Functionalized Nanoparticles in Drug Delivery: Strategies to Enhance Direct Nose-to-Brain Drug Delivery via Integrated Nerve Pathways

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Abstract

Nose-to-brain drug delivery system is becoming a desirable alternative approach to conventional drug delivery systems used for the treatment of various neurological disorders. Trigeminal and olfactory routes are implicated to deliver drugs

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from the nose-to-brain, which bypasses the blood-brain barrier and the first-pass metabolism. In this review, nanocarrier systems are evaluated, screened, and tested in order to evaluate its physiochemical features and configuration to enhance the bioavailability of drugs in the brain after intranasal intervention. The application of specific ligand, surface modifications, and use of permeation enhancers to increase brain targeting are discussed. Furthermore, we discuss the in vivo animal and in vitro cell line-based models, which are actively being employed to explore the nanomaterial-driven drug transport mechanisms via the intranasal route. These models can be used to study absorption, diffusion, permeation, and toxicological and pharmacokinetic profile of the active pharmaceutical ingredient. Our review provides evidence to conclude that the potential of nose-to-brain delivery and role of functionalization of nanomaterials enhance the drug efficacy in brain diseases. We also conclude that the biorecognitive surface modifiers have the ability to enhance and optimize the drug delivery to the brain, and we provided our insights and outlooks to address challenges and opportunities for nanosystems to speed up clinical translation.

Keywords

Nose-to-brain · Nanomaterials · Nerve pathways · Bioavailability · Neurological disorders

21.1 Introduction

About 1.5 billion people are suffering from different types of neurological ailments, and this situation will worsen by reaching 1.9 billion people by the end of 2021 (Pardeshi and Belgamwar 2018). Traditionally, a wide variety of therapeutic agents can be administered intranasally for topical, systemic, and central nervous system (CNS) action for the treatment of local ailments such as nasal allergy, sinusitis, nasal infections, and nasal congestion. This is because it is a reliable, safe, noninvasive, and convenient route for high-level and fast rate of drug absorption (Pardeshi and Belgamwar 2013). The target tissue for nasal drug delivery is the nasal mucosa as it offers many advantages over the oral route because of its large surface area, high blood flow, porous endothelial membrane, avoidance of hepatic first-pass metabolism, and its accessibility (Mittal et al. 2014). However, one of the challenges faced by CNS drugs is to enter into the brain due to the different physiological barriers such as the presence of blood-brain barrier (BBB), first-pass metabolism, enzymatic degradation, inadequate blood perfusion, systemic clearance, peripheral side effects, and reduced bioavailability (Agrawal et al. 2018). Previously, some drugs with high molecular weight and almost all the drugs with low molecular weight are unable to cross the BBB (Kulkarni et al. 2015). Moreover, the drugs that require large doses to enter into the CNS for their therapeutic effect may be effective at relatively lower doses with fewer adverse effects, when administered through the nose (Warnken et al. 2016). Drugs administered through the intranasal route avoid first-pass metabolism and degradation in the stomach. However, nasal mucosa provides benefits by increasing the safety and the rate of drug absorption and decreasing the onset of

the therapeutic action (Piazzini et al. 2019). Diseases related to CNS include neurodegenerative diseases such as Parkinson's disease, Alzheimer's, multiple sclerosis, and cerebral ischemia representing a broad spectrum of pathological conditions that leads to a change in neural functions (Bonferoni et al. 2019). Various dosage forms, i.e., oral, topical, and IV injections, are available for the treatments of CNS disorders that reach CNS, but even after crossing the different physiological barriers, these methods have limited therapeutic efficacy. On the other hand, surgical intervention is a highly invasive short-term method of treatment (Agrawal et al. 2020). However, the ability of drugs to efficiently pass through the blood-brain barrier (BBB) is an important parameter in the development of drug products for the treatment of brain neurological disorders (Martins et al. 2019). Few novel drugs have been brought to market in the past four decades, and pharmaceutical companies are spending less on the development of psychiatric treatments. Indeed, only 7% of developed psychiatric treatments reach the market (Quintana et al. 2016).

Nasally administered drugs can adequately cross the BBB and reach the CNS through different pathways. The main and direct pathway for the nose-to-brain drug delivery is through olfactory nerves. There are also the trigeminal nerves, which have nerve endings in the respiratory epithelia and respiratory epithelium through which the drugs reach the systemic circulation by crossing through the BBB (Piazzini et al. 2019). A thick layer of mucous surrounds the human nasal cavity which is adequately supplied with the blood vessels responsible for removing and transporting foreign particles from the nasopharynx into the esophagus through mucociliary motion. The nasal cavity has a total volume and surface area of 15–20 mL and 150–200 cm^2, respectively (Feng et al. 2018). The nasal cavity is divided by the nasal septum into two halves which are open to the facial side and the rhino pharynx, *via* anterior and posterior nasal apertures, respectively. Each nasal cavity is further divided into three regions, i.e., the nasal vestibule, the olfactory region, and the respiratory region (Mistry et al. 2009).

Therefore, there are two pathways for nose-to-brain drug delivery, indirect pathway and direct pathway. The indirect pathway lies in the respiratory region mucosa, which is highly vascularized by blood capillaries that allow the drugs to be absorbed into the systemic circulation and then enter into CNS after crossing BBB (Martins et al. 2019). There are two primary pathways through which a drug can be transported, i.e., extracellular olfactory and trigeminal nerve fibers and intracellular pathway. Intracellular transport is also known as endocytosis in which the drug is absorbed by olfactory sensory neurons after depositing on the olfactory epithelium. Hydrophobic molecules with a lower molecular weight are more likely to use this mode of transport (Quintana et al. 2016). Figure 21.1 illustrates the nose-to-brain delivery pathway and intranasal administration. The most dominant path is an olfactory neuronal path which is linked to the nasal cavity from the olfactory bulb of the brain directly by crossing the cribriform plate. The drug transport takes place by passive diffusion in the case of small lipophilic molecules, whereas for hydrophilic drugs and large moieties, transport occurs by endocytosis (Agrawal et al. 2020).

Figure 21.1 also depicts the nasal administration of nanoparticles and pathways or fate of nanoparticles after administration. In the context of the aforementioned details and in continuation of efforts from our groups related to the synthesis of

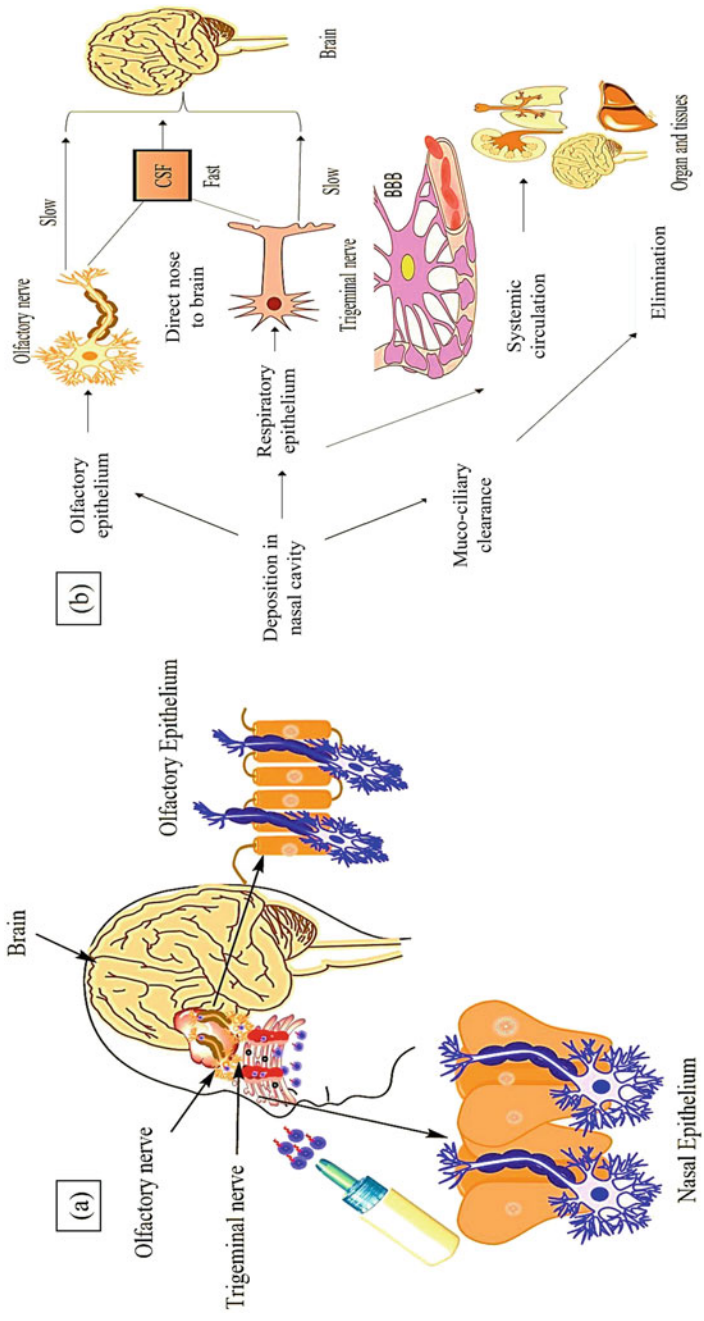

Fig. 21.1 (**a**) Nasal administration and (**b**) nose-to-brain delivery pathways of drug delivery or fate of nanoparticles after intranasal administration

nanomaterials and investigation about their potential bio applications (Barani et al. 2019a, b; 2020a, b, c, d, 2018; ; Bilal et al. 2020; Das et al. 2020; Davarpanah et al. 2018; Ebrahimi et al. 2018; Hajizadeh et al. 2019a; Hajizadeh et al. 2019b; Rahdar et al. 2020a, b, c, d, e, f; 2019a, b; Torkzadeh-Mahani et al. 2020; Taimoory et al. 2018; Nikazar et al. 2020a; Pillai et al. 2020; Saravani et al. 2020; Sivasankarapillai et al. 2020a, b; Sayadi et al. 2020; Davarpanah et al. 2019; Baranei et al. 2020; Nikazar et al. 2020b; Ghazy et al. 2020a, b; Sivasankarapillai et al. n.d.; Mukhtar et al. 2020), we here review different strategies to enhance the direct nose-to-brain delivery *via* integrated nerve pathways by nanomaterials.

21.2 Intranasal Barriers for Nose-to-Brain Drug Delivery System

By following simple formulation strategies, scientists can easily formulate a nasal drug delivery system, but various intranasal barriers impact the absorption of therapeutic drugs (Upadhyay et al. 2011). A thin lining of lipophilic mucous surrounds the nasal cavity that only allows the permeation of lipophilic molecules (Agrawal et al. 2018). One of the factors that limit the nasal absorption of polar drugs is that most of these drugs have a large molecular weight of the drugs which lead to low membrane permeability. However, polar drugs with low molecular weights, less than 1000 Da, prefer paracellular and transcellular routes by which the drugs cross the epithelial membrane through the concentration gradient by receptor-mediated or vesicular transport mechanisms *via* tight junctions between the cells (Jadhav et al. 2007). Therefore, the nasal route is suitable for the smaller-size, lipophilic drug molecules while restricting the permeation of hydrophilic drugs (Agrawal et al. 2018). Large molecules like peptides and proteins which are not permeable across the nasal cavity are destroyed in the lumen of the nasal cavity due to enzymatic degradation of the drug molecule in the lumen of the nasal cavity or while passing through the epithelial membrane (Upadhyay et al. 2011).

Enzymes such as epoxide hydroxylase, carboxylesterase, aldehyde dehydrogenases, glutathione S-transferases, cytochrome P-450, UDP-glucuronyltransferase, and glutathione transferase are responsible for the degradation of drugs in the human nasal mucosa, while cytochrome P450 metabolizes some drugs such as cocaine, nicotine, alcohols, decongestants, and progesterone in the nasal mucosa (Bahadur and Pathak 2012). The pH of the nasal secretions varies in adults and infants from 5.5 to 6.5 and 5.0 to 7.0, respectively. A drug is better absorbed at lower pH of the nasal mucus than the drug's pKa because the drug is predominantly in a unionized state. Therefore, changing the pH of nasal secretions can change the amount of drug absorbed by altering the drug ionization. As the pH of the nasal mucus changes the pH of the drug formulations and vice versa, therefore, the pH of a drug should ideally be within the range of 4.5–6.5 with a significant buffering capacity (Misra and Kher 2012). The nasal mucociliary clearance plays a vital role in removing foreign particles such as dust, allergens, and bacteria that are usually trapped during inhalation on the mucus blanket. This also affects the contact time between the drug and the nasal mucosa which leads to varied amounts of drug

absorptions. On the other hand, the mucociliary clearance decreases the contact time, and thus, it is inversely related to the drug absorption (Tafaghodi et al. 2004). There are some limitations regarding nose-to-brain targeting. For instance, it is still an immense challenge to calculate the exact dose of the drugs to be administered intranasally, which is one of the main reasons that subcutaneous insulin injections are not yet replaced by insulin administered intranasally (Nasulin®) (Stützle et al. 2015).

As a result of which, administration methods depict a wide variety of variations, and they require adjustments according to anatomical characteristics of the individuals. Furthermore, due to a relatively small and confined nasal cavity, the dose quantity is limited. Moreover, while developing formulation, it must be in consideration to use such type of materials that do not cause mucosal toxicity or any such material that might cause an allergic reaction/irritation. Another key consideration should be the patient's health status. Essentially, if patients have flu symptoms or if they have any kind of allergies, they may face some issues while using intranasal drug delivery devices. Moreover, one must also consider that the nasal mucosal surface shouldn't be damaged by the use of such devices frequently. Drug reproducibility in the olfactory region also depicts that nose-to-brain targeting shows efficient and safe results (Pardeshi and Belgamwar 2013). pKa of drug and pH also affect the extent of nasal drug absorption at the specific absorption site. Hence, the pH of the formulation should be tuned accordingly to ensure drug stability for allowing a large amount of non-ionized drug absorption. Usually, the pH of the formulation should be similar to the human nasal mucosa, i.e., 5.0–6.5; otherwise, it can cause nasal mucosa irritation (Dae-Duk 2007). Moreover, the pH often prevents the growth of bacteria and also responsible for the integrity of nasal mucosa pH (Rahdar et al. 2019a). The viscosity of the formulation is directly proportional to the contact time between nasal mucosa, drug and any enhancers within it, which ultimately results in a potential increase of drug absorption. Moreover, increased viscosity of drug increases its permeability by interfering with the normal ciliary mechanisms (Dhakar et al. 2011). According to recent research study, it has also been reported that the viscosity of the solution may provide a larger therapeutic period of nasal formulations (Zaki et al. 2006).

21.3 Strategies to Improve Nasal Absorption

While considering systematic drug delivery in CNS, a vast range of drugs show promising results through nasal drug delivery systems. However, low bioavailability of drug remains a challenge for many drugs which are administered intranasally. There may be several reasons due to which dugs show low bioavailability which might be due to low solubility, rapid degradation of enzymes in the nasal cavity, their poor membrane permeability, or that the drugs might clear rapidly from a mucous membrane. To overcome these hindrances, several mechanisms have been adopted in the literature (Bahadur and Pathak 2012). Drugs that are administered nasally usually surpass the GIT tract and hepatic first-pass effect, but some drugs are

metabolized by the enzymes existing in the lumen of the nasal cavity. To prevent the degradation of enzymes, several techniques have been used, and among them, the most recommended is by using proteases and peptidases inhibitors. For example, for aminopeptidase inhibitors, comostate amylase and bestatine have been used, and for calcitonin degradation, trypsin inhibitor aprotinin is used. Furthermore, to prevent enzymatic degradation of drugs like leucine, human growth hormone, enkephalin, amastatin, boroleucin, bacitracin, and puromycin are widely used. Moreover, few enzymatic inhibitors also show the ability as permeation enhancers. For example, for treating Alzheimer's disease, disodium ethylenediaminetetraacetic acid has been used which reduces the beta-sheet peptide enzyme degradation by enhancing drug absorption (Ying 2008). Several other excipients have been used to increase absorption and permeation of drugs which include fusidate derivatives, surfactants, bile salts, laureth-9 sulfate, fatty acids, hydrophilic polymers, cyclodextrins, etc.

Methylated β-cyclodextrins form the inclusion complexes with drugs, thus resulting in enhanced absorption of lipophilic drugs that have poor water solubility. Mucus interaction has been shown by hydrophobic and positively charged excipients; however, excipients that are hydrophilic and are negatively charged do not show mucus interaction. Poly(lactic-co-glycolic) acid (PLGA) is used as a nanoparticle/emulsions for developing a formulation that can penetrate the mucus membrane easily. Moreover, to eliminate the particle's hydrophobic interactions with mucus, PEGylation is used, and hydrophilic properties of the particles are ensured by coating processes (Gänger and Schindowski 2018). Usually, when the drugs are administered in solution form, they undergo dissolution before absorption. Despite poor water solubility, lipophilic drugs are absorbed easily through the nasal membrane. Therefore, to achieve an aqueous formulation of lipophilic drugs by using compounds of higher hydrophilic character, the prodrug technique can be used. One should also ensure that the prodrug must be converted into a patent drug when the finished formulation reaches the systematic circulation. To increase the retention time of drugs in the nasal cavity, several techniques have been adopted like the use of polymers chitosan or polycarbophil that act as bioadhesive or increase the formulation viscosity. Nasal drug absorption is also affected by the behavior of drugs, excipients, preservatives, or absorption enhancers that might inhibit or stimulate the nasal mucociliary clearance (Stevens et al. 2009).

21.4 Application of Nanomaterials for Nose-to-Brain Delivery

To overcome several difficulties to deliver the drug from the nose to the brain, various techniques are used to design formulations like solutions, mucoadhesives, microemulsions, and nanoparticles that may be polymeric or lipid base, including novel combinatorial therapies. These formulations are usually designed by considering the physicochemical properties of the drug (Warnken et al. 2016). The lipid-based nanocarriers are site-specific controlled drug delivery systems. Along with the targeting ability, there are several inherent traits of lipid nanocarriers which include excellent biodegradability, controlled drug release, improved stability,

biocompatibility, and feasibility of carrying both lipophilic and hydrophilic drugs. Ideally, the lipid-based nanoemulsion-based carriers are suitable for therapeutic drug delivery. They are usually made up to omega-3 fatty acids which belong to the class of polyunsaturated fatty acid, and it easily permits the nanoemulsions to cross the membranes of the cell.

Neuro nanoemulsions are those types of nanoemulsions that are loaded with neurotherapeutic agents and are usually used for the treatment of neurological disorders. When neuro nanoemulsions are surface-modified with mucoadhesive agents, they are usually considered mucoadhesive neuro nanoemulsions. For the rapid clearance of drugs through the nose by mucociliary action, polymer-based mucoadhesive dosage forms are usually prepared (Pardeshi and Belgamwar 2018). It constitutes "soft" nanomaterials, which are prepared by several standard solution-based organic chemistry methods. A wide range of drugs which include proteins, chemotherapeutic drugs, nucleic acids, and contrast agents can be encapsulated in polymeric nanoparticles due to their low density and less rigid properties. For drug delivery, polymeric nanoparticles are considered as the most suitable carriers because of the presence of a wide range of different kinds of polymers along with their access to a greater surface area containing functional groups with which conjugation of biomolecules occurs (Illum 2007). Figure 21.2 demonstrates the application of different nanomaterials for enhanced brain uptake *via* intranasal administration.

21.5 Lipid Nanoparticles

Lipid nanoparticles are suitable drug carrier systems as they provide protection of embedded active pharmaceutical ingredient (API) from glycoproteins (P-gp) efflux/enzymatic transporters and from chemical destabilization. One of the key characteristics of developing the intranasal dosage form is their toxicological assessment. The prolonged contact of the formulations with the nasal epithelial may lead to the ciliotoxicity, tissue damage, and localized irritation that further leads to a microbial infection. Above all, the protection of the olfactory nerves and sense of smell is very critical while screening the carrier system, for intranasal delivery (Battaglia et al. 2018). The lipid nanoparticle system including liposomes, niosomes, and nanoemulsion are the most significant and efficient drug delivery approaches because of their biocompatible nature. The lipid nanoparticle average particle size is placed within the range of 50–1000 nm. Among lipid nanocarriers, solid-lipid nanoparticles (SLNs) are considered to be one of the efficacious vehicle systems. It comprises of lipid core surrounded by a layer of surfactants in an aqueous phase. Nanolipid carrier systems show low burst release and also have reduced drug expulsion as compared to the other nanoparticle system. However, almost all lipid nanoparticles have limited drug loading capacity; therefore, lipid-drug-conjugate nanoparticles have been fabricated (Yasir and Sara 2014). All categories of lipid nanoparticles can be effectively and remarkably used for scale-up production on the industrial level.

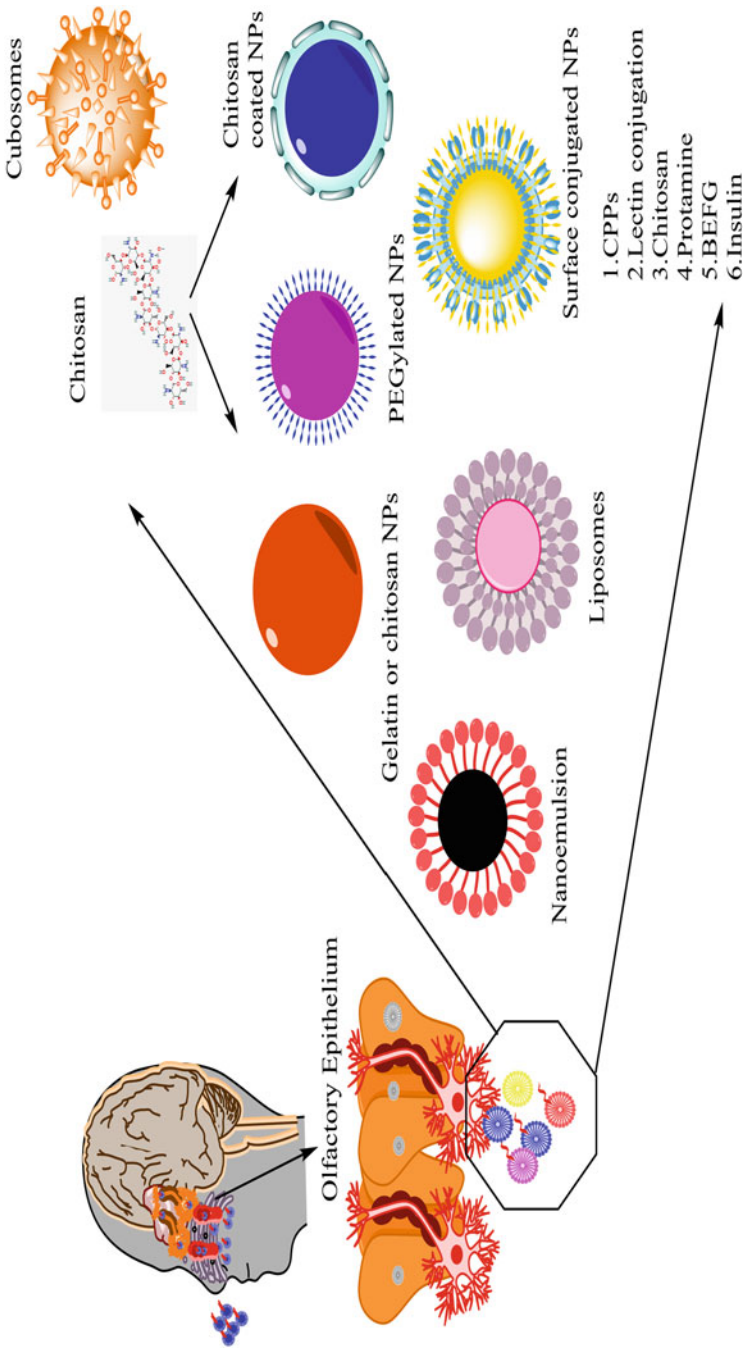

Fig. 21.2 Applications of different nanomaterials for intranasal delivery that can induce stability against enzymatic degradation, access to the CNS either through passive or active targeting, increased half-life, and enhanced concentration in brain

Moreover, several advantages including high scale-up, high biocompatibility, and ease of functionalization make lipid nanoparticles more efficient carrier systems than others. For instance, Giovanna Rassu et al. designed an efficient delivery system comprising of chitosan-coated and chitosan-uncoated solid-lipid nanoparticles which were subjected to intranasal delivery. Both of these formulations were tested to check the significance of olfactory and trigeminal nerve pathway for use in drug delivery to the brain. The system directed toward an optimal nose-to-brain delivery of BACE1siRNA in the treatment of the Alzheimer's disease. The short peptide also called as RVG-9R is a cell-penetrating peptide which is used to enhance the transcellular pathway (Rassu et al. 2017).

The coating process elucidates the significant effect of particle charge on siRNA protection. The cationic formulation ensured enhanced mucoadhesiveness to the particles and also enhanced the stay time in the nasal mucosa. The cellular transportation of siRNA released from the SLNs using Caco-2 as a model has also been studied. It is concluded that siRNA released from both uncoated and coated formulation permeates the monolayer to the large extent. Sonal Patel et al. developed risperidone (RSP)-loaded solid-lipid nanoparticles and measured the possibility of targeting the brain *via* intranasal route. The RSLNs paw test using perspex platforms has shown greater hind-limb retraction time as compared to the RSP solution. This suggests preference of RSLNs over the pure drug solution for brain delivery. The pharmacokinetics studies revealed that the value of brain-to-blood ratio of RSLNs in intranasal environment was five- to tenfold higher with respect to the RS and RSLNs. The results of gamma scintigraphy imaging of mice brain following intranasal and intravenous administration revealed the localization of risperidone in the brain. The results concluded that the existence of direct intranasal delivery for nanoparticle intervention to the brain (Patel et al. 2011). Laurent Salade et al. developed ghrelin encapsulated liposomes for treating cachexia. They compared anionic liposomes decorated with chitosan in either a dry powder formulation or in liquid. The dry chitosan powder formulation showed good adhesion to mucins and greater encapsulation efficiency. This also provides protection against enzymes with decreased ghrelin storage degradation at 25 °C. The chitosan-coated powder formulation has stronger adhesive property to mucins. They used device for deposition of a greater quantity of powder in the olfactory region. The combined evaluation of the device and powder could provide significant treatment against cachexia (Salade et al. 2017; de Barros et al. 2020; Aderibigbe and Naki 2019). S. Cunha et al. combine the literature evidences supporting the lipid nanoparticles suitability for targeting delivery. These lipid nanoparticles (liposomes, solid lipid nanoparticles, nanostructured lipid carriers) loaded with drug showed greater efficacy in treating brain disorders. The intranasal route also has greater potential to treat infections, cardiovascular diseases, and menopausal syndrome. It is obvious that in the near future, lipid nanoparticles play a vital role in targeting the intranasal route by circumvention of the blood-brain barrier (BBB) (Battaglia et al. 2018).

21.6 Mucoadhesive Nanoparticles

Mucociliary clearance is the most significant factor that can have drastic impact on intranasal transport. This defensive role of the respiratory tract efficiently eliminates the noxious substances and microbes in the mucus layer. These are limitations that hinder the delivery of traditional nasal formulations that could help by increasing the residence time, reduce variations in nasal absorption, increase the viscosity, and improve the bioavailability of nanoformulation. Different polymers have the ability to provide bioadhesion such as hydrophilic polymers which have intimate contact with mucus, electrostatic attractive forces, hydrogen, and van der Waals bonds (Sonvico et al. 2018). These polymers including natural, synthetic, and semi-synthetic, alginates, starch and gelatin, cellulose, and different acrylates, respectively, have been applied for nasal delivery of drugs. The nose-to-brain delivery via the olfactory region in humans has several applications of polymers like pectins and chitosan to prolong the residence time (Ugwoke et al. 2005). The sodium hyaluronate has been used for improved delivery of higher-molecular-weight model compounds like 4 kDa dextran after nasal administration to rats. These mucoadhesive polymers' adhesion mechanism when used in formulations of nanocarriers or for functionalization will remain the same. However, the higher surface area translates into a broader interface for more prolonged residence time. The particle size lower than 500 nm allows nanoparticles to squeeze in the nonviscous aqueous pores within the entangled mucin network. The hydrophobic and positive interactions with the mucin network further enhance the interaction with the mucus at a molecular level (Sosnik et al. 2014). However, surface functionalization can decrease the mucoadhesivity, and these characteristics are exploited by mucus-penetrating nanocarriers. There are several reasons for which mucoadhesivity features of nanocarriers have been broadly studied for intranasal delivery. Betbeder and his coworkers developed morphine-loaded nanoparticles for targeting the direct delivery pathway between the CNS and olfactory mucosa. The nanoparticles were composed of cationic polymer (maltodextrin)-coated particles surrounded by a lipid bilayer. These particles were studied for antinociceptive activity when co-encapsulated with the opioid in mice in comparison to morphine solution. The results concluded the enhanced transport of morphine-encapsulated nanoparticles via nose-to-brain delivery. However, the level of morphine or concentration of morphine in brain tissues was not that much high. The research find out that the cationic interaction of nanoparticles with nasal mucus layer may enhance the stay time and absorption from olfactory region in laboratory mice (Betbeder et al. 2000). Silvia Guterres et al. developed nanocapsule system encapsulated with olanzapine. This nanocapsule system comprises of methacrylic poly(ε-caprolactone) copolymer as a mucoadhesive carrier system for nose-to-brain delivery. Nanocapsule interaction with mucin was evaluated via NTA (nanoparticle tracking analysis test). The mucodhesivity was tested in terms of prolongation of residence time and mucoadhesion of olanzapine-encapsulated nanocapsules on porcine. In vivo studies ensured twice-fold enhanced accumulation of olanzapine in CNS tissues after intranasal administration. The authors reported that the brain accumulation of

olanzapine was higher in the present study as compared to olanzapine-encapsulated PLGA nanoparticles and concluded the enhanced mucoadhesivity of coated nanocapsule (Fonseca et al. 2015). Among all synthetic polymers, polysaccharides are the most useful materials to design mucoadhesive polymers. Polysaccharides have prominent features that make them useful materials for nasal delivery including biodegradability, biocompatibility, and biomimetic recognition and ease of chemical functionalization. Applications of polysaccharides can be incorporated in three possible ways, by copolymerization, covalent attachment, or directly developing the polysaccharide comprising nanoparticles. Ondansetron-encapsulated nanolipid carriers were formulated for nose-to-brain delivery from *Delonix regia* gum. In vitro mucoadhesion testing was performed by evaluating the binding efficiency of DRG-NLC toward mucin. The study concluded the enhanced brain targeting of or direct brain targeting efficiency of about (DTE) 506% and direct transport percentage (DTP) of about 97% as compared to IV intervention of marketed ondansetron injection as a control. Alginate nanoparticles encapsulated with venlafaxine were developed for nose-to-brain delivery against treatment and management of depression. Ex vivo study results concluded venlafaxine-loaded nanoparticles have twice drug permeation via nasal mucosa compared to drug solution. Alginate nanoparticles performed good results as compared to controls in depressed animals. However, limitations including swallowing and inhalation of nanoparticle suspension are found when applied in relatively higher amount. An increase in absorption and reduction in nasal mucociliary clearance can increase mucosal permeation, and alteration of P-gp efflux transporters is a mechanism elaborated by pharmacokinetic results (Devkar et al. 2014). The results concluded the reduction of systemic side effects after direct nose-to-brain intervention. Chitosan polysaccharides have been concluded as a very advantageous material for nose-to-brain delivery. Wang et al. developed chitosan nanoparticle-encapsulated estradiol for nose-to-brain delivery in targeting Alzheimer's disease. In vivo study results showed DTP around about 68% and DTE about 320% in CSF (that was measured in cerebrospinal fluid) after intranasal administration. The results concluded enhanced chitosan potential to mucin binding along with paracellular transport. In several other studies, chitosan nanoparticles developed by ionotropic gelation have been suggested for nose-to-brain delivery. Chitosan nanoparticles were encapsulated with different drugs such as rasagiline or ropinirole for Alzheimer's disease and Parkinson's disease and tapentadol for pain management. There is one more study in which selegiline HCl was encapsulated in thiolated chitosan nanoparticles. The results concluded the enhanced anti-inflammatory and neuroprotective efficacy of thiolated polysaccharides in in vivo experiment (Wang et al. 2008). Di Gioia et al. evaluated and developed the dopamine-encapsulated chitosan nanoparticles for delivery to the striatum. The results concluded that the nanocarriers enhance the bioavailability of drugs that have good penetration in traditional formulation such as solution (Di Gioia et al. 2015). Another study developed chitosan functionalized PLGA nanoparticles encapsulated with chlorpromazine HCl for nose-to-brain delivery. The results concluded good mucoadhesion, enhanced permeation on sheep nasal mucuosa, and controlled release of the PLGA nanoparticles (Chalikwar et al. 2013).

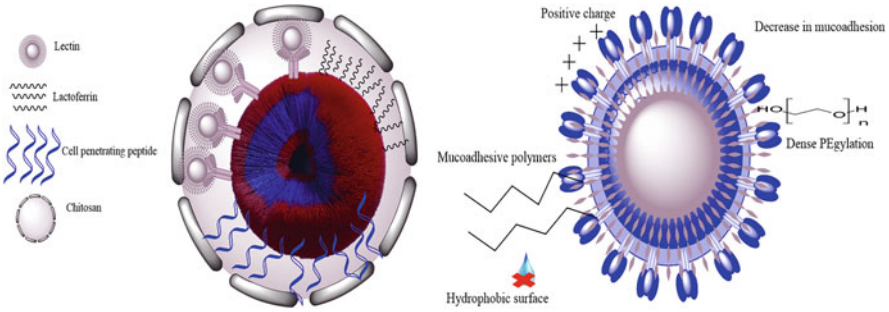

Fig. 21.3 Surface chemistry of nanomaterials affecting mucoadhesive behavior and conjugation of different peptidal moeities

Liposomes grafted with chitosan derivative and encapsulated with ghrelin were developed for intranasal administration. The results showed chitosan-coated liposomes attached to mucin have more mucoadhesivity in comparison to uncoated liposomes. These thiolated chitosan-decorated liposomes show more permeation through Calu-3 cell monolayer that was used as model for upper airways epithelial barrier (Mathieu 2019). For the nose-to-brain delivery of statins, Clementino et al. developed hybrid chitosan nanocapsule. The biodegradation of these nanoparticles provides a more efficient release of drug in the nasal mucosa. Gamma scintigraphy studies were significantly higher for 99mTc labelled simvastatin through intranasal administration. Maria Jose Alonso and her colleagues developed polyethylene glycol-coated nanocarriers that showed increased mucus permeation via nose-to-brain delivery. The results showed increased mucus diffusivity while minimizing interaction with mucins and providing close contact with epithelium (Clementino et al. 2016). Sekerdag et al. developed lipid/PEG-PLGA nanoparticles as mucus-penetrating carriers of farnesylthiosalicylic acid for nose-to-brain delivery. Intranasal administration of nanoparticles significantly decreased the tumor volume. Figure 21.3 shows the surface chemistry of mucoadhesive nanomaterials and surface grafting of peptides. The results concluded the dose reaching to the brain was 0.04% of the injected dose as part of drug accumulated into the liver was very low in comparison to IV administration (Sekerdag et al. 2017).

21.7 Penetration-Enhancing Nanocarriers

Besides developing the pegylated nanoparticles or stealth nanoparticles, many researchers developed particles whose composition showed enhanced penetration across the nasal mucosa. Chitosan acts as both mucoadhesive agent and penetration enhancer. However, penetration-enhancing particles are composed of components that have the ability to change the barrier property of the nasal mucosa such as surfactants. Examples of these types of carrier system encapsulating serotonin agonists (zolmitriptan, sumatriptan) comprise of PEG 400, vitamin E,

Transcutol P, and Pluronic® F127. Surfactants such as Transcutol P and vitamin E were previously used to enhance and solubilize the absorption of drugs through the nasal mucosa. Olanzapine encapsulated into nanocubic vesicles by utilizing the surface-active triblock copolymer poloxamer 188 or 407, in the lipid bilayer. Pharmacokinetic studies in rats showed improved and enhanced bioavailability as compared to the control nanoformulation (Guo et al. 2013; Anand et al. 2012). In relation to that, Albderahman et al. studied the nanovesicle-loaded risperidone. The following formulation used span 60, risperidone, and ethanol solution into PVA aqueous solution (Abdelrahman et al. 2017). The results showed enhanced permeation, greater viscosity, and improved CNS accumulation. Another study developed gelatin nanostructured lipid carriers for nose-to-brain delivery of fibroblast growth factor in Parkinson's disease. The intranasal administration enhanced the absorption of growth factor in the olfactory bulb without disturbing the integrity of the nasal mucosa. The reason for this improved attribute is because of poloxamer 188 and its ability to decrease the barrier property of the mucus layer. Other penetration enhancers or surfactants have similar effects, for example, SLNs encapsulated with rosmarinic acid applied for treating Huntington's disease (Kulkarni et al. 2015; Md et al. 2018). The improved level of oxidative stress and low behavioral abnormalities was observed in lab animals via application through intranasal route. Zolmitriptan-encapsulated novasomes were formulated (Abd-Elal et al. 2016). The following formulation showed enhanced brain concentration when compared with intravenous drug solution. Coumarin-encapsulated micelles were formulated that showed enhanced brain distribution after intranasal administration under in vivo experiment. The results stated enhanced penetration ability of these micelles intracellularly (Kanazawa et al. 2011). Another study showed micelles functionalized with CPP and encapsulated with camptothecin showing enhanced cytotoxic effect as compared to control group. The siRNA was used and condensed with Tat-mPEG-PCL to get the polyplexes. The brain distribution of the polyplexes after intranasal delivery results in increased accumulation of siRNA in the brain in comparison to controls (Sawant and Torchilin 2010). The results showed enhanced micelle permeation of the nasal mucosa within the trigeminal and olfactory nerves. However, these CPP conjugated formulations have few limitations including lack of efficient transport to the cytoplasm. Considering these limitations, Paolo Giunchedi developed a delivery system for nose-to-brain targeting. The RVG-siRNA complex was developed and encapsulated into SLNs. The results concluded the enhanced stability due to mucoadhesive nanocarrier that helps in crossing the mucosal barrier (Sonvico et al. 2018).

21.8 Lectin-Grafted Nanocarriers

Lectins are basically proteins of non-immunological origin found in all living organisms. Lectin interaction with transformed glycans can be used in the diagnosis and treatment of diseases. Selective targeting toward glycans has attracted the nanobiotechnology in designing the lectin functionalized nanoparticles. Conjugated

lectins on the surface of nanocarriers can stimulate the development of the system with fewer side effects. The glycoprotein obtained from plants has high specificity to get attached at the surface receptors of the different cell types (Chen et al. 2012). These proteins have been proposed as targeting ligands for the drug delivery system. The high quantitative and qualitative work has been reported relevant to the significance of use about lectins by various researchers. The following data suggested that horseradish peroxidase conjugate can get attached to the receptor of the olfactory sensory cells. The wheat germ agglutinin (WGA) has tendency to aggregate at the olfactory nerve site via intranasal route at higher concentrations, that is, 100 times greater than IV administration (Muralidharan et al. 2014). This plant obtained glycoprotein from *Triticum vulgare* which binds specifically to sialic acid residue and N-acetyl-D-glucosamine in the nasal epithelium. WGA is the most studied ligand among nanocarriers for intranasal delivery. The PEG-PLA nanoparticles were developed with functionalization of WGA along with encapsulation of fluorescent dye 6-coumarin. When these conjugated nanoparticles were administered intranasally, they enhance the concentration of PEG-PLA at both sites in the brain and in blood. In several studies, WGA decorated PEG-PLA nanoparticles were encapsulated with different CNS agents via nasal administration to the laboratory animals. These studies concluded that nanoparticle transport to the brain was very high via olfactory, extracellular, and trigeminal nerves; however, the cerebrospinal fluid contributes very little part in this transport (Gao et al. 2008, 2006). A team of researchers also studied the PEG-PLA conjugated WGA encapsulated with neuroprotective peptide (VIP) via intranasal administration for targeting brain diseases. In pharmacokinetic study of brain drug distribution, it is found that WGA grafting improved brain concentration of VIP about sevenfold compared to non-conjugated nanoparticles. The WGA-ligated PEG-PLA nanoparticles were encapsulated with QDs (quantum dots) aiming to develop specific brain imaging agents for CNS targeting (Ong et al. 2014). The brain targeting ability of PEG-PLGA nanoparticles was grafted to other lectins such as Ulex europeus agglutinin I (UEA I), Solanum tuberosum lectin (STL), and odorranalectin (Gupta 2020). The STL-conjugated nanoparticles encapsulated with haloperidol were given through intranasal route resulting in enhanced concentration in the brain by threefold compared to non-functionalized nanoparticles. The immunogenic reaction is one of the main causes of lectins. However, odorranalectin is a peptide with lectin-like activity; this compound was evaluated as a potential ligand with low immunogenic response. The small peptide-loaded PEG-PLG nanoparticles were reported to have enhanced efficacy in Parkinson's disease (PD). The lectins somehow have potential toxicity issues; that's why it's compulsory to do toxicological assay of the lectins grafted carrier system at both local and systemic sites (Piazza et al. 2014). Xiaoling Gao et al. developed lectin functionalized biodegradable nanoparticles, a novel way to enhance the brain uptake of agents encapsulated into PEG-PLA nanoparticles by intranasal administration. Ulex europaeus agglutinin I(UEAI) belongs to the I-fucose that is at broad level located at the olfactory site (Guo et al. 2011; Xia et al. 2011). The in vitro study of this formulation suggested that UEA I conjugation at nanoparticles facilitated the permeation and absorption of coumarin fluorescent

marker via intranasal administration. UEA I grafting also enhances the brain delivery of nanoparticles. The biodistribution of UEA I conjugated nanoparticles showed higher affinity of the olfactory mucosa than to the respiratory mucosa. Hence, results concluded that the UEA I grafted nanoparticles proved as potential carriers for neurodegenerative disorders (Gao et al. 2006, 2007a).

21.9 Cell-Penetrating Peptides as Surface Ligands

The positively charged cell penetrating peptides are more feasible for extracellular internalization and transport. This internalization and transport mechanism of these cell-specific proteins can be studied through model called as HIV transactivator of transcription (Tat) protein (Kanazawa et al. 2013). These CPPs are nonselective to the cell type and has the ability to transport the proteins, nucleic acids, small molecules, and nanocarriers across different barriers, for example, BBB, skin, etc. Several features like this make CPPs more efficient as functionalization component for intranasal delivery. In one study, researchers concluded that the grafting of CPPs to lipids and polymeric nanocargo clearly improved the ability to cross the in vitro olfactory model (Lin et al. 2016). Several other studies including PEG-PLA nanoparticles functionalized with low-molecular-weight protamine were found to aggregate in 16HBE14O cell line in higher concentration than the unmodified nanoparticles. Among all studies relevant to the CPPs, the HIV Tat peptide is the most commonly applied until now (Xia et al. 2011). The cell-penetrating features have been directly linked with the guanidinium groups of arginine that induce electrostatic bonding on the cell surface. T. Kanazawa et al. studied the significance of RNA-based active components for brain disorders in in vitro study. To significantly improve the siRNA transport to the brain, the intranasal delivery system comprises of CPP modified nanomicelles PEG-PCL copolymers. In this research, MPEG-PCL-Tat developed as model siRNA. The nose-to-brain delivery of dextran with MPEG-PCL-Tat enhanced brain targeting compared to IV delivery of dextran with or without conjugation of Tat. The results demonstrated the MPEG-PCL-Tat enhanced delivery along the trigeminal and olfactory pathway due to increased permeation across the nasal mucosa (Kanazawa et al. 2013, 2019; Samaridou et al. 2020).

Takanori Kanazawa et al. Tat conjugated MPEG-PCL amphiphilic copolymers via ester bond. The researchers evaluated the brain distribution of model compound coumarin after systemic and intranasal delivery of MPEG-PCL. The concentration of coumarin in the brain was very high after intranasal delivery. It is concluded that the application of nanosized micelles with Tat has proven efficacy for the direct targeting to the brain. In one study the authors developed nanolipid carrier system grafted with Tat-conjugated chitosan for nose-to-brain targeting. The results concluded the surface functionalization of Tat peptide chitosan encapsulated with GDNF (glial cell derived neurotropic factor) led to a potential increment of the therapeutic potential in PD. The PLGA nanoparticles surface functionalized with the cationic Tat peptide were able to accumulate approximately 7 times in the olfactory

bulb in comparison to non-functionalized NPs. In one more study, surface conjugated MPEG-PCL nanomicelles with cationic surface charge were developed and studied for antitumor activity. The nanomicelles were encapsulated with camptothecin for targeting brain tumor via intranasal route. The MPEG-PCL micelles grafted with arginine based CPPs were developed for the study of nose-to-brain delivery. The in vivo study including imaging concluded that the formulation was reached to the olfactory bulb in no time or with zero delay (Kanazawa et al. 2011, 2012; Okada 2014). The short peptide fragments produced by enzymatic degradation known as protamine. In comparison to other peptides, these CPPs have low immunogenic response and very low toxicity. The grafting of short-chain peptide on PEG-PLGA nanoparticles led to a potential increase in nose-to-brain delivery of the model compound coumarin. All these following results of different studies including those mentioned in Table 21.1 describe the significant potential of nanoparticle mediated transport of peptides or larger molecules via intranasal route (Xia et al. 2011; Kanazawa 2015; Shamarekh et al. 2020; Kamei et al. 2016) (Table 21.2).

21.10 Mechanism to Enhance Direct Targeting of NPs via Neurological Pathway

There are many studies related to the enhanced brain delivery of nanoparticles in comparison to the free drug formulation. There are only few data regarding the mechanism of nanoparticles that can increase drug delivery in the brain. There are different mechanisms involved, but the simplest one in which the nanocarriers bind at the mucus layer and (Xia et al. 2011) release the drug in the mucus. The most significant mechanism is when drug-loaded nanoparticles cross the mucosal barrier. Moreover, these nanoparticles translocate along the nerve axons to reach the brain. Amid that, two scenarios involve nanoparticle uptake into the neuroepithelium. The free drug diffuse out into the perineural spaces of the CNS. Hence, the fate of nanoparticles rely on the physiochemical properties of nanoparticles (Nehoff et al. 2014). The size, morphology, and surface hydrophilicity can affect nanocarrier interaction with the biological environment (Yokoyama 2005). The properties of nanocarriers can influence the mucus interaction, the uptake by the neuroepithelial cells, and the transport to the brain by diffusion. Some authors study in vitro transport of nanoparticles along the olfactory monolayers, ex vivo study across the nasal mucosa, or in vivo in mammalian models like rodent model in order to elaborate the effect of charge, particle size, hydrophobicity, etc. Gartziandia et al. worked on and checked the permeation of nanoparticles across the olfactory mucosa having different physiochemical properties (Alexander et al. 2019). A fluorescent probe (DiR; 1-10dioctadecyl-3,3,30,30-tetranethylindotricarbocyanine) was encapsulated into nanoparticles to analyze their pathway. The results showed the material used for formulation has potential effect on permeation of nanoparticles. For instance, the lipid nanocarrier penetrated to the higher extent compared to the PLGA nanoparticles with same particle charge (−23 mV). The alteration of zeta

Table 21.1 Nanomaterial-based lipid carrier system for nose-to-brain delivery

Drug	Nanocargo system	Ligand molecule	Animals used	Therapeutic effects	Ref
Liposomes	H102 peptide	–	Rats	Threefold enhanced area under curve (AUC) in the brain than in solution	Zheng et al. (2015)
Oil in water nanoemulsion	CsA	–	Rats	Six-time increase in concentration of the brain in comparison to CsA solution	Yadav et al. (2015)
PEGylated cubosomes	Derivative of humanin	OL	Rats	1.7–3.5 times increase of coumarin distribution	Wu et al. (2012)
Cationic liposomes	OVA	–	Rats	Ten times enhanced efficacy. Four times greater AUC of brain-to-blood ratio	Migliore et al. (2010)
Gelatin NCL	SP		Rat	Significant increase of therapeutic effect	Lu et al. (2015)
NCL coated with chitosan	hIGF-I	–	Mice	Enhanced stay time in nasal epithelium and enhanced concentration in the brain	Gartziandia et al. (2015)
NCL coated with chitosan	GDNF	–	Rat	Significant increase of neuroprotective effect	Gartziandia et al. (2016)
NCL gelatin	bFGF	–	Rat	~Twofold increase of brain concentration of bFGF	Zhao et al. (2014)
NCL gelatin	bFGF	–	Rat	Increased concentration of peptide in the brain in comparison to simple solution	Zhao et al. (2016)

potential from negative to positive by coating with chitosan enhanced the intranasal transport 3 times compared to uncoated nanolipid carriers (Salem et al. 2020). Surface modifications using cell-penetrating peptides further increase the nanoparticle transport. The composition of nanocarrier system has different penetration effects, for example, formulation composed of poloxamer and polysorbate 80 PLGA nanoparticles in comparison to formulation without surfactant has low permeation, as well as high mucus-penetrating effect of PEG and the mucoadhesive features of PVA-coated particles. Musumeci and coworkers developed PLA and PLGA nanoparticles using Tween 80 surfactant and rhodamine as fluorescent dye. PLGA nanoparticles having surfactant were found with greater uptake in olfactory ensheathing cells as compared to other nanoparticles. Mistry et al. developed nanoparticles of different sizes and with different zeta potentials (Sonvico et al.

Table 21.2 Examples of targeting ligands and surface modification of nanocarriers for nose-to-brain delivery along with various in vivo models

Nanocarrier	Surface modification	Targeting ligand	Animal model used	Ref
PEG-PCL-NPs	Lactoferrin		Rats/mice	Samaridou and Alonso (2018), Liu et al. (2013), Hernando et al. (2018)
Chitosan coated NCL		Tat	Mice	Hernando et al. (2018)
PLGA NPs	Lactoferrin	Tat	Mice	Meng et al. (2018)
PEG-PLGA NPs	STL		Mice	Chen et al. (2012) Zhang et al. (2014)
PEG-PLA NPs	WGA		Rats/mice	Gao et al. (2006, 2007b)
PEG-PLGA NPs	OL		Rats	Gao et al. (2011)
Nanomicelles, MPEG-PCL		Tat	Rats	Kanazawa et al. (2011), Taki et al. (2012)
PEG-PLA NPs	UEA1		Rats	Xia et al. (2011), Kanazawa et al. (2017)
Nanomicelles		CH2R4H2C	Rats	Kanazawa et al. (2017)
PEG-PLA NPs		LMWP	Rats	Wu et al. (2012), Xia et al. (2011)
Pegylated cubosomes	OL		Rats	Wu et al. (2012)

2018; Musumeci et al. 2018). Among all these studied particles, the polysorbate 80-coated nanoparticles or PEGylated nanoparticles penetrated into the deeper layer of the nasal epithelium as compared to the uncoated one. In vivo study was performed on mouse model to check the nanoparticle uptake mechanism. A 15 μL of nanoparticles having particle size of 276, 163, and 107 nm chitosan-coated (+30 & +23 mV, respectively) or 180 and 107 nm Tween 80-coated NPs (−24 and −21 mV) were implicated for 3 days (Huckaby and Lai 2018). Among these studies the particles decorated with tween 80 have smaller size (between 107-180 nm) and showed more penetration as compared to larger size particles. The chitosan coated nanoparticles showed very little penetration in comparison to other pairs of coated particles. Ahmad et al. studied and compared nanoemulsions with droplet sizes of 900, 500,200, and 80 nm. It was evaluated that the nanoparticles with smaller droplet size have quite higher stay time in the nasal mucosa. The cationic-charged chitosan-grafted nanoparticles have higher stay in the nasal mucosa and in anionic-charged epithelial membranes (Ahmad et al. 2018). A recent study resulted in greater brain accumulation of PLGA nanoparticles after intranasal intervention in rats. The researchers developed rhodamine-loaded PLGA NPs coated with Tween 80 having zeta potential of −26 mV and particle size of 118 nm and chitosan PLGA-NPs 213 nm and +69 mV. The results showed that both types of nanoparticles either anion and cationic charged reached the neural cells. The exact site of particles

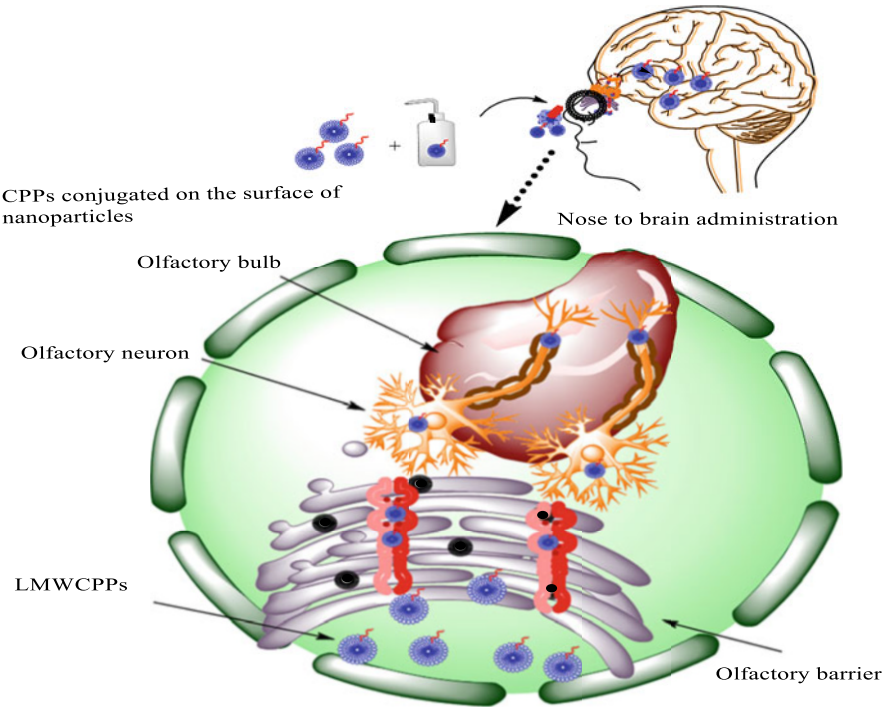

Fig. 21.4 Mechanism behind nose-to-brain delivery of CPP functionalized nanoparticles

deposition was different in brain cells depending on the surface charge on particles. The quite slower brain uptake of positively charged nanoparticles was seen in the nasal cavity after mucus nanoparticle interactions (Shamarekh et al. 2020). Kanazawa et al. also described the relationship between the brain distribution and nanocarrier characteristics by using peptide-based carriers. In this study, two stable micellar formulations were developed along with conjugation of arginine-rich oligopeptide. The particle size of both stable formulations including PEG-PCL peptide micelles and stearate peptide was 50 and 100 nm, and surface charge was +15 and +20 mV. The intranasal administration was performed along with controlled group of formulation. The results concluded the increase uptake of both nanoformulations into the brain. The hydrophobic stearate peptide showed higher penetration as compared to the PEG-PCL peptide (Kanazawa et al. 2019, 2017; Ghosh et al. 2019; Grossen et al. 2017). The results concluded that PEG-PCL peptide nanocarrier penetration was higher across the nasal mucosa through the trigeminal and olfactory nerves. Gabal et al. studied the nose-to-brain delivery of nanocarrier system depending on surface charge by developing cationic and anionic nanolipid carriers having particle sizes of 160 and 175 nm and zeta potential of +34 and −34 mV. The pharmacokinetic study of both nanoparticle formulations was performed in albino rats. Moreover, results show higher bioavailability for both charge particles due to enhanced stay time in the nasal mucosa (Gabal et al. 2014).

Figure 21.4 illustrated the mechanism behind the nose-to-brain delivery of nanomaterials functionalized with CPPs.

21.11 In Vivo/In Vitro Models for Testing Nose-to-Brain Delivery

The development of futuristic nanomedicines to treat malignant gliomas and central nervous system-related malignancies demands prospective approaches to improve drug availability. In vivo animal models and in vitro cell lines-based models are being employed to explore nanomaterial-driven drug transport mechanisms via the intranasal route. These models are used in different studies; for example, absorption and toxicological and pharmacokinetic profile of the active pharmaceutical ingredient are determined by in vivo animal-based models, whereas in vitro models can study diffusion, permeation, and mechanisms (Hornof et al. 2005; Urtti 2006; Sabir et al. 2020). The selection of in vivo models is highly important for the anatomical studies of the nasal cavity. The rat is among the foremost animal models applied to intranasal examination, and subsequently, many other animal models, such as monkeys, mice, rabbits, and sheep, have also been used. For preliminary absorption evaluation, rat and mouse models are generally recommended, whereas sheep, dog, rabbit, and monkey models are employed for adequate pharmacokinetic investigations (Sousa and Castro 2016). For example, (Azambuja et al. 2020) developed a cationic nanoemulsion to treat glioblastoma by delivering CD73siRNA through the nasal route. After nasal delivery, the NE-siRNA CD73R could be noticed in rat brain and serum resulting in a 60% reduction in tumor growth in glioma-carrying Wistar rats. This cationic nanoemulsion showed no toxicity in astrocytes or rat models. Male Sprague-Dawley rats were used to evaluate microemulsion efficacy for intranasal delivery of mebendazole for glioblastoma treatment. Results revealed a significant improvement in survival time in the C6 rat model than control groups without any damage in the epithelium (Mena-Hernández et al. 2020).

In vitro models were designed as a substitute for the in vivo models. The extrapolation of absorption and kinetics data recorded from the animal models to humans is quite challenging. Moreover, animal experiments in biomedical research are often criticized for high-cost, labor-intensive, time, and ethical concerns (Hornof et al. 2005). Many countries have imposed restrictive legislation to limit animal-based experimentations. These issues have rekindled researchers' attention to seeking in vitro methods as a potential alternative to swapping animal experiments and inspired investigators to recruit cell culture models that offer noteworthy platforms to investigate different cancers. Cell models are regarded as a suitable system for investigating barrier functions, cellular uptake, and transport mechanisms (Barar et al. 2009). They could be easily established and applied to various molecular and cellular studies, like biomarker detections, cellular metabolism, and the development of new therapeutic tools, including nanobodies, monoclonal antibodies, and genome-based nanotherapeutics. Being an extremely defined system, the utilization of cell culture models from human resources can provide reliable data and

reproducible results (Barar et al. 2009). Nevertheless, it is important to choose adequate in vitro cell lines reproducing results at substantially low costs. A large number of in vitro cell culture models, such as Calu-3 (human lung adenocarcinoma), CaCo-2 cell lines (human colon carcinoma), BT (bovine turbinates), NAS2BL (rat nasal squamous carcinoma), 16HBE14o- (human normal bronchial epithelium of male heart-lung transplant patient), and RPMI 2650 (human nasal epithelial tissues) are available and tested (Sousa and Castro 2016). Among the cell lines mentioned above, RPMI 2650 and CaCo-2 are applied to study permeability and absorption via the nasal route. Nevertheless, some demerits are also associated with these cell lines; for instance, RPMI 2650 (undifferentiated cells) experience the restricted expression of goblet and ciliated cells. The lack of a well-developed monolayer renders this model cells unrealistic for transport studies. On the other hand, the Calu-3 cell line is suitable for transport evaluation because it grows in monolayers, but this does not originate from the normal epithelium of the nasal cavity. Due to high transepithelial electrical resistance (TEER), the 16HBE14o-cell line is appropriate for transportation study but originates from a male heart and lung transplant patient and normal bronchial epithelial cells. (Ullah et al. 2020) used human (U87MG) and rat (C6) glioblastoma cells for investigating the therapeutic effects of paclitaxel-incorporated nanoparticles against glioblastoma multiforme following nose-to-brain delivery. The intranasal administration of paclitaxel-incorporated nanoparticles significantly reduced tumor burden by impeding tumor proliferation and inducing apoptosis without impacting the healthy brain cells. Various formulations of low-molecular-weight heparins were administered via the nasal route to examine their absorption behavior in anesthetized rats. In vitro cell culture model was used for absorption-improving mechanism studies of cyclodextrins (Yang et al. 2004).

21.12 Comparative Analysis of In Vivo Studies of Nanomaterials vs Permeation Enhancer

Merkus and van den berg defined the selection criteria for animal study that aimed to increase evidences or justification to prove nose-to-brain delivery. These rules include (1) screening of particular administration quantity and volumes, (2) the pharmacokinetic evaluation in CNS and in plasma, (3) the comparison of the results after analysis with those obtained after intravenous intervention of the same product, and (4) the brain distribution evaluation of given product. Many other researchers elaborated on potential of various intranasal delivery strategies. These approaches included direct transport percentages (DTP%) and drug targeting efficiency % (DTE %). DTE% showed the potential of the drug to reach the brain in comparison to the blood following nose-to-brain delivery (Mistry et al. 2009; Merkus and van den Berg 2007). DTP% is defined as the percentage of the that delivered into the brain due to nose-to-brain route with respect to the total concentration of drug present in the brain. The following two equations elaborated on the mathematical expression of these two strategies (van Den Berg et al. 2002, 2004):

Drug targeting efficiency %(DTE)

$$\mathrm{DTE}\% = \frac{(\mathrm{AUCbrain}/\mathrm{AUC\ blood})\mathrm{intranasal}}{(\mathrm{AUC\ brain}/\mathrm{AUCblood})\mathrm{parentral}} * 100$$

Here, AUC brain and AUC blood are the area under the curve of the drug in the brain and blood, evaluated every time for respective route.

Direct transport percentage %(DTP)

$$\mathrm{DTP}\% = \frac{(\mathrm{Bin} - \mathrm{Bx})}{\mathrm{Bin}} * 100$$

Here, Bin is the AUC of the brain after nose-to-brain delivery and Bx is the AUC of brain fraction from the blood after intranasal application. The most data present regarding this do not clearly mentioned the pharmacokinetic and brain distribution but only represent quantitative bio-distribution results (Van Den Berg et al. 2003). Some studies did not elaborate on the comparison data systemic circulation that makes it difficult to conclude the direct nose-to-brain delivery pathway or mechanism. This is significant to mention that a number of studies showed ability of nanocarriers to pass through the olfactory pathway and deliver and release the encapsulated moiety at various brain targeting sites. However, the quantitative data related to nose-to-brain delivery of nanocarriers is not present in literature. The most intranasally applied nanocarrier used polymer and lipid-based systems. In related studies, the reported greater efficacy of peptide conjugated cationic liposomes of mean diameter up to 300nm showed 10 times enhanced bioavailability in the brain. PLA nanoparticles coated with chitosan were observed to have 9.5-fold increased amount of neurotoxin-i in the neuronal cells (Van Den Berg et al. 2003). Zhang et al. studied the PEG-PLGA particles grafted with STL, having negative zeta potential of −32 mV for intranasal delivery of growth hormone (bFGF). The tracing and screening method enabled tracing of protein molecule after its IV and IN intervention. The results showed greater DTE% and DTP% (~1050% and ~90.44% in olfactory bulb). In short, all study data until now showed that cationic or modified nanoparticles showed greater efficacy in comparison to anionic charge particles. However, there is no exact data regarding comparative studies for different nanomaterial intranasal deliveries (Li et al. 2001, 2011). Therefore, more extensive study in this arena will be more appreciated and needed in the near future. There are a huge list of studies regarding enhanced delivery of nanoparticles co-encapsulated with peptides via olfactory passage. The most common natural permeation enhancer used is chitosan, but Morishita's group of researchers used L-penetratin in comparison to free protein solution. Vaka et al. described ~14 times enhanced brain concentration of BDNF and NGF when applied intranasally. The peppermint oil is also used to have tight junction opening property. Zheng et al. studied the comparison between chitosan and PEGylated liposome formulation for intranasal delivery (Zhang et al. 2014). The results concluded 3 times higher concentration of the drug for liposomal formulation. It is concluded from the study that comparative studies

are required to evaluate the conclusion between nanoparticles and permeation enhancers (Chen et al. 2012).

21.13 Conclusion and Future Perspectives

This review discussed on the physicochemical and delivery-related intranasal barriers that influence the absorption of therapeutic drugs, with attention to details relevant to novel, noninvasive, safe, and effective strategies that help overcome intranasal barriers, published in various research articles. The new nanomaterial and nanotechnology is more phenomenal in this emerging field, which may provide a significant potential in incapacitating the limitation and barriers in targeting this route. The present literature study also pointed out the enormous role of physiochemical features like nanoparticle size and surface potential in brain delivery. Materials including lipids, PEGylation, use of surfactant as permeation enhancer, and surface grafting of peptides (CPPs) were evaluated showing more compatible results. Both in vivo animal and in vitro cell line-based models are being employed to explore nanomaterial-mediated drug transport mechanisms via the intranasal route. In contrast to in vivo models, in vitro cell models are regarded as a suitable system for investigating barrier functions, cellular uptake, and transport mechanisms. They could be easily applied to various molecular and cellular studies and to develop new therapeutic tools, including nanobodies, monoclonal antibodies, and genome-based nanotherapeutics. Nevertheless, it is important to choose adequate in vitro cell lines reproducing results at substantially low costs. The chapter concludes and highlights the potential and significance of nanomaterial application in brain targeting. However, there is more pharmacokinetic and pharmacodynamic studies needed, and also mechanism behind uptake of nanoparticles needs to be more explicatory.

References

Abd-Elal RM et al (2016) Trans-nasal zolmitriptan novasomes: in-vitro preparation, optimization and in-vivo evaluation of brain targeting efficiency. Drug Deliv 23(9):3374–3386

Abdelrahman FE et al (2017) Response surface optimization, Ex vivo and In vivo investigation of nasal spanlastics for bioavailability enhancement and brain targeting of risperidone. Int J Pharm 530(1-2):1–11

Aderibigbe BA, Naki T (2019) Chitosan-based nanocarriers for nose to brain delivery. Appl Sci 9(11):2219

Agrawal M et al (2018) Nose-to-brain drug delivery: an update on clinical challenges and progress towards approval of anti-Alzheimer drugs. J Control Release 281:139–177

Agrawal M et al (2020) Stimuli-responsive In situ gelling system for nose-to-brain drug delivery. J Control Release

Ahmad N et al (2018) Impact of ultrasonication techniques on the preparation of novel Amiloride-nanoemulsion used for intranasal delivery in the treatment of epilepsy, Artificial Cells, Nanomedicine, and Biotechnology. 46(supp 3):S192–S207

Alexander A et al (2019) Recent expansions of novel strategies towards the drug targeting into the brain. Int J Nanomedicine 14:5895

Anand U, Feridooni T, Agu RU (2012) Novel mucoadhesive polymers for nasal drug delivery. Recent Adv Novel Drug Carrier Syst:315–330

Azambuja J et al (2020) Nasal administration of cationic nanoemulsions as CD73-siRNA delivery system for glioblastoma treatment: a new therapeutical approach. Mol Neurobiol 57(2):635–649

Bahadur S, Pathak K (2012) Physicochemical and physiological considerations for efficient nose-to-brain targeting. Expert Opin Drug Deliv 9(1):19–31

Baranei M et al (2020) Anticancer effect of green tea extract (GTE)-loaded pH-responsive niosome coated with PEG against different cell lines. Mater Today Commun:101751

Barani M et al (2018) Lawsone-loaded Niosome and its antitumor activity in MCF-7 breast Cancer cell line: a Nano-herbal treatment for Cancer. DARU J Pharm Sci 26(1):11–17

Barani M et al (2019a) Evaluation of carum-loaded niosomes on breast cancer cells: physicochemical properties, in vitro cytotoxicity, flow cytometric, DNA fragmentation and cell migration assay. Sci Rep 9(1):1–10

Barani M et al (2019b) In silico and in vitro study of magnetic niosomes for gene delivery: the effect of ergosterol and cholesterol. Mater Sci Eng C 94:234–246

Barani M et al (2020a) A new formulation of hydrophobin-coated niosome as a drug carrier to cancer cells. Mater Sci Eng C:110975

Barani M et al (2020b) Nanotreatment and nanodiagnosis of prostate cancer: recent updates. Nanomaterials 10(9):1696

Barani M et al (2020c) Comprehensive evaluation of gene expression in negative and positive trigger-based targeting niosomes in HEK-293 cell line. Iran J Pharm Res 19(1):166–180

Barani M et al (2020d) Nanotechnology in ovarian cancer: diagnosis and treatment. Life Sci:118,914

Barar J et al (2009) Ocular drug delivery; impact of in vitro cell culture models. J Ophthalmic Vis Res 4(4):238

de Barros T et al (2020) Cachexia: pathophysiology and ghrelin liposomes for nose-to-brain delivery. Int J Mol Sci 21(17):5974

Battaglia L et al (2018) Lipid nanoparticles for intranasal administration: application to nose-to-brain delivery. Expert Opin Drug Deliv 15(4):369–378

Betbeder D et al (2000) Biovector™ nanoparticles improve antinociceptive efficacy of nasal morphine. Pharm Res 17(6):743–748

Bilal M et al (2020) Nanomaterials for the treatment and diagnosis of Alzheimer's disease: an overview. NanoImpact:100,251

Bonferoni MC et al (2019) Nanoemulsions for "nose-to-brain" drug delivery. Pharmaceutics 11(2): 84

Chalikwar SS et al (2013) Self-assembled, chitosan grafted PLGA nanoparticles for intranasal delivery: design, development and ex vivo characterization. Polym-Plast Technol Eng 52(4): 368–380

Chen J et al (2012) Solanum tuberosum lectin-conjugated PLGA nanoparticles for nose-to-brain delivery: in vivo and in vitro evaluations. J Drug Target 20(2):174–184

Clementino A et al (2016) The nasal delivery of nanoencapsulated statins–an approach for brain delivery. Int J Nanomedicine 11:6575

Dae-Duk K (2007) Drug absorption studies: in situ, in vitro and in silico models. Springer, New York

Das SS et al (2020) Stimuli-responsive polymeric nanocarriers for drug delivery, imaging, and theragnosis. Polymers 12(6):1397

Davarpanah F et al (2018) Magnetic delivery of antitumor carboplatin by using PEGylated-Niosomes. DARU J Pharm Sci 26(1):57–64

Davarpanah AM et al (2019) (1-x) BaFe12O19/xCoFe2O4 hard/soft magnetic nanocomposites: Synthesis, physical characterization, and antibacterial activities study. J Mol Struct 1175:445–449

van Den Berg MP et al (2002) Serial cerebrospinal fluid sampling in a rat model to study drug uptake from the nasal cavity. J Neurosci Methods 116(1):99–107
Devkar TB, Tekade AR, Khandelwal KR (2014) Surface engineered nanostructured lipid carriers for efficient nose to brain delivery of ondansetron HCl using Delonix regia gum as a natural mucoadhesive polymer. Colloids Surf B Biointerfaces 122:143–150
Dhakar RC et al (2011) A review on factors affecting the design of nasal drug delivery system. Int J Drug Deliv 3(2):194
Di Gioia S et al (2015) Intranasal delivery of dopamine to the striatum using glycol chitosan/sulfobutylether-β-cyclodextrin based nanoparticles. Eur J Pharm Biopharm 94:180–193
Ebrahimi AK, Barani M, Sheikhshoaie I (2018) Fabrication of a new superparamagnetic metal-organic framework with core-shell nanocomposite structures: characterization, biocompatibility, and drug release study. Mater Sci Eng C 92:349–355
Feng Y et al (2018) An update on the role of nanovehicles in nose-to-brain drug delivery. Drug Discov Today 23(5):1079–1088
Fonseca FN et al (2015) Mucoadhesive amphiphilic methacrylic copolymer-functionalized poly (ε-caprolactone) nanocapsules for nose-to-brain delivery of olanzapine. J Biomed Nanotechnol 11(8):1472–1481
Gabal YM et al (2014) Effect of surface charge on the brain delivery of nanostructured lipid carriers in situ gels via the nasal route. Int J Pharm 473(1-2):442–457
Gänger S, Schindowski K (2018) Tailoring formulations for intranasal nose-to-brain delivery: a review on architecture, physico-chemical characteristics and mucociliary clearance of the nasal olfactory mucosa. Pharmaceutics 10(3):116
Gao X et al (2006) Lectin-conjugated PEG–PLA nanoparticles: preparation and brain delivery after intranasal administration. Biomaterials 27(18):3482–3490
Gao X et al (2007a) UEA I-bearing nanoparticles for brain delivery following intranasal administration. Int J Pharm 340(1-2):207–215
Gao X et al (2007b) Brain delivery of vasoactive intestinal peptide enhanced with the nanoparticles conjugated with wheat germ agglutinin following intranasal administration. J Control Release 121(3):156–167
Gao X et al (2008) Quantum dots for tracking cellular transport of lectin-functionalized nanoparticles. Biochem Biophys Res Commun 377(1):35–40
Gao M et al (2011) Synthesis and characterization of superparamagnetic Fe3O4@ SiO2 core-shell composite nanoparticles. World Jf Condensed Matter Phys 1(2):49–54
Gartziandia O et al (2015) Chitosan coated nanostructured lipid carriers for brain delivery of proteins by intranasal administration. Colloids Surf B Biointerfaces 134:304–313
Gartziandia O et al (2016) Intranasal administration of chitosan-coated nanostructured lipid carriers loaded with GDNF improves behavioral and histological recovery in a partial lesion model of Parkinson's disease. J Biomed Nanotechnol 12(12):2220–2280
Ghazy E et al (2020a) Scrutinizing the therapeutic and diagnostic potential of nanotechnology in thyroid cancer: edifying drug targeting by nano-oncotherapeutics. J Drug Delivery Sci Technol:102,221
Ghazy E et al (2020b) Nanomaterials for Parkinson disease: recent progress. J Mol Struct:129,698
Ghosh S et al (2019) Surface engineered liposomal delivery of therapeutics across the blood brain barrier: recent advances, challenges and opportunities. Expert Opin Drug Deliv 16(12):1287–1311
Grossen P et al (2017) PEG-PCL-based nanomedicines: a biodegradable drug delivery system and its application. J Control Release 260:46–60
Guo J et al (2011) Aptamer-functionalized PEG–PLGA nanoparticles for enhanced anti-glioma drug delivery. Biomaterials 32(31):8010–8020
Guo Y et al (2013) The applications of Vitamin E TPGS in drug delivery. Eur J Pharm Sci 49(2):175–186
Gupta A (2020) Emerging applications of lectins in cancer detection and biomedicine. Mater Today: Proc 31:651–661

Hajizadeh MR et al (2019a) In vitro cytotoxicity assay of D-limonene niosomes: an efficient nanocarrier for enhancing solubility of plant-extracted agents. Res Pharm Sci 14(5):448
Hajizadeh MR et al (2019b) Diosgenin-loaded niosome as an effective phytochemical nanocarrier: physicochemical characterization, loading efficiency, and cytotoxicity assay. DARU J Pharm Sci 27(1):329–339
Hernando S et al (2018) Intranasal administration of TAT-conjugated lipid nanocarriers loading GDNF for Parkinson's disease. Mol Neurobiol 55(1):145–155
Hornof M, Toropainen E, Urtti A (2005) Cell culture models of the ocular barriers. Eur J Pharm Biopharm 60(2):207–225
Huckaby JT, Lai SK (2018) PEGylation for enhancing nanoparticle diffusion in mucus. Adv Drug Deliv Rev 124:125–139
Illum L (2007) Nanoparticulate systems for nasal delivery of drugs: a real improvement over simple systems? J Pharm Sci 96(3):473–483
Jadhav KR et al (2007) Nasal drug delivery system-factors affecting and applications. Curr Drug Ther 2(1):27–38
Kamei N et al (2016) Visualization and quantitative assessment of the brain distribution of insulin through nose-to-brain delivery based on the cell-penetrating peptide noncovalent strategy. Mol Pharm 13(3):1004–1011
Kanazawa T (2015) Brain delivery of small interfering ribonucleic acid and drugs through intranasal administration with nano-sized polymer micelles. Med Devices (Auckland, NZ) 8:57
Kanazawa T et al (2011) Cell-penetrating peptide-modified block copolymer micelles promote direct brain delivery via intranasal administration. Pharm Res 28(9):2130–2139
Kanazawa T et al (2012) Suppression of tumor growth by systemic delivery of anti-VEGF siRNA with cell-penetrating peptide-modified MPEG–PCL nanomicelles. Eur J Pharm Biopharm 81(3):470–477
Kanazawa T et al (2013) Delivery of siRNA to the brain using a combination of nose-to-brain delivery and cell-penetrating peptide-modified nano-micelles. Biomaterials 34(36):9220–9226
Kanazawa T et al (2017) Enhancement of nose-to-brain delivery of hydrophilic macromolecules with stearate-or polyethylene glycol-modified arginine-rich peptide. Int J Pharm 530(1-2): 195–200
Kanazawa T et al (2019) Therapeutic effects in a transient middle cerebral artery occlusion rat model by nose-to-brain delivery of anti-TNF-alpha siRNA with cell-penetrating peptide-modified polymer micelles. Pharmaceutics 11(9):478
Kulkarni AD et al (2015) Nanotechnology-mediated nose to brain drug delivery for Parkinson's disease: a mini review. J Drug Target 23(9):775–788
Li Y-P et al (2001) PEGylated PLGA nanoparticles as protein carriers: synthesis, preparation and biodistribution in rats. J Control Release 71(2):203–211
Li J et al (2011) Targeting the brain with PEG–PLGA nanoparticles modified with phage-displayed peptides. Biomaterials 32(21):4943–4950
Lin T et al (2016) Nose-to-brain delivery of macromolecules mediated by cell-penetrating peptides. Acta Pharm Sin B 6(4):352–358
Liu Z et al (2013) Lactoferrin-modified PEG-co-PCL nanoparticles for enhanced brain delivery of NAP peptide following intranasal administration. Biomaterials 34(15):3870–3881
Lu C-T et al (2015) Gelatin nanoparticle-mediated intranasal delivery of substance P protects against 6-hydroxydopamine-induced apoptosis: an in vitro and in vivo study. Drug Des Devel Ther 9:1955
Martins PP, Smyth HD, Cui Z (2019) Strategies to facilitate or block nose-to-brain drug delivery. Int J Pharm 570:118635
Mathieu V (2019) Development and characterization of formulations for the nose-to-brain delivery of ghrelin and the management of cachexia. Université de Mons.
Md S et al (2018) Nano-carrier enabled drug delivery systems for nose to brain targeting for the treatment of neurodegenerative disorders. J Drug Delivery Sci Technol 43:295–310

Mena-Hernández J et al (2020) Preparation and evaluation of mebendazole microemulsion for intranasal delivery: an alternative approach for glioblastoma treatment. AAPS PharmSciTech 21(7):1–12
Meng Q et al (2018) Intranasal delivery of Huperzine A to the brain using lactoferrin-conjugated N-trimethylated chitosan surface-modified PLGA nanoparticles for treatment of Alzheimer's disease. Int J Nanomedicine 13:705
Merkus FW, van den Berg MP (2007) Can nasal drug delivery bypass the blood-brain barrier? Drugs in R & D 8(3):133–144
Migliore MM et al (2010) Brain delivery of proteins by the intranasal route of administration: a comparison of cationic liposomes versus aqueous solution formulations. J Pharm Sci 99(4): 1745–1761
Misra A, Kher G (2012) Drug delivery systems from nose to brain. Curr Pharm Biotechnol 13(12): 2355–2379
Mistry A, Stolnik S, Illum L (2009) Nanoparticles for direct nose-to-brain delivery of drugs. Int J Pharm 379(1):146–157
Mittal D et al (2014) Insights into direct nose to brain delivery: current status and future perspective. Drug Deliv 21(2):75–86
Mukhtar M et al (2020) Nanomaterials for diagnosis and treatment of brain cancer: recent updates. Chemsensors 8(4):117
Muralidharan P et al (2014) Inhalable PEGylated phospholipid nanocarriers and PEGylated therapeutics for respiratory delivery as aerosolized colloidal dispersions and dry powder inhalers. Pharmaceutics 6(2):333–353
Musumeci T et al (2018) Tangential flow filtration technique: an overview on nanomedicine applications. Pharm Nanotechnol 6(1):48–60
Nehoff H et al (2014) Nanomedicine for drug targeting: strategies beyond the enhanced permeability and retention effect. Int J Nanomedicine 9:2539
Nikazar S et al (2020a) Revisiting the cytotoxicity of quantum dots: an in-depth overview. Biophys Rev:1–16
Nikazar S et al (2020b) Photo-and magnetothermally responsive nanomaterials for therapy, controlled drug delivery and imaging applications. ChemistrySelect 5(40):12,590–12,609
Okada H (2014) Targeted siRNA therapy using cytoplasm-responsive nanocarriers and cell-penetrating peptides. J Pharm Investig 44(7):505–516
Ong W-Y, Shalini S-M, Costantino L (2014) Nose-to-brain drug delivery by nanoparticles in the treatment of neurological disorders. Curr Med Chem 21(37):4247–4256
Pardeshi CV, Belgamwar VS (2013) Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood–brain barrier: an excellent platform for brain targeting. Expert Opin Drug Deliv 10(7):957–972
Pardeshi CV, Belgamwar VS (2018) N, N, N-trimethyl chitosan modified flaxseed oil based mucoadhesive neuronanoemulsions for direct nose to brain drug delivery. Int J Biol Macromol 120:2560–2571
Patel S et al (2011) Brain targeting of risperidone-loaded solid lipid nanoparticles by intranasal route. J Drug Target 19(6):468–474
Piazza J et al (2014) Haloperidol-loaded intranasally administered lectin functionalized poly (ethylene glycol)–block-poly (D, L)-lactic-co-glycolic acid (PEG–PLGA) nanoparticles for the treatment of schizophrenia. Eur J Pharm Biopharm 87(1):30–39
Piazzini V et al (2019) Chitosan coated human serum albumin nanoparticles: a promising strategy for nose-to-brain drug delivery. Int J Biol Macromol 129:267–280
Pillai AM et al (2020) Green synthesis and characterization of zinc oxide nanoparticles with antibacterial and antifungal activity. J Mol Struct:128,107
Quintana DS et al (2016) The promise and pitfalls of intranasally administering psychopharmacological agents for the treatment of psychiatric disorders. Mol Psychiatry 21(1):29–38

Rahdar A et al (2019a) Effect of tocopherol on the properties of Pluronic F127 microemulsions: physico-chemical characterization and in vivo toxicity. J Mol Liq 277:624–630
Rahdar A et al (2019b) Synthesis and characterization of highly efficacious Fe-doped ceria nanoparticles for cytotoxic and antifungal activity. Ceram Int 45(6):7950–7955
Rahdar A et al (2020a) The synthesis of methotrexate-loaded F127 microemulsions and their in vivo toxicity in a rat model. J Mol Liq:113449
Rahdar A et al (2020b) Synthesis, characterization, and intraperitoneal biochemical studies of zinc oxide nanoparticles in Rattus norvegicus. Appl Phys A 126:1–9
Rahdar A et al (2020c) Behavioral effects of zinc oxide nanoparticles on the brain of rats. Inorg Chem Commun 119:108,131
Rahdar A et al (2020d) Copolymer/graphene oxide nanocomposites as potential anticancer agents. Polymer Bull:1–22
Rahdar A et al (2020e) Gum-based cerium oxide nanoparticles for antimicrobial assay. Appl Phys A 126:1–9
Rahdar A et al (2020f) Deferasirox-loaded pluronic nanomicelles: synthesis, characterization, in vitro and in vivo studies. J Mol Liq:114,605
Rassu G et al (2017) Nose-to-brain delivery of BACE1 siRNA loaded in solid lipid nanoparticles for Alzheimer's therapy. Colloids Surf B Biointerfaces 152:296–301
Sabir F, Ismail R, Csoka I (2020) Nose-to-brain delivery of antiglioblastoma drugs embedded into lipid nanocarrier systems: status quo and outlook. Drug Discov Today 25(1):185–194
Salade L et al (2017) Development of coated liposomes loaded with ghrelin for nose-to-brain delivery for the treatment of cachexia. Int J Nanomedicine 12:8531
Salem LH et al (2020) Coated lipidic nanoparticles as a new strategy for enhancing nose-to-brain delivery of a hydrophilic drug molecule. J Pharm Sci
Samaridou E, Alonso MJ (2018) Nose-to-brain peptide delivery–the potential of nanotechnology. Bioorg Med Chem 26(10):2888–2905
Samaridou E et al (2020) Nose-to-brain delivery of enveloped RNA-cell permeating peptide nanocomplexes for the treatment of neurodegenerative diseases. Biomaterials 230:119657
Saravani R et al (2020) Newly crocin-coated magnetite nanoparticles induce apoptosis and decrease VEGF expression in breast carcinoma cells. J Drug Delivery Sci Technol 60:101,987
Sawant RR, Torchilin VP (2010) Multifunctionality of lipid-core micelles for drug delivery and tumour targeting. Mol Membr Biol 27(7):232–246
Sayadi K et al (2020) Atorvastatin-loaded SBA-16 nanostructures: synthesis, physical characterization, and biochemical alterations in hyperlipidemic rats. J Mol Struct 1202:127,296
Sekerdag E et al (2017) A potential non-invasive glioblastoma treatment: Nose-to-brain delivery of farnesylthiosalicylic acid incorporated hybrid nanoparticles. J Control Release 261:187–198
Shamarekh KS et al (2020) Development and evaluation of protamine-coated PLGA nanoparticles for nose-to-brain delivery of tacrine: in-vitro and in-vivo assessment. J Drug Delivery Sci Technol:101,724
Sivasankarapillai VS et al (2020a) Cancer theranostic applications of MXene nanomaterials: recent updates. Nano-Struct Nano-Objects 22:100,457
Sivasankarapillai VS et al (2020b) On facing the SARS-CoV-2 (COVID-19) with combination of nanomaterials and medicine: possible strategies and first challenges. Nanomaterials 10(5):852
Sivasankarapillai V et al Progress in natural polymer engineered biomaterials for transdermal drug delivery systems. Mater Today Chem 19:100,382
Sonvico F et al (2018) Surface-modified nanocarriers for nose-to-brain delivery: from bioadhesion to targeting. Pharmaceutics 10(1):34
Sosnik A, das Neves J, Sarmento B (2014) Mucoadhesive polymers in the design of nano-drug delivery systems for administration by non-parenteral routes: a review. Prog Polym Sci 39(12): 2030–2075
Sousa F, Castro P (2016) Cell-based in vitro models for nasal permeability studies. In: Concepts and models for drug permeability studies. Elsevier, pp 83–100

Stevens J et al (2009) A new minimal-stress freely-moving rat model for preclinical studies on intranasal administration of CNS drugs. Pharm Res 26(8):1911–1917
Stützle M et al (2015) Nose-to-brain delivery of insulin for Alzheimer's disease. ADMET and DMPK 3(3):190–202
Tafaghodi M et al (2004) Evaluation of the clearance characteristics of various microspheres in the human nose by gamma-scintigraphy. Int J Pharm 280(1-2):125–135
Taimoory SM et al (2018) The synthesis and characterization of a magnetite nanoparticle with potent antibacterial activity and low mammalian toxicity. J Mol Liq 265:96–104
Taki H et al (2012) Intranasal delivery of camptothecin-loaded tat-modified nanomicells for treatment of intracranial brain tumors. Pharmaceuticals 5(10):1092–1102
Torkzadeh-Mahani M et al (2020) A combined theoretical and experimental study to improve the thermal stability of recombinant D-lactate dehydrogenase immobilized on a novel superparamagnetic Fe3O4NPs@ metal–organic framework. Appl Organomet Chem 34(5): e5581
Ugwoke MI et al (2005) Nasal mucoadhesive drug delivery: background, applications, trends and future perspectives. Adv Drug Deliv Rev 57(11):1640–1665
Ullah I et al (2020) Nose-to-brain delivery of cancer-targeting paclitaxel-loaded nanoparticles potentiates antitumor effects in malignant glioblastoma. Mol Pharm 17(4):1193–1204
Upadhyay S et al (2011) Intranasal drug delivery system-a glimpse to become maestro. J Appl Pharm Sci 1(03):34–44
Urtti A (2006) Challenges and obstacles of ocular pharmacokinetics and drug delivery. Adv Drug Deliv Rev 58(11):1131–1135
Van Den Berg MP et al (2003) Hydroxocobalamin uptake into the cerebrospinal fluid after nasal and intravenous delivery in rats and humans. J Drug Target 11(6):325–331
Van Den Berg MP et al (2004) Uptake of melatonin into the cerebrospinal fluid after nasal and intravenous delivery: studies in rats and comparison with a human study. Pharm Res 21(5): 799–802
Wang X, Chi N, Tang X (2008) Preparation of estradiol chitosan nanoparticles for improving nasal absorption and brain targeting. Eur J Pharm Biopharm 70(3):735–740
Warnken ZN et al (2016) Formulation and device design to increase nose to brain drug delivery. J Drug Delivery Sci Technol 35:213–222
Wu H et al (2012) A novel small Odorranalectin-bearing cubosomes: preparation, brain delivery and pharmacodynamic study on amyloid-β25–35-treated rats following intranasal administration. Eur J Pharm Biopharm 80(2):368–378
Xia H et al (2011) Low molecular weight protamine-functionalized nanoparticles for drug delivery to the brain after intranasal administration. Biomaterials 32(36):9888–9898
Yadav S et al (2015) Comparative biodistribution and pharmacokinetic analysis of cyclosporine-a in the brain upon intranasal or intravenous administration in an oil-in-water nanoemulsion formulation. Mol Pharm 12(5):1523–1533
Yang T et al (2004) Cyclodextrins in nasal delivery of low-molecular-weight heparins: in vivo and in vitro studies. Pharm Res 21(7):1127–1136
Yasir M, Sara UVS (2014) Solid nanoparticles for nose to brain delivery of haloperidol: in vitro drug release and pharmacokinetics evaluation. Acta Pharm Sin B 4(6):454–463
Ying, W., The nose may help the brain: intranasal drug delivery for treating neurological diseases. 2008.
Yokoyama M (2005) Drug targeting with nano-sized carrier systems. J Artif Organs 8(2):77–84
Zaki N et al (2006) Rapid-onset intranasal delivery of metoclopramide hydrochloride: Part I. Influence of formulation variables on drug absorption in anesthetized rats. Int J Pharm 327(1-2):89–96

Zhang C et al (2014) Intranasal nanoparticles of basic fibroblast growth factor for brain delivery to treat Alzheimer's disease. Int J Pharm 461(1-2):192–202

Zhao Y-Z et al (2014) Gelatin nanostructured lipid carriers-mediated intranasal delivery of basic fibroblast growth factor enhances functional recovery in hemiparkinsonian rats. Nanomed Nanotechnol Biol Med 10(4):755–764

Zhao Y-Z et al (2016) Intranasal delivery of bFGF with nanoliposomes enhances in vivo neuroprotection and neural injury recovery in a rodent stroke model. J Control Release 224: 165–175

Zheng X et al (2015) Intranasal H102 peptide-loaded liposomes for brain delivery to treat Alzheimer's disease. Pharm Res 32(12):3837–3849