinal fluid concentration) if related to the cases of neat lipid particles (loaded with resveratrol) administered through the nasal cavity or via intravenous administration [14].

Pharmacological studies revealed that their intranasal administration can increase drug bioavailability in body fluids with enhanced neuroprotective effects. The same results were obtained also for hydrophobic drugs thanks to chitosan characteristics as mucoadhesive and permeability enhancer. Not only natural-based NPs can be used, indeed poly(L-lactide-co-glycolide) (PLGA) NPs have shown to optimize the intranasal delivery of olanzapine (10-time respect to the liquid form) with consequent reduction of seizure in an epileptic mouse model [15]. PLGA-based NPs showed great results in Alzheimer's disease treatment when loaded with tacrine. These NPs were prepared via nanoprecipitation and its formulation was optimized using factorial design analysis, a statistical method to study the effects of two or more independent variables on a dependent variable. The obtained NPs were then functionalized with protamine-sulfate onto their surface. In vivo studies revealed an ameliorated efficacy in terms of brain targeting after intranasal administration compared to uncoated NPs, with better brain bioavailability of the loaded drug molecules ($265.24 \pm 62.99\%$) [16]. The selectivity of PLGA-based NPs can be enhanced after conjugation with different compounds that can be specific for nasal epithelium [17]. In particular, the combination with chitosan proved a significant optimization of brain targeting. Once loaded with huperzine-A, NPs also facilitated drug distribution as shown by an increase in targeting index in olfactory bulb, hippocampus, cerebrum, and cerebellum of about 2, 1.9, 1.6, and 1.9, respectively [18]. Lipid-based NPs, starting from liposomes, have made significant progresses in the last year and can guarantee formulations with great promises for intranasal administration nowadays. Many of them showed improved stability and lower cost if compared with NPs prepared from polymers. In this field, strong attention should be given to the composition of the lipid phase. Indeed, phosphatidylserine, phosphatidylcholine, and phosphatidylethanolamine are known as P-gp substrates for the nasal epithelium leading to extremely rapid clearance if administered intranasally without reaching the CNS [19]. Solid lipid NPs represent an exciting formulation strategy with higher stability respect to liposomes being in solid form together with slower and more sustained release rates.

Many relevant research studies were done not only for the delivery of anticancer therapies but also for intranasal delivery to the CNS. In particular, solid lipid NPs loaded with risperidone, 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl] ethyl]-6,7,8,9-tetrahydro-2-methyl-4 H-pyrido[1,2-a]pyrimidin-4-one, an atypical antipsychotic agent, prepared using solvent emulsification-solvent evaporation method, showed higher hindlimb retraction time – a measure of anti-psychotic potential of the drug – indicating the superiority of NPs over the liquid drug with enhanced and optimized brain targeting. The biodistribution and pharmacokinetics studies in mice exhibited a brain/blood ratio 1 h after administration of 1.36 ± 0.06,

nearly 10-fold higher compared with intravenous administration: 0.17 ± 0.05 for drug alone (intravenous) and 0.78 ± 0.07 for NPs, respectively [20]. Lipid NPs showed also promising results in Alzheimer's disease treatment if co-encapsulated with α-mangostin and β-site APP cleaving enzyme 1 siRNA using a microfluidic approach [1]. This dual system can synergistically combine the microglia reprogramming ability of α-mangostin with the transcriptional silencing typical of the enzyme via siRNA. In vivo studies in mouse models of pathology, showed cognitive recovery as well as a reduction in amyloid plaque load, oxidative stress, and neuroinflammation.

5. Expert opinion

The delivery of drugs using polymer or lipid NPs through nasal cavity presents many advantages if compared with traditional administration routes. In particular, nasal administration is easy to apply, not invasive and painless. In addition, a faster action, avoidance of first-pass metabolism and lower drawbacks related to a more specific targeting and release at lower drug doses can increase the ratio benefit/risk associated with all the pharmacological therapies. However, despite very good results attained in recent times, some challenges have remained still unsolved and this represents the real obstacle to their use in common practice. Firstly, all the possible toxic effects should be considered to avoid delays during the regulatory approval.

Then also the stability during time of the final formulation, together with manufacturing strategies in large scale, represent big problems that should be solved to reach the bedside. In summary, a multitude of targets should be considered and cannot be achieved by a single player. Indeed, a collaborative interaction between industry, universities and regulatory stakeholders is necessary to make NPs patient-accessible products to treat CNS diseases.

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