# Significance of Intranasal Drug Delivery Systems: Recent Trends and Clinical Investigations in Brain Disorders

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**Abstract**

Intranasal drug administration has enormous research potential, including both drugs designed specifically for intranasal use and off-label applications of commercially available generic medications. The olfactory canal architecture has a well-vascularized mucosal framework, which permits the drug molecule to be transported fast through a single epithelium layer and into the systemic bloodstream without having to go through hepatic and intestinal processing first. The majority of CNS therapy treatments now available rely on systemic medication delivery to the brain via the oral route and intravenous injection. The current CNS therapy treatments mostly rely on systemic medication delivery to the brain via the oral route and intravenous injection. The primary drawback of these approaches is the limited pharmacological access of therapeutic compounds in

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the blood supply to the brain, which is linked with decreased therapeutic efficacy and, eventually, increased peripheral adverse effects. The current study highlights the clinical status of numerous medications employed in intranasal drug delivery systems invented by diverse scientists for various brain illnesses. The paper also focuses on current advancements in intranasal medication delivery systems modeled for brain transport.

**Keywords**

CNS · Blood–brain barrier · Intranasal · Non-invasive route

## 19.1 Introduction

### 19.1.1 Central Nervous System Overview

The central nervous system (CNS), one of the two basic divisions of the nervous system, is made up of the brain and spinal cord. The other division is the peripheral nervous system (PNS), which is found outside of the brain and spinal cord. The CNS's primary role is to consolidate incoming information, coordinate, and impact the functioning of all bodily components. CNS and brain ailments impact more than a hundred million individuals globally, according to a World Health Organization (WHO) estimate, and require long-term therapy (World Health Organization 2006). There are various illnesses affecting the brain and CNS that impair a person's motor functional activity. It has proven difficult to get drugs to the brain to treat neurological illnesses (Barchet and Amiji 2009; MacDonald et al. 2000). The most effective route to transport medications to any part of the body is orally, intranasally, or intravenously. There are several obstacles to these medication delivery pathways for brain targets (Bozdağ Pehlivan 2013).

## 19.2 Barriers to Brain Drug Delivery

Physiological barriers that prevent medications from accessing the brain commonly hamper the treatment of CNS diseases. Despite the availability of a number of brain targeting methods, none have proved successful in producing therapeutic concentrations in the brain (Lesniak and Brem 2004). Three primary barriers separate blood and the CNS: the BBB, the blood–cerebrospinal fluid barrier (BCSFB), and the blood–tumor barrier. Aside from these obstacles, efflux transporter proteins such as P-glycoprotein (P-gp) and others operate as gatekeepers, preventing drug molecules from reaching the brain (Ricci et al. 2006).

## 19.2.1 Blood–Brain Barrier

The blood–brain barrier (BBB) is a capillary-based endothelial barrier that runs throughout the brain parenchyma. Endothelial tight junctions contain intracellular junction proteins termed occludin and claudin. These structures provide a barrier to the flow of chemicals between the bloodstream and the brain (Sanchez-Covarrubias et al. 2014; Chen and Liu 2012).

The existence of tight junctions between cells, which inhibits paracellular transport owing to high electrical resistance, is one of the key properties of BBB (Abbott et al. 2006). The absence of fenestrations, the existence of P-gp, which is implicated in drug efflux, and the presence of fewer endocytic vesicles, which reduces transcellular flow (Chang et al. 2009), are all factors that limit transcellular flux (Sanchez-Covarrubias et al. 2014). As a result, most medications are limited from crossing the BBB, and only tiny lipophilic molecules can pass the endothelium/BBB (Krol 2012).

Important nutrients are transported across the BBB by particular transportation mechanisms. However, it prohibits xenobiotic entrance, implying that each peptide molecule has a unique pathway for entry (Pardridge 1983). Endogenous and exogenous solutes are metabolized by mitochondria and metabolizing enzymes such as adenylate cyclase, guanylate cyclase, etc. (Brownlees and Williams 1993). As a result, these tight connections prevent ion or molecule exchange between the systemic circulation and the central nervous system. As a result, active drug transport into brain tissue is reduced, resulting in the failure of CNS therapies for diseases including Alzheimer's, schizophrenia, epilepsy, and depression (Löscher and Potschka 2005) (Fig. 19.1).
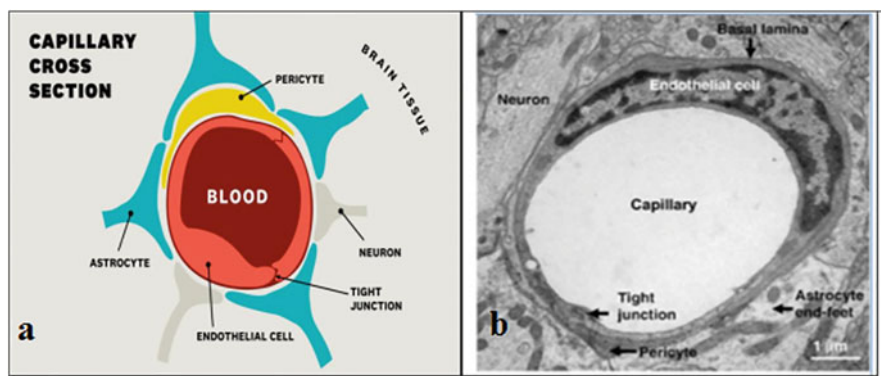


**Fig. 19.1** (**a**) Representation and (**b**) Scanning Electron Microscope Image of the Capillary (Pardridge 2006)
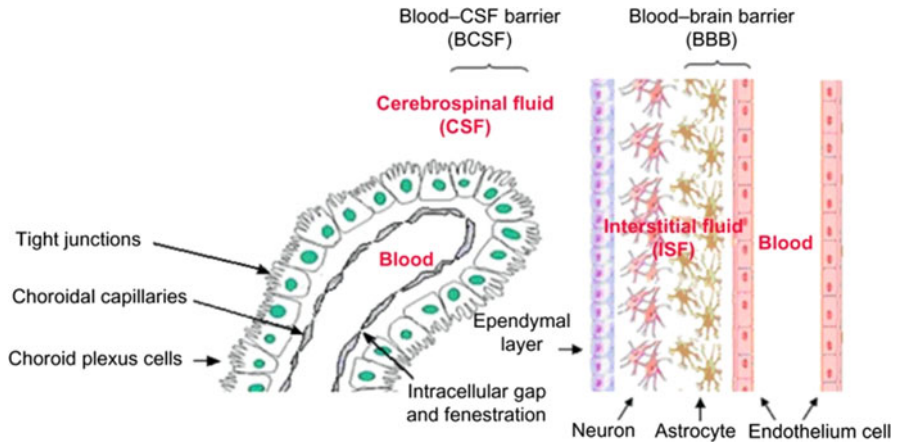
**Fig. 19.2** Blood–cerebrospinal Fluid Barrier Schematic Diagram (BCB) (Alam et al. 2010)

## 19.2.2 Blood–Cerebrospinal Fluid Barrier

The blood–cerebrospinal fluid barrier (BCB) controls the passage of blood-carried chemicals into the CSF. CSF and brain parenchymal interstitial fluid can exchange chemicals. Because of their intimate connections, the arachnoid membrane and choroid plexus provide an important function as barriers between the blood and CSF (Misra et al. 2003). Figure 19.2 shows a diagram of the BCB (Alam et al. 2010).

## 19.2.3 Blood–Tumor Barrier

The major issue in brain tumors is permeability. The first variable regarding capillary permeability is the tumor microvessel population, also known as the blood–tumor barrier, and the second variable is the spatial distribution of the target capillaries (Groothuis 2000).

## 19.3   Drug Transport Through Blood-Brain-Barrier (BBB)

Transport over the BBB is a major hurdle to drug absorption, and the BBB is reinforced by many parallel barriers, mainly the capillary bed in the vascular BBB, the BCB, and the choroid plexus, all of which offer strong endothelial resistance. Essential solutes enter the CNS via one of the two methods listed below (Pardridge 2006). Figure 19.3 depicts the route of drug penetration through the BBB.
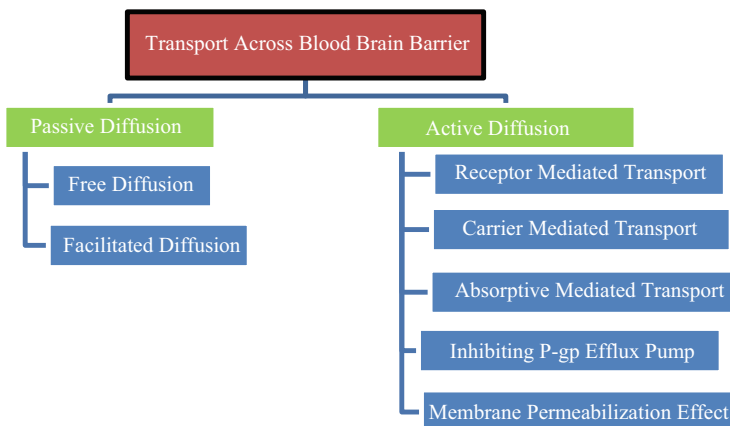
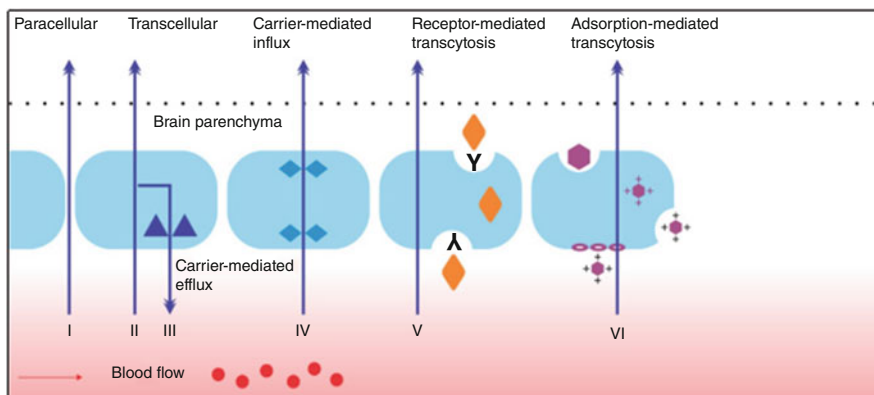Fig. 19.3 Drug penetration route across the blood–brain barrier



**Fig. 19.4** (**a**) Efflux transport mechanisms prevent numerous chemicals from entering the brain. (**b**) Saturable transport is in charge of the transfer. (**c**) Transcellular lipophilic route for lipophilic agent diffusion. (**d**) A biological route that allows extremely tiny quantities of hydrophilic substances to diffuse. (**e**) Endocytosis of essential proteins such as insulin, transferrin, and cytokines is mediated by particular receptors. (**f**) Adsorptive endocytosis is caused by the cationization of certain molecules, such as albumin

### 19.3.1 Passive Diffusion

As illustrated in Fig. 19.4, highly lipophilic molecules of low molecular weight can extensively infiltrate the BBB via passive diffusion via multiple routes. Uncharged molecules partition easily between tissues and are absorbed in the brain due to their lipophilic nature (Jouyban and Soltani 2012). A molecule moving passively across the BBB has an average molecular mass of 357 Da, or less than 1 nm (Jain 2012).

There are two processes that control passive diffusion:

**Free diffusion**: Some molecules go between cells outside of the cell membrane (e.g., Sucrose). Because of the tight connections, transport is limited, particularly for hydrophobic substances, certain molecules travel transcellular across the cells (e.g., ethanol).

**Facilitated diffusion**: In this sort of transport, solutes are moved from one side of the membrane to the other by altering the conformation of certain membrane proteins (Alam et al. 2010). Molecular weight, lipophilicity, ionization, and hydrogen bonding are all variables that influence passive diffusion through the BBB.

## 19.3.2 Active Transport

Active transport is a sort of membrane transport that is energy driven and works in the opposite direction of the electrochemical gradient. This method is required to avoid any interruption in the passage of important substances such as glucose from the blood to the brain and vice versa for normal brain metabolism and activity (Nau et al. 2010; Begley 2004).

### 19.3.2.1 Receptor-Mediated Transcytosis
Large chemicals necessary for brain homeostasis enter the BBB via specialized receptors found in the endothelial membrane, such as insulin receptors, transferrin receptors, LDL receptors, and so on. Table 19.1 lists key receptor-mediated transporter systems at BBB (Patel et al. 2011).

### 19.3.2.2 Adsorptive-Mediated Transcytosis
Adsorptive-mediated transcytosis (AMT) (Gabathuler 2010) refers to the nonspecific transport of charged [cationic] peptide molecules such as protamine and albumin across the BBB. The transcytosis routes and enzymatic characteristics, together with the large number of mitochondria in endothelial cells, produce a shove for molecules to travel across the endothelial cytoplasm (Sauer et al. 2005; Xiao and Gan 2013).

**Table 19.1** Key receptor-mediated transporter systems at BBB (Khosrow Tayebati et al. 2013)

| Sr. No | RMT systems | Molecules transported |
|--------|-------------|----------------------|
| 1 | TfR | Transferrin |
| 2 | INSR | Insulin |
| 3 | LEPR | Leptin |
| 4 | SR-BI | LDL particles |
| 5 | FcGRT | Immunoglobulin |
| 6 | IGF-1R, IGF-2R | IGF |

### 19.3.3 Carrier-Mediated Transport

Select membrane-confined transporters carry endogenous chemicals, including vital nutrients, from the blood to the brain parenchyma. Changing the drug/substrate to imitate a nutrient/endogenous substrate capable of transporting, or employing one of the current carrier systems, are two options for CMT.

#### 19.3.3.1 Drug Delivery Strategies Across the BBB

In the case of CNS disorder, conventional drug delivery enters the brain through systemic circulation. To get the appropriate therapeutic concentration at the intended site, systemic drug levels must be increased by the repeated dosage or extended administration. This might lead to an increase in toxicity. Invasive, non-invasive, and miscellaneous techniques are the three types of strategies for crossing the BBB.

#### 19.3.3.2 Intranasal Drug Delivery Systems

In CNS disorders, conventional medication delivery enters the brain via systemic circulation. Systemic drug levels must be raised by repeated dosing or longer administration to achieve the optimal therapeutic concentration at the target location. This might lead to an increase in toxicity. There are three types of strategies for crossing the BBB: invasive, non-invasive, and various.

## 19.4 The Nasal Cavity's Anatomy and Physiology

The human nasal cavity is around 12–14 cm long, with a total capacity of 15–20 mL. According to (Ali et al. 2010), the nasal cavity is divided into two parts by a vertical barrier called the nasal septum. In an anterior–posterior orientation, from the nostrils to the nasopharynx, the nasal cavity extends. Following delivery into the nasal canal, the drug might be deposited in one of three anatomically distinct sites. The drug must pass through the olfactory membrane as well as the arachnoid membrane, which covers the arachnoid space, which contains cerebrospinal fluid, before reaching the CNS through the nasal cavity (Vyas et al. 2005). Figure 19.5 depicts an overview of the nasal cavity.

### 19.4.1 Nasal Vestibule

The most anterior section of the nasal cavity is made up of a 0.6 cm$^2$ patch with sebaceous glands that is composed of stratified squamous and keratinized epithelium. Although the nasal vestibule provides considerable resistance to hazardous environmental chemicals, medication absorption becomes extremely difficult in this location (Djupesland 2013).
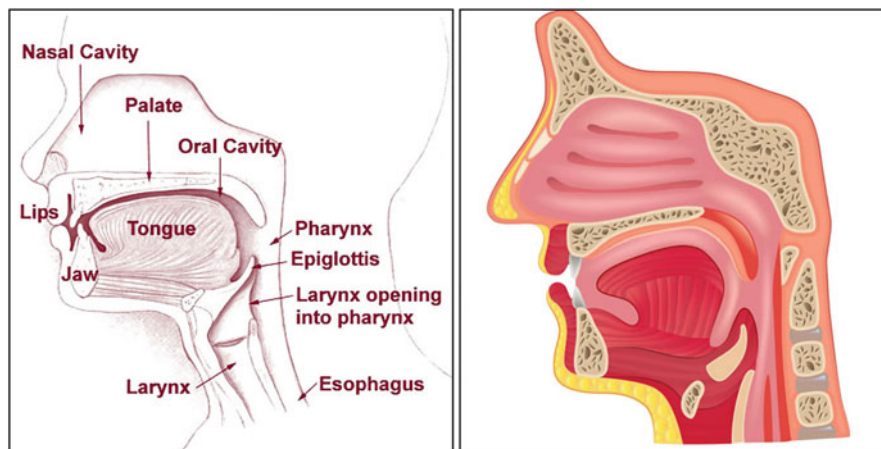
**Fig. 19.5** A glimpse of the nasal cavity

### 19.4.2 Respiratory Region

In humans, the nasal respiratory area, also known as the conchae, is the biggest component, lining roughly 80–90% of the nasal cavity. It has a huge surface area and high vascularity, allowing for increased medication absorption via the respiratory epithelium. The cilia, which are hair-like projections on the surface of epithelial cells, are responsible for the epithelium's expanded surface area. Furthermore, these cilia aid in the transmission of mucus to the nasopharynx (Ozsoy et al. 2009). Mucociliary clearance is the activity of clearing mucous into the gastrointestinal channel (MCC). This protective effect of mucous results in the quick removal of medications from the body. This protective effect of mucous results in the quick clearance of medicines from the nasal cavity by reducing the drug's dwell time in the nasal cavity. Mucin, which is found in the mucous layer, is responsible for trapping big molecular weight drugs such as proteins and peptides (Charlton et al. 2007). Figure 19.6 displays an overview of respiratory mucosa with structural demonstration (Mandpe et al. 2013).

### 19.4.3 Olfactory Region

The olfactory region is made of three types of cells: olfactory receptor cells, supportive epithelial cells, and basal cells. The only portion of the CNS that is connected directly to the physical realm is the neuroepithelium (Lochhead and Thorne 2012; Talegaonkar and Mishra 2004). Figure 19.7 shows an overview of the organization of the human olfactory region (Desai et al. 2015).
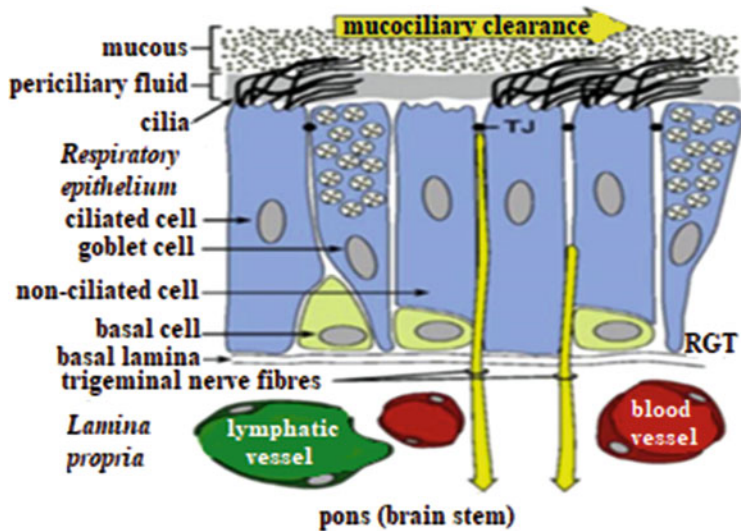
**Fig. 19.6** Overview of respiratory mucosa with structural demonstration (Mandpe et al. 2013)
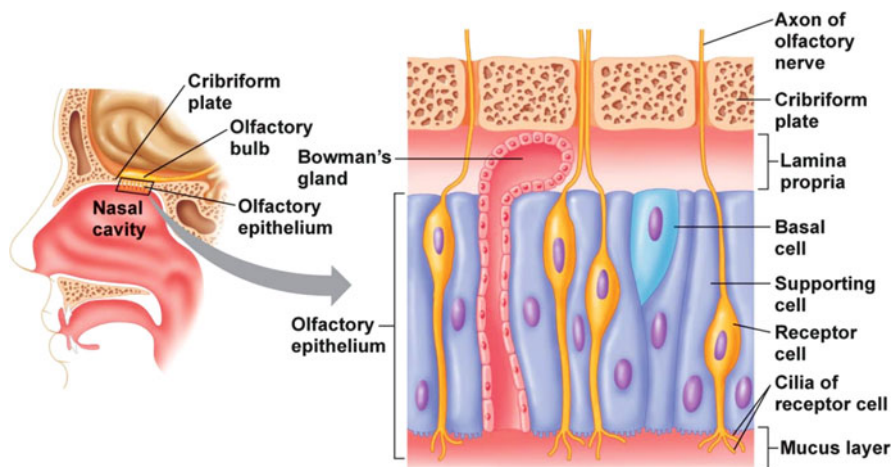


**Fig. 19.7** Human olfactory region (Desai et al. 2015)

## 19.4.4 Applications of Nasal Route for Delivery and Therapeutic Opportunities

Many benefits of the nasal mucosal structure have been identified, including the capacity to deliver medications with a rapid beginning of the action, increased bioavailability, and patient compliance.

#### 19.4.4.1 Nasal Delivery of Systemic Drugs

Nasal delivery is regarded to be an interesting option for drugs that are having difficulty with current conventional techniques. Needle-free administration as an alternative to injections and lower chances of drug degradation, among other benefits, has resulted in the availability of systemically acting drugs with many currently being investigated (Gangurde et al. 2019).

#### 19.4.4.2 Nasal Route for Vaccine Delivery

Nasal delivery is seen to be an intriguing possibility for treatments that are not working well with current methods. Needle-free delivery as a substitute for injections, as well as a reduced risk of drug degradation (Gangurde et al. 2019).

#### 19.4.4.3 Nasal Route for Topical Delivery

Allergies impact between 5% and 10% of the global population. Topical steroids are the preferred treatment option for individuals suffering from chronic allergic and non-allergic mucosal inflammation, rhinitis, and sinusitis (Illum 2012). Treatment with topical steroids remains inadequate in certain instances due to insufficient distribution to the nose and sinuses. This opens up the possibility of developing innovative topical medications with unique nasal delivery methods to treat diverse allergy diseases and increase patient compliance (Illum 2004).

#### 19.4.4.4 Nasal Route for Brain Delivery

Treatment of CNS illnesses such as Alzheimer's disease, depression, epilepsy, and schizophrenia has many obstacles with the existing standard administration technique due to therapeutic agent delivery constraints. This channel delivers drug molecules to the brain by circumventing the BBB. The amount of drug entering systemic circulation, as well as the accompanying side effects, can be reduced in this way (Bahadur and Pathak 2012; Upadhyay et al. 2011).

## 19.5 Drug Absorption Through Nasal Mucosa

The passage of the mucous membrane is the initial stage in medication absorption from the nasal cavity. This layer is easily penetrated by small, unaltered particles. Large or charged particles, on the other hand, may have difficulties crossing them. Because of environmental changes, structural alterations in the mucous layer are conceivable (i.e., pH, temperature, etc.).

### 19.5.1 Nasal Drug Delivery Technique Benefits and Drawbacks

Advantages are as follows:

- Non-invasive,
- Bypass the BBB,

- Therapeutic agents do not need any modification,
- Does not require any trained person for medication,
- Avoidance of environmental conditions like chemical and enzymatic degradation of drugs,
- Rapid,
- Feasible and convenient route of delivery to CNS,
- Prevents first-pass metabolism,
- Allowing increased bioavailability (Jadhav et al. 2014).

Nasal delivery has a few disadvantages as follows:

- Including nasal irritation,
- Tissue toxicity,
- The risk of local side effects,
- Nasal congestion,
- Large molecular weight drugs cannot be given (Jadhav et al. 2014).

## 19.5.2 Factors Influencing Nasal Drug Absorption

To have a systemic influence or to penetrate the brain a medicine or formulation must pass through various membranes or barriers when administered intranasally. Furthermore, the rate and extent of nasal drug absorption are influenced by the drug's physicochemical properties and many more as shown in Fig. 19.8.
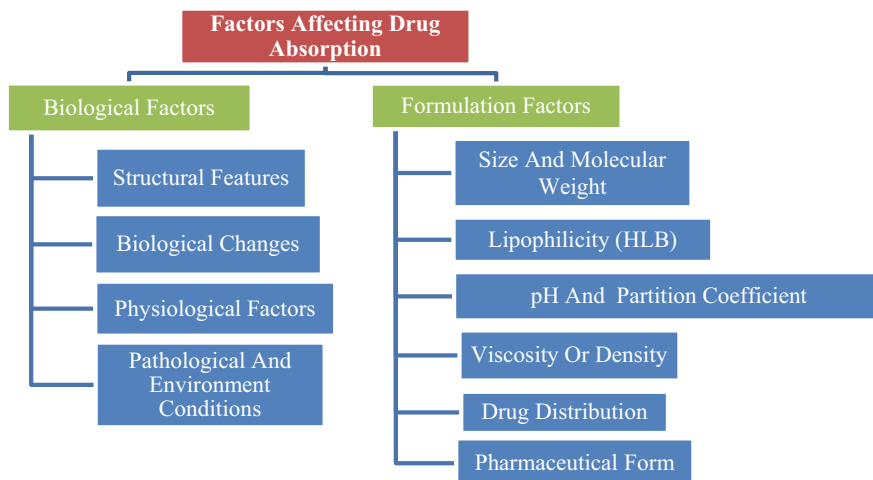


**Fig. 19.8** Factors affecting drug absorption

### 19.5.2.1 Biological Factors

#### 19.5.2.1.1 Structural Features
The nasal cavity is divided into five sections anatomically. The respiratory mucosa is the primary site of medication absorption via the nasal route. Columnar cells, vasculature, and other defense systems comprise it. The nasal cavity is well supplied with vasculature, which gets the greatest quantity of lachrymal secretion, which is responsible for the cavity's warmth and humidification.

#### 19.5.2.1.2 Biochemical Changes
The nasal route was chosen over the oral route to increase bioavailability and prevent first-pass metabolism. Drugs are partially broken down by metabolic enzymes which are released into mucus. Enzymatic degradants include mono and di amino peptides, serine, and cysteine (Boddupalli et al. 2010).

### 19.5.2.2 Physiological Factors
Blood supply and neural regulation, nasal cavity pH, mucociliary clearance (MCC), and ciliary beat frequency are all physiological factors that influence nasal drug absorption (CBF).

### 19.5.2.3 Pathological and Environmental Conditions
Because all systems are interrelated, any change in the micro-environment in the nose, such as MCC, CBF, pH, or any slight alteration in the structure of the mucous layer, triggers a defensive reaction, reducing medicine bioavailability (Costantino et al. 2007).

Enzymatic degradation.
Transporters and efflux systems.
Effect of pathological conditions.

### 19.5.2.4 Formulation Factors
Drug transport is affected by numerous factors that are explained in the following:

#### 19.5.2.4.1 Size and Molecular Weight
Transcellular passive diffusion, which comprises molecules moving across the cell membrane between cells, allows polar molecules with a molecular weight of less than 1 KD (Kilo Dalton) to travel across the membrane. Molecules bigger than 1 KD, on the other hand, prefer passive diffusion outside of the cell, transcytosis, or carrier-mediated transport. This route, however, is only partially penetrated.

#### 19.5.2.4.2 Lipophilicity
Though mucous is polar due to its high-water content and nasal membrane underneath, it is lipophilic, allowing lipophilic medicines to enter transcellular and achieve fast bioavailability.

### 19.5.2.4.3 pH and Partition Coefficient

Drug absorption is also affected by pH and partition coefficient. HLB modification allows for the successful delivery of drugs with a wide pH range. Many researchers determined in the early 1980s that medications with unionized states have more absorption/penetration than those with ionized states. Unionized forms of drugs absorb better in a wide pH range (Kushwaha et al. 2011).

### 19.5.2.4.4 Viscosity/Density

Higher viscous liquids improve permeability by coating the CBF and MCC; drug retention duration is enhanced, and absorption is improved. For example, the incorporation of hydroxyl propyl methyl cellulose (HPMC) helped improve drug absorption by the nose by extending the therapeutic action of the formulation through the development of a high-viscosity gel (Chaturvedi et al. 2011).

### 19.5.2.4.5 Drug Distribution

A dosage form is essential in the field of application. When opposed to aerosols, nasal drops have a greater spreadability (coverage area) and a longer retention period on the mucosa. Typically, solutions produce dosage uniformity issues (Greimel et al. 2007).

### 19.5.2.4.6 Solubility

In rare cases, intranasal administration of drugs with limited water solubility and/or higher doses might be difficult (Greimel et al. 2007).

### 19.5.2.4.7 Pharmaceutical Form

Higher viscosity formulations may have difficulties in administration. Metered dosage pumps and actuators have recently become accessible, allowing nasal spray systems to provide precise doses ranging from 25 to 200 μL.

## 19.6    Nasal Drug Absorption Methodologies

As previously stated, nasally given drugs have a number of limitations, including low drug solubility, limited membrane penetration quick enzymatic degradation, and rapid MCC. Table 19.2 explains the challenges and possible solutions for bioavailability problems through the intranasal route.

## 19.7    Brain Disorders

### 19.7.1 Epilepsy

Seizures are neurological disorders caused by abnormally high neuronal activity in the brain. This aberrant brain activity can emerge in a variety of ways, ranging from convulsive activity to experiential events that are not easily observable by an

**Table 19.2** Challenges and possible solutions for bioavailability problems through intranasal route

| Problems | Challenges | Possible solution |
|---|---|---|
| Poor physical and chemical characteristics of the drug | Improve the drug's physicochemical characteristics and formulation | Cosolvents addition Use of cyclodextrins Pro-drugs Change pharmaceutical excipients Formulate novel carrier systems |
| The nasal membrane has a low permeability | Increase drug solubility and penetration across the lipid membrane in the bodily fluids | Co solvents Pro-drugs approach |
| | Modify the nasal membrane | Use of absorption enhancers |
| | Extend the length of the drug's stay in the nasal cavity | Mucosal adhesive systems Viscosity modifiers |
| Degradation by enzymes | Reduce the drug affinity to nasal enzymes | Pro-drugs approach |
| | Due to the presence of nasal enzymes, the drug is degraded | Use enzymatic inhibitors Co solvents Pro-drugs approach |

observer, depending on the distribution of discharges. During a seizure, certain brain cells send out aberrant signals that prevent other cells from functioning normally. This anomaly may result in a brief shift in sensation, behavior, movement, or awareness (El-Zaafarany et al. 2018). Drugs used in epilepsy and their clinical status are given in Table 19.3.

## 19.7.2 Parkinson's Disease

Parkinson's disease is characterized by a loss of dopaminergic neurons in the brain's substantia nigra pars compacta. It is classified as a mobility disorder. Cerebral palsy, ataxia, and Tourette syndrome are examples of movement problems. They happen when a shift in the neurological system impairs a person's capacity to move or remain motionless. It affects the neurological system, and the symptoms worsen over time. It occurs when nerve cells in the brain do not create enough dopamine, a brain neurotransmitter. The bulk of unfavorable neuronal loss in Parkinson's disease is caused by complex 1 defects in the respiratory chain. The clinical status of drugs used in PD is given in Table 19.4.

**Table 19.3** Clinical status of drugs used in epilepsy

| S. No | Drug | Intranasal dose | Model | MOA | Outcome |
|---|---|---|---|---|---|
| 1 | Oxcarbazepine (OXC) | 0.5 mg/kg | Rats | Blockage of voltage-sensitive sodium channels | In rats, PLGA NPs had a lower dosage frequency than the free drug and were able to control seizures (Alam et al. 2015) |
| 2 | Lamotrigine | – | – | Binding with sodium channels leads to stabilization of presynaptic neuronal membranes | In comparison to oral administration of drug solution, nano-formulation has a greater concentration and residence period of drug in the brain, resulting in a higher brain concentration (Patel et al. 2016a, b, c) |
| 3 | Carbamazepine (CMP) | 0.18–0.2 mg/kg | Rats | Stabilization of hyper-excited neural membranes due to blockage of voltage-sensitive sodium channels | In comparison to IV CMPME, the IN CMPMME and CMPME/Brain/Blood ratio rose 2–3 fold at all sample sites after IN administration of CMPMME, indicating a higher extent of CMP distribution in the brain (Czapp et al. 2008) |
| 4 | Phenobarbital | 5.4 mg/kg | Rats | Acts on GABA receptors, increasing synaptic inhibition and elevating seizure threshold | IN SLN/2.4-fold rise in $C_{max}$ values in cortical dialysates (Eskandari et al. 2011) |
| 5 | Valproic acid | 20 mg/kg | Rat | Blockage of voltage-gated ion channels and inhibiting histone deacetylase | IN SLN/After intranasal delivery of VPA NLCs, the brain:plasma concentration ratio increased (Eskandari et al. 2011) |

**Table 19.4** Clinical status of drugs used in PD

| S. No | Drug | Intranasal dose | Model | MOA | Outcome |
|---|---|---|---|---|---|
| 1 | Glutathione | 100 mg GSH/mL | Human | Increase dopaminergic transporter activity | Increased glutathione level in CNS and improvement in motor movements (Mischley et al. 2016) |
| 2 | Bromocriptine | 5 μL | Mice | Decreasing the amount of prolactin in the body | Stimulates the nerves that control movement (Md et al. 2014) |
| 3 | Rasagiline | 0.00189/ day | Mice | Covalent binding to the flavin residue of the N5 nitrogen, resulting in irreversible inactivation of the enzyme | Following administration of RAS-loaded CG-NPs, there was a significant increase in bioavailability in the brain (Mittal et al. 2016) |
| 4 | Rotigotine | 50 μL | Rat | It binds with D3 receptor with highest affinity. Inhibit dopamine uptake and prolactin secretion | Non-ergoline agonists of DOPA are found to be very effective for the treatment of PD (Bhattamisra et al. 2020) |
| 5 | Levodopa | 16 mg/kg | Mice | Decarboxylates to doxylamine and stimulates the dopaminergic receptors | An increase in bioavailability, ultimately decreases the unfavorable side effects of levodopa (Arisoy et al. 2020) |

### 19.7.3 Psychosis

Patients suffering from psychosis have a distorted worldview in which they are unable to discern between their personal, subjective experiences, and the reality of the outside world. They have hallucinations or delusions that they feel are real, and they may behave and converse inappropriately and incoherently. Delusions, hallucinations, and disorganized speech are some of the symptoms. The clinical status of drugs used in psychosis is given in Table 19.5.

### 19.7.4 Schizophrenia

Schizophrenia is a diverse condition characterized by disruptions in language, perception, thought, social behavior, emotion, and violation. Symptoms of

**Table 19.5** Clinical status of drugs used in psychosis

| Sr. No | Drug | Intranasal dose | Model | MOA | Outcome |
|---|---|---|---|---|---|
| 1 | Olanzapine (OZP) | 1 mg/kg | Rats | Binding to histamine H-1, alpha-1, dopamine, muscarinic, and 5-HT2 receptors, among others | The brain/blood ratio increased by 5–6 times after OZP was injected into the brain. When compared to intravenous olanzapine microemulsion, it appeared to be greatest for intranasal olanzapine mucoadhesive microemulsion (Patel et al. 2016a, b, c) |
| 2 | Risperidone (RSP) | 35 mg/kg | Rats | Decrease dopaminergic and serotonergic pathway activity in the brain | Risperidone mucoadhesive Nano Emulsion (I.N.) transfers RSP quicker and to a higher extent in the rat brain than Risperidone (I.V.) and Risperidone nanoemulsion (I.N.) and Risperidone nanoemulsion (I.V.) (Kumar et al. 2008) |
| 3 | Haloperidol | 2 mg/kg | Rats | Inhibit the effects of dopamine and increase its turnover | The behavioral effects generated by intranasal administration of 6.7 times lower doses of the dendrimer haloperidol formulation were comparable to those caused by intraperitoneal injection of haloperidol formulations (Katare et al. 2015) |
| 4 | Remoxipride | 4–16 mg/kg | Rats | Weaker binding to $D_2$ dopaminergic receptors that dopamine. This weaker binding is thought to account for the reduced incidence of parkinsonism | Bioavailability increased by 89% following intranasal dosing. When compared to IV delivery, IN resulted in longer brain ECF exposure (Stevens et al. 2011) |

(continued)

**Table 19.5** (continued)

| Sr. No | Drug | Intranasal dose | Model | MOA | Outcome |
|---|---|---|---|---|---|
| 5 | Clozapine | 0.05 mg/ 0.1 mL | Rat | Blockage of serotonin (5-HT$_{2A}$/5HT$_{2C)}$ receptors and dopamine(D1–4) receptors | When compared to oral delivery, there is a 3.56-fold increase in brain/plasma drug concentration and a 5.28-fold lower drug dosage (Ravikrishna and Janapareddi 2019) |

schizophrenia include hallucinations, confused ideas, and emotions of fear and paranoia. Psychiatrists evaluate symptoms, examinations, and medical history before prescribing drugs and psychotherapy. There are no pathogenomic characteristics. Table 19.6 depicts the clinical status of drugs used in schizophrenia.

### 19.7.5 Alzheimer Disease

Alzheimer's disease (AD) is a progressive decline of mental capacities that begins with moderate memory loss and progresses to loss of ability to keep employment, plan and execute normal tasks, reason, and exercise judgment. Skills in communication, emotions, and attitude are all harmed. Alzheimer's disease is the fourth leading cause of death in individuals, behind heart disease, cancer, and stroke. Alzheimer's Association (Alzheimer's Association 2017); Alzheimer's disease causes cognitive changes that follow a regular pattern, starting with memory loss and advancing to language and visuospatial problems. The symptom starts with memory loss, such as forgetfulness, and progresses to more distressing losses. The patient may forget the names of family members or what was stated at the start of a sentence. Table 19.7 explains the clinical status of drugs used in Alzheimer's disease.

### 19.8 Novel Formulation Approaches for Intranasal Drug Delivery

The pharmacological characteristics, delivery mechanism, and nasal physiology should all be researched in order to generate a nasal formulation with acceptable performance and commercial features. It is better to concentrate on extending the stay and ensuring optimal medicine absorption. Table 19.8 summarizes recent research on intranasal drug delivery devices in the treatment of brain diseases.

**Table 19.6** Clinical status of drugs used in schizophrenia

| S. No | Drug | Intranasal dose | Model | MOA | Outcome |
|---|---|---|---|---|---|
| 1 | Haloperidol | 0.89 mg/kg | Rat | Blocks dopamine $D_2$ receptor in brain | Increase conc. of drug in brain, increase in bioavailability (Katare et al. 2017) |
| 2 | Apomorphine hydrochloride | 2 mg/kg | Mice | It is a dopaminergic agonist that stimulates regions of brain involved in motor control | Enhances motor function, suppress prolactin release, cause vasodilatation and behavior effect (Patel et al. 2016a, b, c) |
| 3 | Paliperidone (PALI) | 12 mg/kg | Rats | Antagonist activity at D2 receptor ($\alpha_1$ and $\alpha_2$), adrenergic receptor, and $H_1$ receptor | Increased brain activity approc 6–8 times after IN administration of PALI-Mucoadhesive microemulsion as compared to intravenous PALI-Microemulsion (Scarff and Casey 2011) |
| 4 | Zotepine (ZTP) | 4.4 mg/kg | Rats | Serotonin receptors antagonism and inhibition of noradrenaline reuptake and serotonergic activity | In comparison to intravenous ZTP solution, intranally given Zotepine nano suspension resulted in an 8.6-fold rise in AUC0–24 h and a 10.79-fold increase in AUC0–24 h (Pailla et al. 2019) |
| 5 | Iloperidone | 1 mg/kg | Rat and mice | Antagonism of certain receptors, such as dopamine D2 and serotonin 5-hydroxytryptamine (5HT) receptor 2A | Intranasal administration of iloperidone nanostructured lipid carriers resulted in a 3.05-fold increase in AUC0–$\infty$ when compared to pure drug solution (Mandpe et al. 2013) |

## 19.8.1 Mucoadhesive Solutions

Mucoadhesive solutions, such as chitosan, cellulose polymers, polycarbophil, poloxamers, and other mucoadhesive polymers, have been found to increase

**Table 19.7** Clinical status of drugs used in Alzheimer's disease

| S. No. | Drug | Intranasal dose | Model | MOA | Outcome |
|---|---|---|---|---|---|
| 1 | Insulin | 160 IU | Human or animal | It increases brain insulin receptor sensitivity | Improved cognitive processes in both healthy and impaired humans due to increased brain signaling (Hallschmid et al. 2008) |
| 2 | Deferoxamine | 200 mg / KG | Mice | Shifting APP processing to a nonamyloidogenic route reduced APP protein expression and phosphorylation | Intranasal iron chelation decreased iron-induced amyloidogenic APP processing and corrected behavioral changes (Fine et al. 2015) |
| 3 | Donepezil | 0.5 mg/ mL | Rat | It binds reversibly to ach esterase enzyme and inhibits the hydrolysis of acetylcholine | Facilitate the cholinergic neurotransmission and regulate memory function (Noetzli and Eap 2013) |
| 4 | Rivastigmine | 0.068 mg/ kg | Rat | It promotes cholinergic function by inhibiting both AChE and BChE enzymes in the brain | Increase conc. of Ach in brain which improve cognition and memory function (Fazil et al. 2012) |
| 5 | Galantamine | 3 mg/kg | Rat | Reversibly inhibit AChE and enhance the intrinsic action of acetylcholine and nicotine | Increase cholinergic neurotransmission level in CNS (Hanafy et al. 2016) |

intranasal drug penetration. Gel formulations with the appropriate rheological properties lengthen the time in contact with the mucosa at the absorption site. The polymer in the gel has mucoadhesive properties as well as the formulation's physicochemical characteristics, restricting removal through protective mechanisms in the nose and eyes (Ugwoke et al. 1999; Vidgren et al. 1992). Several studies have stated that mucoadhesive polymers such as cellulose derivatives, polyacrylates, starch, and so on can be used in the formulation of mucoadhesive solutions. (Gavini et al. 2012) and colleagues created a mucoadhesive formulation that demonstrated regulated dopamine release in the brain following intranasal application.

**Table 19.8** Recent investigations on intranasal drug delivery systems used in brain disorders

| Sr. No | Drug | Approach | Recent investigation | Composition | Application | Reference |
|---|---|---|---|---|---|---|
| 1 | Resveratrol + curcumin | Mucoadhesive nanoemulsion | Increased concentration of both the polyphenols when they were encapsulated in mucoadhesive nanoemulsion with antioxidant activity preserved | Hyaluronic acid, Labrafac PG, tween 80 Cremophor RH 40 | Alzheimer | Nasr (2016) |
| 2 | Nimodipine | Mucoadhesive Nanoemulsion | Improved behavioral activities with nanoformulations like nanoemulsion showed high plasma and brain concentrations of nimodipine | Carbopol 934 P, chitosan, Capmul MCM, Labrasol, Transcutol P | Senile dementia | Pathak et al. (2014) |
| 3 | Selegiline | Mucoadhesive Nanoemulsion | Tremendous improvement in behavioral activities of rats when administered intranasal selegeline nanoemulsion as compared to oral administration | Tween 80, Grape seed oil, Sefsol 218 | Parkinson | Fang et al. (2009) |
| 4 | Celecoxib | Liposomes | Celecoxib liposomes when administered intranasally had much high concentration as compared to free drug when determined by fluoroscence analysis | Phospholipid:Cholesterol | Alzheimer | Guo et al. (2017) |
| 5 | Donepezil | Liposomes | Pharmacokinetic parameters like higher $C_{max}$, longer half-life and higher AUC (doubled) was achieved with the liposomal drug as compared to free drug | DSPC:CHOL:PEG | AD | Al Asmari et al. (2016) |
| 6 | Rivastigmine | Liposomes | In a study comparing intranasally delivered solution with liposomes, it was discovered that intranasally administered solution had a greater drug level and a larger plasma AUC | EPC:CHOL Poloxamer 188 | AD | Yang et al. (2013) |

**Table 19.8** (continued)

| Sr. No | Drug | Approach | Recent investigation | Composition | Application | Reference |
|---|---|---|---|---|---|---|
| 7 | Lurasidone-HCl | Polymeric micelles | When compared to pure drug, in vivo (single dose) pharmacokinetic investigations following intranasal delivery revealed a significant concentration of drug in the brain | Gelucire 44/14 (GL44), Pluronic F127 (PF127) Carbapol-940 | Bipolar disorder | Pokharkar et al. (2020) |
| 8 | Zolmitriptan | Micelles | In vivo biodistribution tests of zolmitriptan showed that it was far superior than the drug's intravenous and nasal formulations when it came to brain targeting | TCP and BA. PF127, PEG-400 TvPGS | Migraine | Jain et al. (2010) |
| 9 | Insulin | Nanogel | With regard to free insulin administration, an increase in NG-in distribution to different brain locations and biological activity, as evaluated by Akt activation levels, was shown | PVP K60 and acrylic acid (AA), dimethyl sulfoxide (DMSO), carbodimide hydrochloride (EDC), N-hydroxysulfosuccinimide sodium salt (Sulfo-NHS), Acido 2-(N-morpholino) ethanesulfonic acid hydrate | Alzheimer | Picone et al. (2018) |
| 10 | Clonazepam | Microspheres | The clonazepam microspheres had a greater brain concentration and a high drug targeting index, indicating that they have a lot of promise as a brain-targeted drug delivery method | Sodium lauryl sulfate, paraffin oil, glutaraldehyde-saturated toluene, chitosan PEG 400 | Seizures | Shaji et al. (2009) |
| 11 | Methotrexate (MTX) | Microspheres | MTX-loaded chitosan microspheres exhibited good swelling index, showed controlled release pattern and minor irritation to cilia. Relative bioavailability increased to 118% | Chitosan | Brain cancer | Sun et al. (2012) |

| | | | | | |
|---|---|---|---|---|---|
| 12 | Haloperidol | Dendrimers | A 6.7 times reduction in the dose of dedrimer base haloperidol formulation when administered intranasally gave same behavioral response when compared with the other haloperidol formulations given intraperitoneally | PAMAM dendrimer 1,4diaminobutane core, amine ended, gen 5.0, tween 20, ethanol, and ammonium acetate, PAMAM dendrimer 1,4 diaminobutane core, amine terminated | Anti-psychotic | Katare et al. (2015) |
| 13 | $^{32}$P-labeled siRNA | Dendriplexes | Increased radioactivity was observed with in the olfactory bulb when $^{32}$PSiRNa was complexed with dendrimers and incorporated in the gel | Poly(amidoamine)G7, dendrimers, lipofectamine™ 2000 | | Perez et al. (2012) |
| 14 | Huperzine A | PLGA nanoparticles | The distribution of HUPA in the brain was improved after intranasal administration of PLGA nanoparticles, and the drug targeting index in the mouse was measured at various intervals | PLGA  50:50  2A,Chitosan Lf, 2-iminothiolan bicinchoninic acid | Alzheimer | Meng et al. (2018) |
| 15 | Oxcarbazepine | PLGA nanoparticles | Immunohistochemical investigations demonstrated that OXC PLGA NPs had a neuroprotective effect after 16 days of treatment, demonstrating the viability of developing a novel non-invasive nose-to-brain delivery technique | Methanol, acetonitrile, ethyl acetate, polymer Resomer® 502 H poly-OXC, tween® 80, 7-n-propylxanthine (7n-PX), and bovine serum albumin (BSA) | Epilepsy | Musumeci et al. (2018) |

## 19.8.2 Microspheres

Microspheres are tiny spherical particles that range in size from 1 to 1000 mm in diameter. Microspheres are also called microparticles in some situations. Microspheres may be made from a variety of polymeric materials, both natural/synthetic, as well as inorganic materials.

Microspheres, particularly mucoadhesive microspheres, are a prominent type of novel drug delivery technology. Microspheres may stay in touch with the nasal mucosa for extended periods, resulting in increased drug absorption rate and volume (Ugwoke et al. 2005). Microspheres for nasal applications are typically made from biocompatible materials such as starch, albumin, hyaluronic acid, chitosan, and gelatin, as well as HPMC, Carbopol 934P, dextran, and other polymer combinations (Patil and Sawant 2011; Takeuchi et al. 2003).

A team of researchers created a comparison report between Methotrexate (MTX) solution and MTX-chitosan loaded microspheres, which revealed that MTX-loaded chitosan microspheres exhibited rapid and controlled drug release after intranasal administration compared to MTX solution due to their ability to transport more drug to the brain. Furthermore, chitosan employed as a mucoadhesive polymer was found to be safe and aid in medication mucoadhesion in the olfactory area, resulting in enhanced drug bioavailability (Sun et al. 2012).

## 19.8.3 Liposomes

Liposomes are spherical vesicles that have a hydrophilic core within and an impenetrable lipophilic phospholipid bilayer on the outside, similar to cells. They may entrap drugs in both aqueous and lipid phases due to their unique structure. Lipophilic drugs are nearly completely enclosed in the lipid bilayers of liposomes, and because they are not water-soluble, problems like drug loss during storage are rare. Hydrophilic drugs can be located in the watery cores of liposomes or the surrounding water phase.

Liposome nasal clearance half-life was four times longer than usual human nasal clearance half-life, showing liposomal systems' mucoadhesion capabilities and nasal application potential (Jaafari et al. 2010; Andresen et al. 2005). Furthermore, liposomes have the benefit of being able to be changed to efficiently target a specific region of interest, such as the BBB. As a result, targeted liposomes have mostly been explored for the detection and therapy of brain illnesses (Mourtas et al. 2011).

Liposome research has yielded encouraging findings in drug delivery via the nasal transport system. Seok Hong and colleagues explored how surface modification of liposomes with targeting moieties, PEGylation methods, and the integration of various carrier systems with liposomes can boost drug bioavailability.

### 19.8.4 Nanoparticles

The drug substance is either encapsulated inside the matrix or conjugated or adsorbs to the particle surface in nanoparticles. To enable delayed, regulated drug therapy, nanoparticles are frequently comprised of polymers, lipids, or a mix of the two.

### 19.8.5 Exosomes

#### 19.8.5.1 Natural Bioactivities of Exosomes

Exosomes are membrane nanovesicles that develop spontaneously and have a diameter of 50–150 nm (Simons and Raposo 2009). They came from the endosomes of immune cells such as dendritic cells (Théry et al. 2006), macrophages (Bhatnagar et al. 2007), B-cells (Clayton et al. 2005), and T-cells (Nolte'Hoen et al. 2009), as well as mesenchymal stem cells, cancer cells, and endothelial cells.

### 19.8.6 Nanoemulsions

Nanoemulsions (NEs) are surfactant-stabilized oil-in-water (O/W) or water-in-oil (W/O) colloidal carriers of two immiscible liquids with a mean droplet diameter of around 100 nm, but maximum size limitations of up to 300 nm have been recorded in the literature. Because the droplet size is much smaller than the wavelength of visible light, NEs seem translucent or milky-white (Rodrigues et al. 2005).

NEs can be made into a number of dosage forms, such as liquids (Sarker 2005), creams, gels, foams, sprays, and so on, and can be taken orally, parenterally, ocularly, or nasally. Much study has been done on nanoemulsions that target the brain via the nasal route.

### 19.8.7 Polymeric Micelles

Polymeric micelles are nano-shell structures generated by the co-polymerization of hydrophobic and hydrophilic block copolymers. These micelles have the ability to operate and change their shape for medication delivery (Wang et al. 2012). The medication, which is present inside the brain and targets the hydrophobic core, is stabilized from the external aqueous environment by the hydrophilic shell, which increases polymer water solubility. Karami et al. (2019) investigated magnetic brain targeting of naproxen-loaded polymeric micelles in recent work. The findings indicated that polymeric magnetic micelles with diameters less than 150 nm might be a suitable carrier for improving therapeutic drug accumulation in the brain for the treatment of CNS illnesses.

### 19.8.8 Nanogels

Nanogels are nano-sized polymeric systems having cross-linked swellable polymeric hydrophilic chains that can withstand significant amounts of water when immersed in an aqueous media without dissolving. They have several qualities, including the capacity to be ready physically or chemically manipulated, good swelling properties, high encapsulation efficiency, high permeability, stability, and so forth.

This polymeric system has received extensive investigation, highlighting its critical role in brain targeting. Because of their site-specificity, nanogels offer a wide range of applications in the treatment of cancers and neurological illnesses. Various studies show that nanogels may be used to deliver oligonucleotides, tiny therapies, proteins, as contrast agents, optical imaging, multimodal imaging, and diagnostic agents, among other things (Cherry 2006).

The effectiveness of cCHP-based nanoemulsion as a universal protein-based antigen-delivery vehicle for adjuvant-free intranasal vaccination has been demonstrated (Nochi et al. 2010). These nanogels are made by self-assembly in water and trap a variety of proteins via hydrophobic interactions, displaying chaperone-like activity due to protein hydration without aggregation. They may then be gradually released back to their original condition (Desale et al. 2013).

### 19.8.9 Dendrimers

Dendrimers are a new type of polymer with well-defined structures created by the sequential addition of layers to the branching groups around the core molecule. This results in structural regularity and minimal heterogeneity, making them an appealing candidate for next-generation nanomedicines (Harush-Frenkel et al. 2008). Their unusual design boosts their utility as radioligands, detecting agents, and targeting components, among other things. Recent improvements demonstrate their great utility in gene transfer, diagnostic agents, contrast agents, photodynamic treatment, and other fields. (Zaman et al. 2011) created a polyacrylate dendritic polymer-based completely synthesized peptide sub-unit vaccination candidate.

### 19.8.10 Niosomes

Niosomes are intriguing new nanocarriers in which the medication is encapsulated in multi-lamellar structures generated by the self-association of nonionic surfactants. Niosomes are biocompatible, biodegradable, non-immunogenic, non-toxic, and non-carcinogenic, among other properties (Mahale et al. 2012; Seleci et al. 2016). The capacity of a nonionic surfactant to generate bilayer vesicles is determined by the surfactant's HLB value. The functioning of niosomes is similar to that of liposomes in that they improve medication bioavailability by decreasing clearance.

## 19.9   Conclusion

Intranasal medicine delivery systems have several advantages over typical oral dosage methods. Several intranasal medicine delivery systems have been created, allowing medications to be administered directly to the brain through the nasal mucosa. Recent trends and clinical research suggest that novel carrier systems with improved bioavailability, efficiency, and fewer side effects should be used. The properties of the drug candidate, the nose-to-brain transport pathway, and transit to and within the brain must all be better understood.

**Conflicts of Interest**   None of the authors have any conflict of interest.

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