Advances in Neurotherapeutic Delivery Technologies

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Chapter: Nose-to-Brain Neurotherapeutic Interventions
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Nose-to-Brain Neurotherapeutic Interventions

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Abstract

The delivery of drugs to the brain has been fraught with low bioavailability of drugs in the brain. This is caused by the Blood Brain Barrier (BBB) and the Blood Cerebrospinal Fluid Barrier (BCSFB) which block therapeutics from gaining access to the Central Nervous System (CNS). Drugs that are administered via oral and intravenous are faced with this challenge of BBB thereby making the treatment of neurodegenerative diseases difficult to manage. Delivery of drugs via the nasal route directly to the brain utilizing the olfactory pathway is purportedly known to be more efficient and deliver neurotherapeutics to the brain by circumventing the BBB and thereby increasing bioavailability of drugs in the brain. This chapter explores the nose-to-brain neurotherapeutic interventions by focusing on recent development in nasal drug delivery systems, evidence of direct drug delivery from nose-to-brain, challenges facing intranasal drug delivery, various specialized nasal drug delivery devices and various intranasal delivery approaches that have been employed in circumventing the BBB in order to effectively deliver neurotherapeutic agents to the brain with increase bioavailability. The olfactory pathway as an opportunity for CNS drug delivery and mechanism of direct delivery of therapeutic agents to CNS was discussed. Future advancement was also enumerated in this chapter.

Keywords: Bioavailability; Blood Brain Barrier; Central Nervous System; Intranasal Delivery; Neurotherapeutic; Olfactory Pathway.

Introduction

Delivery of drugs to the brain has been fraught with issues of low bioavailability [1]. The Central Nervous System (CNS) which is made up of the brain and the spinal cord do not have adequate access to the blood compartment due to a Blood Brain Barrier (BBB) and other barriers. CNS disorders have been recorded as the number one source of disability
and account for more extended care and hospitalizations than the combination of most other diseases [2]. For instance, over 36 million people in the world today have CNS related diseases and disorders, the numbers will continue to rise to about 66 million by 2030, and projected to be around 115 million by 2050 [3]. Treating CNS disorders and ailments in general which include Alzheimer’s disease, Parkinson’s, Schizophrenia, Stroke, Epilepsy, AIDS dementia Complex, Brain tumor and Huntington disease is extremely challenging due to the presence of various obstacles that restrict passage of drug across the BBB for onward delivery to the brain [4]. The BBB which is both physiologically and anatomically a biological natural occurrence with no single scientific theory to explain all the events happening therein [5] according to Roth and Barlow five decades ago, the challenges are still on even as of today.

Researchers are therefore searching for the best methods to develop drug delivery systems and techniques to transfer pharmaceutical substances to the brain and CNS for the management of neurodegenerative disorders and delivery of drugs to the brain and the CNS in general having in mind the BBB obstacle. Lipophilic substances with molecular weight less than 600Da are known to permeate the BBB, which implies that the more lipophilic the drug molecules the better the permeability of the drug, the use of prodrug will be an excellent approach in increasing the permeability, the prodrug on getting to the brain will be converted to the parent drug [6]. Several attempts and strategies such as disturbing the BBB [7], carrier mediated drug delivery osmotic BBB disruptions [8], biochemical BBB disruption [9], drug manipulations including prodrugs, receptor-mediated drug delivery, chemical drug delivery, vector-mediated drug delivery [10], alternative routes such as intraventricular and intrathecal route, olfactory pathway, other techniques include injections, catheters, and pumps technique, implant of device directly to the brain, biodegradable polymer wafers, microspheres and nanoparticles techniques, have been explored [2]. The use of intranasal route has been explored by various researchers and has been established to be a promising route of transferring therapeutic substances directly to the brain by employing the olfactory pathway through the nasal mucosa in order to bypass the BBB and its associated problems.

**Biological Barriers as an Impediment to CNS Drug Delivery**

There are biological barriers limiting the delivery of drugs to the CNS thereby contributing to the difficulties in treating CNS diseases and disorder. Due to these biological barriers, transcranial drug delivery has been used to overcome these barriers. This approach entails three types of delivery systems which are intra-cerebroventricular injection, convection enhanced diffusion and intracerebral implantation. These methods however require an invasive approach through into the brain. Implantation of transcranial catheters has been confirmed to be connected to numerous complications and is known to be temporary [11]. These barriers are enumerated below.

**Blood brain barrier**

Knowledge about the BBB might assist researchers in designing better drugs or approaches in fabricating systems for delivering therapeutic agents to the brain. The BBB is a special membranous barrier that distinguishes the CNS from the systemic circulation [2,12,13]. The BBB is naturally designed to protect the brain from foreign organisms and deleterious chemicals in the blood, but allows the supply of necessary nutrients to the brain for the well being of the brain to maintain and regulate the microenvironment for accurate neuronal signaling [14] and other functions. The protection of the Brain and the CNS is sorted by the barrier function of the brain capillary endothelial and the choroid epithelial cells. The blood capillaries of the brain are anatomically different from that of other tissues and organs. The blood capillaries consist of special cells known as endothelial cells;
these cells are sealed with tight junctions with their membrane separating the systemic circulation and the central extracellular fluid of the brain. The vasculature serving the CNS also has capillaries with tight junctions. The arachnoid membrane which is a doubled layered structure covers the brain and constitutes a barrier between the blood and the CSF [15-19]. Therefore BBB is primarily a prominent obstruction in drug delivery to the brain.

**Blood cerebrospinal fluid barrier**

The Blood Cerebrospinal Fluid Barrier (BCSFB) [20] is another barrier that exists, it inhibits the passage of drugs to the CNS during systemic administration [21,22]. BCSFB resides in the epithelium of the choroids plexus [23], the arrangement of which does not permit the movement of therapeutic molecules into the CSF. The choroid plexus and the arachnoid membranes play a major role at the barriers between the blood and CSF [2,21]. It is clear that the endothelium of the cerebral blood vessels and the epithelium of the choroid plexus prevent the penetration of large solutes directly into the brain and CSF.

**Blood tumor barrier**

Blood Tumor Barrier (BTB) is a barrier formation at the local site of the tumor cells that do not permits drugs from reaching brain tumors in therapeutic quantity to exterminate the tumor cells. A range of barriers that are physiologically oriented are found in solid tumors and they prevent drug delivery via the cardiovascular system. Solid tumor consists of neoplastic cells, drug delivery to these cells is hindered because uneven distribution of microvasculature throughout the tumor interstitial resulting into drug delivery inconsistency [2]. Apart from dealing with the BBB, there is also the problem of BTB. Many innovative methods have been used to improve drug delivery to the tumor cells, of which has been reviewed by Groothuis [24].

**Nasal Anatomy as an Aid to CNS Drug Delivery**

It is pertinent to understand the anatomy of the nasal cavity when discussing the intranasal administration, absorption and transporting of drugs to the brain and CNS. Figure 1 shows the anatomy of the nasal cavity. The nasal cavity is located within the skull, it spans from the base of the skull to the roof of the mouth. It is a midline structure that is divided into two equal halves by the nasal septum. Each half which consists of the roof and the floor as well as medial and lateral walls (formed by the bone and cartilage skeleton of the skull) begins from the nostril at the anterior part and ends up at the nasopharynx at the posterior part where the two airways confluence [25]. The nasal cavity roof consists of frontal and nasal bones anteriorly; in the middle is the cribriform plate of ethmoid bone, ala of the vomer and the sphenoidal process of the palatine bone posteriorly [26]. The floor is composed of the bones of the hard palate which are the palatine process of maxilla anteriorly and horizontal plate of palatine bone posteriorly. The middle wall is made up of the nasal septum which passes from the roof to the floor of the nasal cavity [27]. The nasal cavity consists of paranasal sinuses which are frontal sinuses, ethmoid sinuses, maxilla sinuses and sphenoid sinuses; they are air-filled spaces surrounding the nasal cavity and are lined with mucosa membrane with small openings into the nasal cavity [28]. The nomenclatures and locations of these sinuses are derived from the bones in which they lie, which are the frontal, ethmoid, maxilla and sphenoid respectively. Both the frontal and maxilla sinuses open into the nasal cavity through the semilunar hiatus [29–31], sphenoid sinuses open into the sphen ethmoid recess [32] and ethmoid sinuses which consist of the anterior, middle and posterior parts open into the nasal cavity by the infundibulum, ethmoidal bulla and the superior meatus respectively [28,33]. The nasal cavity communicates through the lateral nasal wall with the maxillary and frontal sinuses and more posteriorly with the sphenoid
sinuses. The septum provides support for the nasal structures and regulates nasal passage while the middle concha warms up and humidifies the inspired air [34].

The nasal cavity which has a total volume and surface area of approximately 20ml and 150cm² respectively [35] is split into three areas which are

1. The vestibular section which is the most anterior part of the nasal cavity and surrounded by the nose cartilages with epithelium lining same as that of the skin, the anterior area is between 10-20cm².

2. The respiratory section with area of approximately 130cm², is the main part of the nasal cavity, this is the part where the absorption of therapeutic compounds into the systemic circulation takes place. The respiratory section is made up of the respiratory epithelium which consists of ciliated and non-ciliated columnar cells, mucous secreting goblet cells and the basal cells. Many of the epithelial cells are covered on their apical surface with microvilli. The ciliated cells protrude out of the surface with few micrometers and can make synchronized movement that can push the mucus layer on the surface of the respiratory epithelium towards the nasopharynx, this is a useful action that is responsible for the mucociliary clearance mechanisms which eliminate foreign and undesired substances from the nasal mucosa into the GIT via the nasopharynx.

3. The olfactory section which occupies 10-20cm² in the roof of the nasal cavity [25].

Intranasal drug delivery has fascinated the interest of researchers based on the fact that the nasal mucosa has been established to be a substitute route of delivering high molecular weight therapeutic substances including protein and peptides that are liable to either acidic or enzymatic degradation as well as first pass hepatic metabolism when administered orally. It has also been explored as a promising route for the administration of vaccines [37], and a viable route for the delivery of biopharmaceuticals [38]. The initial use of nasal delivery was largely confined to topical applications, example of such applications include nasal steroids for treatment of nasal allergies, also phenylephrine and oxymetazoline for the treatment of nasal decongestion. These drugs operate locally at the site of administration and does not require passing through the systemic pathway [39]. Intranasal route provides
a non-invasive and alternative method of delivering therapeutic compounds with ease of administration of those drugs that are restricted by the BBB to the brain and CNS than the systemic administration which is associated with various side effects [40]. The nose-to-brain drug delivery is possible because of the position of the trigeminal as well as the olfactory nerves which connect the brain to the nasal cavity. Drugs can be transported directly from the nasal mucosa to the brain through the olfactory region which is strategically located in between the nasal mucosa and the CNS region allowing drugs to bypass the BBB and BCSFB. The penetration of drugs to the brain however depends on several factors such as properties of nasal formulations, types of nasal device, dosing, drug amount and deposition, mechanism of transport, mucociliary clearance and other local site barriers.

There are several advantages of intranasal drug delivery over the systemic delivery of drugs. Table 1 shows the advantages and the limitation of intranasal drug administration. It is obvious that the advantages outweigh the limitations thereby making intranasal administration of drugs a better method of drug administration especially to the brain and CNS than the oral, intravenous, transdermal administration and of course implantations. The delivery systems and devices are considerable factors in intranasal drug delivery because of the physiology and structure of the nose.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The surface area of the nasal mucosa is large for dose administration [2]</td>
<td>Amount of administered drugs is limited to 25-200μl. [41]</td>
</tr>
<tr>
<td>2. Rapid absorption of drug is possible due to rich blood capillaries and vessels in the nasal mucosa [42,43]</td>
<td>Adversely affected by pathological conditions [2,44]</td>
</tr>
<tr>
<td>3. Possibility of Rapid onset action of delivery [19,45]</td>
<td>Drug permeability may be affected due to the ciliary movement [42]</td>
</tr>
<tr>
<td>4. Ease of administration, noninvasive [42,46]</td>
<td>Drug permeability is limited due to enzymatic inhibition [47]</td>
</tr>
<tr>
<td>5. Bypasses BBB [37]</td>
<td>Drug with nasal irritation may not be acceptable through this route [44]</td>
</tr>
<tr>
<td>6. Evade the gastrointestinal tract and first pass metabolism [19,43]</td>
<td></td>
</tr>
<tr>
<td>7. Improved bioavailability [19,48]</td>
<td></td>
</tr>
<tr>
<td>8. Possibility of direct absorption into systemic circulation and CNS [47]</td>
<td></td>
</tr>
<tr>
<td>9. Lower dose amount to reduction of side effects [19,44]</td>
<td></td>
</tr>
<tr>
<td>10. Improved convenience and compliance</td>
<td></td>
</tr>
<tr>
<td>11. Self administration of drugs [44]</td>
<td></td>
</tr>
<tr>
<td>12. It avoids the use of sterile procedure [44]</td>
<td></td>
</tr>
</tbody>
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Table 1: Advantages and Limitation of Intranasal Drug Administration.

The olfactory pathway as an opportunity for CNS drug delivery

The Olfactory region is located at the roof of the nasal cavity just below the cribiform plate of the ethmoid bone and crosses a bit down the septum and lateral wall. Its position is strategic as one end interacts with the nasal cavity and the other end with the CSF. It is therefore the only area of the CNS that has external link to the outside surroundings. Olfactory neurons directly penetrate through the cribiform plate into the olfactory epithelium of the nasal cavity [49]. The olfactory epithelium is formed by the olfactory receptor neurons which are arranged at intervals among the other sustaining cells and the basal cells. The olfactory system is responsible for perceiving smell. Variety and numerous odorant molecules can be perceived by mammals and humans through their sense of smell which is mediated by the olfactory system.

The olfactory system has the ability to detect different kinds of odors by applying
information theory measurements to olfactory bulb activity images [50]. Humans can sense approximately between 10,000 to 100,000 substances as having a distinct odor [51]. The olfactory bulb is a structure found at the bottom of the brains of human and it is being protected and cradled by the cribiform plate which also separates it from the nasal cavity. It is the site that processes information about odors, which is the principal purpose of the olfactory [52]. Figure 2 shows the schematic illustrations of the various types of cell in the olfactory region. Receptor cells which are the neurones are situated among columnar sustentacular cells. The axons of the receptor cells emerge from the epithelium in bundles enclosed by ensheathing glial cells. Spherical globose basal cells and flattened horizontal basal cells lie on the basal lamina. The Bowman’s gland opens on to the surface via their intraepithelial ducts. At the surface are cilia of the receptor cells and microvilli of the supporting cells.

![Illustrations of the various types of cells in the olfactory region](image)

**Figure 2:** Illustrations of the various types of cells in the olfactory region [53].

**Proposed pathways of therapeutic agents introduced into the nasal cavity**

When therapeutic compound is intranasally administered, it is liable to follow different routes as depicted in Figure 3. The drug may find its way into the systemic pathway via the blood vessels and capillaries in the nasal mucosal. The probability of the drug going into the blood is very high considering the fact that the nasal cavity is very rich in blood supply. This is one of the reasons intranasal administrations of drugs is preferred for the drugs that have a high risk of being significantly degraded in the gastrointestinal tract or those that are highly metabolized through the first pass effect of the liver. An example of this is highlighted in the oral administration of Olanzapine [54] where 40 percent of the drug was metabolized in GIT and liver prior to reaching the systemic circulation. The drug may also find its way into the olfactory system and ultimately reach the CNS. The trigeminal pathway is another route the drug may possibly follow when it is in the nasal cavity. The trigeminal nerve which controls the facial sensation has been established to transport drugs to CNS and brain in particular. In the nasal cavity, the drugs that could not make it to the blood, olfactory and the trigeminal pathway may be degraded through the action of the enzymes in the nasal cavity or be eliminated via mucociliary clearance [55]. Drugs that find their way into the systemic circulation may be delivered to the body tissues and organs or be eliminated from the blood by normal clearance mechanism. Drugs may also be distributed from the CNS to brain or migrate from the brain to the CNS. Drugs in the CNS and brain may also be eliminated by clearance into the blood.
Mechanism of direct nasal mucosa to brain delivery via the olfactory pathway

The mechanism of direct nasal mucosa to brain drug delivery has not been firmly established but it has been evidenced by the work of various researchers that intranasal delivery of therapeutic agents is delivered to the brain along the olfactory and trigeminal pathway. For example, Renner et al., [59] intranasally administered fluorescently labeled insulin into mice; the insulin migrated deep into the anterior area of the olfactory region moving across from the nasal mucosa epithelium to the cribiform plate to gain access to the olfactory bulb. Higher quantities of insulin were found in the olfactory nerve layer up to the glomerular layer. Similarly, insulin labeled with nanogold was delivered intranasally to mice, insulin was also found in the olfactory nerve layer of the mice and intracellular nanogold was detected in the nucleus of the cells of the olfactory bulb [59]. Various researchers have demonstrated that molecules can be transported from the nasal mucosa by widely dispersing these molecules throughout the olfactory region, carrying them across to the olfactory bulb and subsequently reaching the brain.

Dhuria et al., [60] described the mechanism involved in the transporting drug molecules to the brain and CNS. They reported that drugs interact with the nasal mucosa comprising nasal epithelium and the drug molecules are distributed by both olfactory and trigeminal nerves where the nerve endings send chemo-sensory information to the brain. Drugs may be transported to the brain through perivascular spaces which is located in the lamina propria or through intracellular and extracellular pathways. On reaching the lamina propria, drugs may pass into the openings formed by ensheathing cells neighboring the olfactory nerves, and then penetrate the olfactory bulb including the CSF. From the CSF, drugs can diffuse and blend with interstitial fluid of the brain via bulk flow mechanisms. Drugs that pass through the perivascular channels may also exit through the same channels; this is an important process by which substances get eliminated from the CNS to the external environment. The mechanism may also involve the passage of the drug into the primary neurons found in the olfactory epithelium and then penetrate to the olfactory bulb via intracellular axonal

![Diagram](image-url)
transport. Axonal transport occurs when the drugs penetrate the neurons by endocytosis for onward movement to the CNS following circulation of the therapeutic into CNS [57].

**Evidence of Nose-to-Brain Drug Delivery**

Nose-to-brain delivery of drugs and neurologic substances such as insulin and other growth factors along the olfactory neural pathway to treat neurological disorders was first proposed and patented in 1989 by W. H Frey II [61]. Intranasal administration of drugs is a harmless and suitable route for delivering drugs to the brain and CNS generally for the treatment of neurodegenerative ailments, for the special reason of the existence of the BBB which does not allow the passage of most therapeutic agents to the brain and CNS. Lipophilic compounds penetrate quickly and effectively passing through the nasal membranes into the systemic circulation which shows the same pharmacokinetic behavior to that of intravenous injection in terms of absorption with bioavailability of drugs up to a 100%. Because of this quick action, lipophilic compounds seldom pass through the olfactory pathway in the nasal cavity. However hydrophilic compounds and larger compounds have serious difficulty in passing across the nasal membrane into the blood circulation for systemic delivery, even if they do cross, they are still faced with the issue of BBB for brain delivery. It has been established that the bioavailability of less lipophilic molecules and large molecules is about 1-10% [57]. The olfactory pathway is therefore an inevitable route for the delivery of these compounds to the brain and CNS via the nasal cavity. Several therapeutic agents have been successfully delivered to the CNS using the intranasal route of administration.

**Delivery of RNA, enzymes, insulin and protein**

Enzymes, proteins and insulin have been successfully delivered to the brain through the nasal mucosa. Trigeminal nerve has been known to also contribute to the movement of drugs to the brain. Renner et al., [61] examined delivery of fluorescently labeled small interfering Ribonucleic Acid (siRNA) from the nasal mucosa to the olfactory bulbs via the olfactory pathway. Their results showed that after thirty minutes of intranasal administration, fluorescently labeled siRNA was detected in the olfactory epithelia, lamina propria as well as the olfactory bulbs along the olfactory pathway and was dispersed throughout the olfactory region as depicted in Figure 4.

Recently, α-l-Iduronidase (IDUA) action was detected widely in the brains of IDUA-deficient mice after concentrated laronidase administration via the nasal mucosa and it was also detected after intranasal treatment with an Adeno-Associated Virus (AAV) vector expressing human IDUA. This was demonstrated by Wolf et al., in the course of providing the first evidence of lysosomal enzyme passing the BBB when administered via the nasal route [62]. Brain-derived neurotrophic factor, ciliary neurotrophic factor and neurotrophin-4/5 can promote neuronal survival in event of injury to the CNS. Delivery of these substances is difficult because of their large molecular weights which prevent them from crossing the BBB. These proteins have been successfully delivered intra-nasally and high concentrations of the proteins were detected in the brain 25 minutes after nasal administration [63]. Delivery of insulin employing the olfactory nerve pathway was carried out by Renner et al., the aim of their study was to deliver insulin directly to the olfactory bulbs through the olfactory nerve pathway employing the intranasal route of administration [61].
Delivery of drug-loaded nanoparticles

Liu et al., [3] modified poly(ethyleneglycol)-poly (ɛ-caprolactone) nanoparticles by conjugating the nanoparticles with Lactoferrin to obtain Lactoferrin-conjugated PEG-PCL nanoparticle (Lf-NP) using a maleimide-thiol reaction for delivering of neuroprotective drugs to treat Alzheimer’s Disease (AD) employing intranasal route for direct nasal mucosa to CNS delivery. In their experiment, the Lf-NP was labeled with Cy5.5 a fluorescein probe for real time imaging and biodistribution in mice. Three hours after intranasal administration, they observed a very strong fluorescent signal of Cy5.5-labeled Lf-NP in the brain of the mice as shown in Figure 5. They used NAP (NAPVSIPQ), an 8-amino acid neuropeptide fragment as model drug. The outcome when their system was evaluated in AD mice intranasally showed an enhancement delivery of the neuroprotective drug in the brain.

Chitosan nanoparticles have demonstrated the potential for enhancing the brain uptake of venlafaxine hydrochloride a drug for the management of depression via nasal route. Venlafaxine side effects such as increased blood pressure, tiredness, pain, tachyarrhythmia, dizziness, sexual dysfunction observed when administered via oral or intravenous make its intranasal delivery to brain and CNS a promising and preferred method [64].

Rivastigmine [65] and thymoquinone [66] loaded Chitosan nanoparticles have been produced by ionic gelation method to increase the uptake of drug to the brain and to
enhance the bioavailability of the drug in CNS following administration through the nasal route. Shadab et al., [67] investigated the potential use of Chitosan nanoparticles for the purpose of delivering therapeutic agents to the brain intranasally. This was achieved by preparing Bromocriptine (BRC) loaded Chitosan nanoparticles using ionic gelation of Chitosan with tripolyphosphate anions with mean size of 161nm. Figure 6 shows the SEM image of the nanoparticle revealing the morphology of the optimized BRC loaded nanoparticles. Optimized technetium labeled BRC was employed in investigating the biodistribution of the BRC in the brain and blood of the mice after intranasal and intravenous administration. At 30 minutes following administration, the brain/blood ratio of BRC loaded chitosan nanoparticles administered intranasally was found to be higher than that of intravenous administration. These results indicated a direct nasal mucosa to brain transport bypassing the BBB. Al-Ghananeem et al., [68] have used Chitosan nanoparticles to delivered didanosine an HIV reverse transcriptase inhibitor to the brain via the nasal mucosa. The didanosine-loaded Chitosan nanoparticles were made by ionotropic gelation of Chitosan with tripolyphosphonate anions. They compared the intranasal delivery to intravenous delivery. Their findings highlighted that the concentration of therapeutics in the olfactory bulb, CSF and brain were considerably higher after intranasal administration than those after intravenous administration of didanosine aqueous solution.

Thermo-sensitive gels with lorazepam microspheres using Chitosan and pluronics were prepared and characterized for nasal delivery to the brain by Jose et al., [69]. In vitro drug release and permeation studies of their investigation showed that the gel formulation is capable of sustaining a 24 hour drug release. This may provide controlled release advantage and improved bioavailability for nasal drug delivery.

Nose-to-brain delivery system in combination with Cell-Penetrating Peptide (CPP) modified nano-micelles comprising Polyethylene Glycol–Polycaprolactone (PEG–PCL) copolymers conjugated with the CPP, Tat (MPEG–PCL–Tat) [70] has been synthesized to deliver siNRA to the brain following intranasal administration. Alexa-dextran (anionic dextran labeled with Alexa Fluor 568) as a model siRNA was complexed with Tat to obtain MPEG–PCL–Tat/Alexa-dextran nano complex. Sprague–Dawley male rats were employed for in vivo study, 100µL was administered intravenously and 80µL intranasally to the rats, the results of intranasal administration were compared with intravenous administration as depicted in Figure 7 revealed the presence of Alexa-dextran in those rats that were dosed intranasally and none
in those that were dosed intravenously. The results confirm intervention of nose-to-brain of therapeutic agents to the brain for managing neurogenerative diseases.

**Figure 7:** Dynamics of MPEG–PCL–Tat complex in brain tissue following intranasal and intravenous administration [70].

**Microemulsion formulations**

Thakkar et al., [71] prepared and characterized mirtazapine microemulsion for intranasal delivery, to determine its brain drug delivery using pharmacokinetic studies to assess its performance pharmacodynamically for the antidepressant activity. Their investigation demonstrated a rapid movement and higher concentration of mirtazapine into the brain with intranasal administration compared to oral administration, which may be helpful for the treatment of depression. Acharya et al., [72] prepared and evaluated intranasal oil in water microemulsion of carbamazepine to improve its solubility and enhance its brain uptake. Intranasal microemulsion of carbamazepine was prepared by water titration method using oleic acid as oil, Tween 80 as surfactant and Transcutol® as co-surfactant. Their experiment resulted in higher brain/plasma ratio with nasal microemulsion in comparison to ratio obtained after intraperitoneal injection of carbamazepine solution. Porecha et al., [73] prepared and characterized microemulsions/mucoadhesive microemulsions of Diazepam, Lorazepam and Alprazolam, evaluated their pharmacodynamic behavior by carrying out comparative sleep induction studies in male albino rats to appraise their role in effectual management of insomnia patients, intranasal administration of these drugs was compared with oral administration, They observed faster onset sleep after intranasal administration compared to oral. The result of their investigation also showed that the mucoadhesive microemulsions of the formulation following intranasal administration indicated rapid and higher drug transport to the rat brain and thereby induced quick sleep and prolonged sleep.

Kumar et al., [74] have prepared nanoemulsions which contain risperidone to achieve brain uptake of drug through the nasal mucosa; they compared a risperidone nanoemulsion and risperidone mucoadhesive nanoemulsion via intranasal and intravenous administration. Their results showed that intranasally administered mucoadhesive nanoemulsion was a more efficient method of delivery and exhibit better brain targeting of risperidone, which is an indication of how important mucoadhesion is in nasal drug delivery. They also prepared nanoemulsions and olanzapine mucoadhesive nanoemulsions employing water titration method, these formulations were intranasally and intravenously administered to rats. It was
observed that the biodistribution of olanzapine in the brain and blood of rats (brain/blood uptake ratios) after intranasal and intravenous administrations of olanzapine formulations at 30 minutes were 0.88 and 0.04 respectively [54]. This result proved that intranasal administration enhances bioavailability of drugs compared to intravenous administration. Zhang et al., [75] while investigating ways of enhancing the solubility of nimodipine and its brain absorption in microemulsion, their results showed absorption of nimodipine in the olfactory bulb to be enhanced three-fold after intranasal administration, compared to intravenous injection.

Dalpiaz et al., [76] have used Solid Lipid Microparticles (SLMs) as an intranasal drug delivery system for antiretroviral drug Zidovudine (AZT) with Ursodeoxycholic Acid (UDCA) (UDCA–AZT) prodrug for direct nose to brain targeting, Figure 8 shows the Environmental Scanning Electron Microscopy (ESEM) images of unloaded (A) and UDCA–AZT loaded (B) SLMs based on tristearin. They employed hot emulsion technique using tristearin and stearic acid as lipidic carrier. Their study showed that in the presence of Chitosan, there are six fold bioavailability of prodrug in the CSF, and about 1.5μg/mL of prodrug in 2.5 hours following intranasal administration, which shows an evidence of direct nose-to-brain delivery pathway.

![Figure 8: Environmental Scanning Electron Microscopy (ESEM) micrographs of unloaded SLMs.](image)

**Figure 8:** Environmental Scanning Electron Microscopy (ESEM) micrographs of unloaded [76].

### Liposomes as delivery vehicle

Galanthamine Hydrobromide (GH) which is an effective therapeutic agent that is widely used in Alzheimer’s disease management has been delivered into the rat brain successfully through the intranasal route of administration employing flexible liposomes as the delivery vehicle [77]. Salama et al., [78] prepared phospholipid based colloidal nanocubic vesicles by integrating non-ionic copolymers, poloxamer 188 or 407, in the lipid bilayer. Their aim was to encapsulate olanzapine in the matrix. Their investigation resulted in development of nanocubic vesicles and enhancement of the delivery of olanzapine to the brain with bioavailability up to 37.9% and brain targeting efficiency of 100% after intranasal administration. Liposomes have been employed in delivering rivastigmine to the brain tissue through intranasal administration. Liposomes as delivery vehicle significantly improved the exposure and thereby resulted in higher concentration of the therapeutic agent in the brain [79,80].

Alam et al., [81] prepared Nanostructured Lipid Carrier (NLC) to confirm and assess the improvement of Duloxetine (DLX) loaded NLC in the brain following intranasal administration, they employed gamma imaging technique to study the localization of DLX, their results revealed about 8 fold of DLX concentration in the brain in comparison to being administered intravenously. Li Weize et al., [77] delivered GH successfully into the rat brain through the olfactory pathway while investigating the intranasal administration effects of GH loaded.
flexible liposomes on the effectiveness of acetylcholinesterase inhibition. Figure 9 shows the TEM image of the GH loaded liposomes. They discovered a quick action of movement of GH into the brain with the flexible liposomes following intranasal administration. Their investigation therefore indicated that the intranasal administration of GH loaded liposomes may be a promising technology to be explored in future for the treatment of Eskandari AD et al., [82] have developed nasal nanostructured lipid carriers of valproic acid for direct nasal mucosa to brain delivery. Their aim was to lower the dosage, provide prolonged action of the drug and evaluate its efficacy against generalized tonic-clonic seizures in rats, their study established that administration of vaproic acid nanostructure via the nasal route is an appropriate method in maintaining vaproic acid effect with a higher brain uptake using much lower dose compare to systemic administration. Migliore et al., [83] evaluated the efficiency of cationic liposomes for the delivery of proteins to the brain by employing the nasal route of administration. They loaded the liposomes with ovalbumin and a 50μg was intranasally administered to rat, it was observed that after 6 hours ovalbumin was widely distributed throughout the brain of the rat. Solid Lipid Nanoparticles (SLNs) have been developed and optimized as intranasal drug delivery system for ondansetron [84] and risperidone [85]. The method employed for preparing the SLNs was solvent diffusion-solvent evaporation method. Significant quantities of therapeutic agents were rapidly delivered to the CNS and brain after intranasal administration of the drug-loaded solid lipid nanoparticles that were formulated.

Polymeric micelles have been developed for intranasal drug delivery. Chiappetta et al., [86] prepared poly(ethylene oxide)–poly(propylene oxide) polymeric micelles for intranasal administration which was loaded with high payloads of efavirenz an antiretroviral drug for treating HIV dementia. Poloxamer F127 and mixed polymeric micelles containing 75% of T904 and 25% of F127 was employed with an attempt to determine the effect on size of the micelles as well as the drug payload. They compared intranasal administration of their formulation with intravenous administration; the result of their investigation shows four times bioavailability enhancement in the CNS for intranasal administration compared to intravenous which is as a result of direct migration of the nanomicelles to the olfactory region for onward delivery to the CNS. The size of the micelles ranged from 13.5nm to 247.3nm when the efavirenz was fully encapsulated.

**Direct drug application into the nasal cavity**

Direct drug application without any protective vessel has been demonstrated by various researchers for example, Deferoxamine (DFO) has been delivered using the noninvasive intranasal method of administration. Hanson et al., [87] reported that employing intranasal route to administer DFO resulted in higher brain uptake of DFO compare to intravenous administration, it also amount to reduction in systemic absorption, and subsequently resulted in prevention and treatment of stroke damage after middle cerebral artery occlusion.
in rats. Fine et al., determined whether intranasal administration of DFO would minimize loss of memory in the P301L mouse and how the treatment might affect AD neuropathology, their finding was that intranasal administration with DFO reduced both inflammation and oxidation which are the two phenomena associated with Alzheimer’s disease [88].

Application of recombinant tissue Plasminogen Activator (tPA) to ischemic stroke has been carried out by Liu et al., using direct nose-to-brain approach because of the BBB issues and the associated side effect of the systemic pathway. Their study examined the therapeutic benefit of tPA when it is intranasally administered for direct CNS targeting for the treatment of stroke in rat model. Their result shows tPA content of 307mg/ml at 30 min in the brain compare to 7mg/ml measured 2 h after intravenous injection of tPA (10mg/kg), signifying intranasal administration to be an effective method of delivering high molecular weight drugs for brain and spinal cord targeting [89].

Cocaine was intranasally and intravenously administered to male Sprague-Dawley rats by Chow et al., [90]. The result of both routes of administration indicated similarity in concentration of cocaine in the brain. The concentration of cocaine in the olfactory lobe was investigated after 1 min of dosing and small fraction of the dose was found delivered in the olfactory bulb via the olfactory pathway, much of the cocaine have been trapped by the blood rich nasal mucosa for onward systemic delivery to the brain and CNS.

Conventional Nasal Drug Delivery Dosage Forms

Nasal drops

The purpose of using nasal drops is to instill the drugs inside the surface of the nasal cavity. Nasal drops are the simplest and most convenient systems that have been developed for intranasal drug delivery. Aukema et al., have used nasal drops to deliver steroids into the middle meatus for the treatment of polyposis and chronic rhinosinusitis with fluticasone propionate [91]. Daley-Yates and Baker in their experiment tried to measure the bioavailability of Fluticasone Propionate administered as a nasal drops and also compare it to being administered as a nasal gel, it was observed that the formulation has low systemic bioavailability which is much lower than when administered as nasal gel [92]. Nasal drops have been however reported to deposit human serum albumin in the nostrils better than nasal sprays [93]. Nasal drops do not have dose precision which is an obvious shortcoming of the system. In addition liquid formulations are more easily emptied to the nasopharynx thereby showing quick clearance from nasal mucosa which is an impediment to sustained drug release [94].

Nasal sprays

Nasal sprays function by the action of hand operated metered dose pumps and actuators to infuse a fine vapor into the nostril, they can therefore delivered exact dose from 25-200μl an advantage over nasal drop. Several nasal sprays have been developed over the years for drug delivery. Some of which are highlighted in Table 2. Chesnut III et al., used Salmon calcitonin nasal spray at a dose of 200IU daily to drastically reduce the threat of new vertebral fractures in postmenopausal women with osteoporosis [95]. Fluticasone nasal spray has been used to reduce the occurrence of pediatric obstructive apneas and hypopneas [96]. Others include: Nicotine nasal spray for tobacco withdrawal [97-100]. Nicotine nasal spray for analgesic purposes [101].

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Functions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>Tobacco withdrawal and cognitive enhancer</td>
<td>[97-100,102]</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Treatment of Refractory Mania</td>
<td>[103]</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>Reduction in the occurrence of pediatric obstructive apneas and hypopneas</td>
<td>[96]</td>
</tr>
</tbody>
</table>
Fentanyl pectin  Pain relief  [104,105]
Oxytocin  Treatment of Autistic or Asperger's Disorder  [106]
Insulin  Treatment of Alzheimer’s disease  [107]

| Table 2: Review of recent development in nasal sprays for delivery of therapeutic agents. |

**Nasal gel**

Gelation occurs usually through polymers crosslinking by forming covalent bond known as chemical crosslinking or by non-covalent bonding and vander waals forces known as physical crosslinking [108]. Gel formulations increase the contact time with the nasal mucosa and also increase efficiently the residence time of the therapeutic substances in the nasal mucosa. These advantages are dependent however on the type of polymers used. Other advantages include reduction of taste impact, reduction of leakages of the formulation from the anterior part and mucosa target for better absorption [35]. Table 3 shows some of the recent development of nasal gel in delivering therapeutic agents through the nasal mucosa.

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Functions</th>
<th>Polymers Used</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam Hydrochloride</td>
<td>Treatment of epilepticus</td>
<td>Pluronic F127</td>
<td>[109]</td>
</tr>
<tr>
<td>Triptans</td>
<td>Anti-migraine</td>
<td>Hydroxypropyl Methycellulose and Carboxymethyl cellulose (CMC)</td>
<td>[110]</td>
</tr>
<tr>
<td>melatonin</td>
<td>Antihistaminic drug</td>
<td>CMC and polyethylene glycol 400</td>
<td>[111]</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Dopamine D2 agonist</td>
<td>Chitosan and hydroxyl propyl methyl cellulose</td>
<td>[112]</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Treatment of migraine and severe headache</td>
<td>Carbopol 934P and Pluronic F127</td>
<td>[113]</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Treatment of status epilepticus</td>
<td>Pluronic F127 and Chitosan</td>
<td>[69]</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Anti-inflammatory, antioxidant for treating Alzheimer's disease</td>
<td>Polyethylene glycol 400 and Pluronic F127</td>
<td>[114]</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Treatment of chronic depression</td>
<td>Methyl cellulose and Pluronic F127</td>
<td>[115]</td>
</tr>
<tr>
<td>Vinpocetine</td>
<td>Prevention of Alzheimer’s disease</td>
<td>Hydroxypropylmethyl cellulose, methyl cellulose and Carboxymethyl cellulose</td>
<td>[116]</td>
</tr>
</tbody>
</table>

| Table 3: Review of recent development in nasal gel for delivery of therapeutic agents. |

**Nasal powder**

The instability of therapeutic agents may inform the development of this delivery system, where solution and suspension dosage form may not be adequate to sustain the drug. Preservative is not required in the formulation and there is possibility of administration of larger doses of therapeutic agents. The suitability of powder for delivery of both peptide and non peptide drugs has been established [35,117]. For nasal powder formulation to be efficient, factors such as aerodynamic properties, particle size, degree of irritancy of the formulation as well as the solubility of the therapeutic compounds must be considered. Nasal powder do not have metered dosage and causes nasal mucosa irritancy on application, these are however some of its disadvantages [118]. Table 4 shows review of some recent development in nasal powder for delivery of therapeutic agents.

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Functions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Treatment of Alzheimer’s disease</td>
<td>[119,120]</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>treatments for Parkinson's disease</td>
<td>[121]</td>
</tr>
<tr>
<td>Norwalk virus-like particles (NV VLP) Antigen</td>
<td>Prevention of norovirus infections</td>
<td>[122]</td>
</tr>
<tr>
<td>Tacrine hydrochloride</td>
<td>Treatment of Alzheimer’s disease</td>
<td>[123]</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>Treatment of nocturnal enuresis</td>
<td>[124]</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Treatment of migraine</td>
<td>[125]</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Treatment of migraine</td>
<td>[126]</td>
</tr>
</tbody>
</table>

| Table 4: Review of recent development in nasal powder for delivery of therapeutic agents. |
The Use of Specialized Intranasal Drug Delivery Systems

In the bid to find solution to the problem of BBB, specialized intranasal drug delivery systems have been developed by researchers to overcome the issue of bioavailability of therapeutic agents to the brain.

Liposomes

There are flexible and conventional liposomes which are differ by their high elastic fluid membranes that permit a number of molecules to pass across via the cellular membranes [77,127]. Liposomes are known to have several striking properties as they are used as pulmonary drug delivery systems especially in controlled drug delivery system. One of the alleged advantages of liposomes is in their capability to effectively encapsulate small and large molecules [128,129] and alter auspiciously the pharmacokinetic profile of the encapsulated substance thereby providing sustained pharmacological effects at the site of administration [109]. The control release profile of the encapsulated therapeutic agent in liposomes is difficult to manage as this may however be a major disadvantage of this system [130]. Table 5 shows recent development in nasal liposomes for delivery of therapeutic agents.

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Functions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovalbumin</td>
<td>Chelating agent</td>
<td>[83]</td>
</tr>
<tr>
<td>Tacrine hydrochloride</td>
<td>Treatment of Alzheimer’s disease</td>
<td>[131]</td>
</tr>
<tr>
<td>Galanthamine hydrobromide</td>
<td>Treatment of Alzheimer’s disease</td>
<td>[77]</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Treatment of schizophrenia</td>
<td>[78]</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Treatment of Alzheimer’s disease</td>
<td>[79,80]</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Treatment of depression</td>
<td>[132]</td>
</tr>
</tbody>
</table>

Table 5: Review of recent development in nasal liposomes for delivery of therapeutic agents.

Microspheres

Microspheres are small spherical particles which are made up of macromolecular compounds of sizes of micrometer range usually from 1 to 1000µm. Microspheres are matrix systems that are manufactured from basically natural and synthetic polymers, drugs can then be incorporated into the matrix system by dispersion throughout the polymeric matrix. Microspheres have the ability to protect the drug from enzymatic degradation and are capable of prolonging the drug effect by sustained drug release. Table 6 shows some recent works done on microspheres as drug delivery system for nasal administration.

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Functions</th>
<th>Polymers Used</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteins (VEGF and GDNF)</td>
<td>Treatment of Parkinson’s disease</td>
<td>Poly(lactic-co-glycolic acid) PLGA</td>
<td>[133]</td>
</tr>
<tr>
<td>Rizatriptan Benzoate</td>
<td>Treatment of migraines</td>
<td>Abelmoschus esculentus polysaccharide</td>
<td>[134]</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Treatment of epileptic seizures and bipolar disorder</td>
<td>Chitosan</td>
<td>[135]</td>
</tr>
<tr>
<td>O6-cyclopentyladenosine</td>
<td>neuronal anti-ischemic agent</td>
<td>Chitosan</td>
<td>[136]</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Treatment of status epileptics</td>
<td>Pluronics PF-127 and PF-68 and Chitosan</td>
<td>[137]</td>
</tr>
</tbody>
</table>

Table 6: Review of recent development in microspheres and microparticles for nasal delivery of therapeutic agents.

Nanoparticles

Nanoparticles are colloidal solid particles with very small size in the nanometer range, usually from 1nm to 1000nm in diameter. Nanoparticulate drug delivery system through the systemic pathway possesses distinct advantages for delivery of drugs to the brain. However,
the bioavailability of the therapeutics in the brain is still not satisfied [138-140]. Intranasal drug delivery of nanoparticles absorb via the olfactory pathway will be a promising way of getting drugs to the brain and CNS in general. Table 7 shows summary of recent development in nanoparticles for intranasal delivery of therapeutic agents.

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Functions</th>
<th>Polymers Used</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Treatment of Alzheimer’s disease</td>
<td>Poly(3-acrylamidophenylboronic acid-ran-N-maleated glucosamine)</td>
<td>[141–143]</td>
</tr>
<tr>
<td>NAPVSIPQ (Neuropeptide)</td>
<td>Treatment of Alzheimer’s disease</td>
<td>Poly(ethylene glycol)-co-poly(ε-caprolactone)</td>
<td>[3]</td>
</tr>
<tr>
<td>Levodopa</td>
<td>Treatment of Parkinson’s disease</td>
<td>PLGA</td>
<td>[144]</td>
</tr>
<tr>
<td>Ropinirole hydrochloride</td>
<td>Treatment of Hypertension</td>
<td>PLGA</td>
<td>[145]</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Treatment of depression</td>
<td>Chitosan</td>
<td>[64]</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Treatment of Alzheimer’s Disease</td>
<td>Chitosan</td>
<td>[65]</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Treatment of Parkinson’s disease</td>
<td>Chitosan</td>
<td>[66]</td>
</tr>
<tr>
<td>Thymoquinone</td>
<td>Treatment of inflammatory disorder</td>
<td>Chitosan</td>
<td>[67]</td>
</tr>
<tr>
<td>Rabies virus glycoprotein (RVG29)</td>
<td>As targeting ligand to acetylcholine receptor</td>
<td>Chitosan</td>
<td>[146]</td>
</tr>
<tr>
<td>Leucine-enkephalin (Leu-Enk)</td>
<td>As endogenous opioid peptide neurotransmitter</td>
<td>Trimethyl chitosan</td>
<td>[147]</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Treatment of Acquired Immunodeficiency Syndrome</td>
<td>Chitosan</td>
<td>[148]</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Treatment of schizophrenia and acute psychosis</td>
<td>poly(ethylene glycol)–block-poly(d,l)-lactic-co-glycolic acid (PEG–PLGA)</td>
<td>[149]</td>
</tr>
</tbody>
</table>

Table 7: Summary of recent development in nanoparticles for intranasal delivery of therapeutic agents.

**Microemulsions**

Microemulsions are made up of oil phase, aqueous phase, surfactant and co-surfactant. Due to their lipophilic nature and their small size, microemulsion has been explored to be a good intranasal delivery system which efficiently improves drug absorption in the nasal mucosa. Microemulsion has advantage of being easy to produce compare to other delivery systems, because its production is mainly by mixing and stirring with magnetic stirrer or sonicator or by titration [150] and requires simple instruments and laboratory equipments. Microemulsion has been discovered to be a novel approach to improve water solubility of poor water soluble drugs and subsequently increase bioavailability [151]. Table 8 shows some of the recent work done using microemulsion as intranasal drug delivery system.

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Functions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nimodipine</td>
<td>Treatment for cerebrovascular spasm, stroke and migraine</td>
<td>[75]</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Treatment of depression</td>
<td>[152]</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Treatment of epilepsy</td>
<td>[72]</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Treatment of schizophrenia</td>
<td>[150]</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Treatment of anxiety disorders, alcohol withdrawal symptoms</td>
<td>[73]</td>
</tr>
</tbody>
</table>

Table 8: Summary of recent development in microemulsion for intranasal delivery of therapeutic agents.

**Nanoemulsions**

Nanoemulsions are thermodynamically stable and are stabilized by surfactants [153]. They can be produced by simple emulsification method such as titration and by mixing oil, water, surfactant and co-surfactant together [154]. They are important vehicles for delivery of hydrophobic compounds, which make them an important intranasal drug delivery system. Due to their characteristic size and properties, which include kinetic stability, they are very effective in encapsulating the drugs and successfully direct them towards the desired targets [155]. They do not have toxic effect on human and animal cells due to their non-
toxicity and non-irritancy [156] which are excellent properties that make them suitable for therapeutic purposes and good candidates for intranasal delivery system. Table 9 shows some of the therapeutic agents that have been recently designed for delivery via intranasal nanoemulsion.

<table>
<thead>
<tr>
<th>Therapeutic Agents</th>
<th>Functions</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Treatment of psychotic disorders</td>
<td>[74,157]</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Treatment of schizophrenia</td>
<td>[54]</td>
</tr>
<tr>
<td>Safranal</td>
<td>Treatment of convulsive disorders</td>
<td>[158]</td>
</tr>
<tr>
<td>Rizatriptan benzoate</td>
<td>Treatment of migraine</td>
<td>[159]</td>
</tr>
</tbody>
</table>

Table 9: Review of recent development in nanoemulsion for nasal delivery of therapeutic agents.

Iontophoretic delivery

Lerner et al., [160] investigated a method to increase the bioavailability and distribution of drug in the brain by employing iontophoresis as an intranasal delivery system to force the passage of drug from the nasal mucosa across to the brain employing an electric field. In their experiment, they charged up electrodes with drug and then applied it directly deep into the nasal neuro-epithelium of the rabbit, they then position a return electrode at the back of the rabbit’s head. When electric current is applied, the charged drug molecules were forcefully driven across the nasal mucosa into the brain via the olfactory pathway. This method actually permits delivery of more therapeutics to the CNS compared to other methods. However, the method is cumbersome and highly invasive since the electrode has to be inserted deep into the nasal cavity potentially damaging the nasal mucosa.

Challenges and Future Trends of Direct Nasal Mucosa to Brain Delivery

There are several challenges facing direct nose-to-brain delivery. It has been recorded that drugs arrive at the CNS and the brain following nasal delivery, but the quantity of drugs recorded to have reached the brain is limited also the evidence of preferential brain delivery documented is limited. The dimension of the nasal cavity may also limit the dosage per time; the capacity of reaching sufficient bio-distribution has not been established by this route of administration. Current intranasal delivery systems available cannot exploit the merits of nasal drug delivery maximally due to large amount of the dose been deposited at the anterior segment of the nose and thereby reducing drastically the amount of drugs that will eventually reach the olfactory region resulting in low bioavailability. The drug remaining at the surface of the nasal cavity may cause irritation and foul taste which may result in patient compliance problem. Most nasal formulations are in form of liquid, powder or gel. Liquid formulation is limited by solubility, stability and dose volume. Powder and gel formulations may be faced with issues of stability, absorption across the mucosal epithelium cells, residence time and degradation. In general nasal drug delivery systems may face the problem of low bioavailability in the CNS and brain due to various factors. Enzymatic barriers which are amongst the limiting factors of drug absorption in the nasal epithelium are caused by the various enzymes such as carboxylesterases that subsist in considerable quantity in the nasal mucosa [161]. The presence of these enzymes may result in degradation of substances introduced into the nasal mucosa due to their metabolic actions and thereby stand as barrier for intranasal drug absorption into the olfactory epithelium. Enzyme inhibitors such as boroleucine and puromycin may be used to minimize enzymatic metabolism of protein and peptide drugs [162]. Permeation through the nasal epithelium cells poses a challenge to intranasal drug delivery as drug administered via the nasal mucosa permeates by passive paracellular and active transcellular transport. Drug can also permeate by transport via intercellular tight junctions, transcytosis and carrier mediated
transport [163]. Low molecular weight and lipophilic drugs can permeate with ease across the nasal mucosa epithelium, but hydrophilic drugs and high molecular therapeutic agents such as peptide and protein have low permeability [164] and therefore present challenges in intranasal delivery. The use of permeation enhancers and prodrugs has been employed to improve permeability in nasal drug delivery.

Mucociliary clearance is a vital defense mechanism of the respiratory system that protects the lung against noxious inhaled pathogens such as bacteria, allergens, virus, toxins and other undesirable substances [165-167]. When these substances reach the nasal mucosa, they adhere and dissolve in the mucus lining and are transported to the GIT through the nasopharynx for onward ejection into the GIT. This is one of the fates of therapeutic agents introduced to the nasal cavity. The clearing mechanism reduces the transport of drugs to the CNS through the nasal cavity and also reduces the residence time of the drugs as well in the nasal mucosa. These factors contribute to limiting the bioavailability of therapeutics in the CNS. Mucociliary clearance depends on the drug site deposition and deposition area also depend on parameters including mode of nasal administration, texture of the formulation, physicochemical properties of the drug and the velocity of the delivered particles [168]. The mucociliary clearance problem can be overcome by using mucoadhesive polymers in formulating nasal drug delivery system. Alginate and Chitosan are good examples of mucoadhesive polymers that can be employed in formulation of nasal drugs. Chitosan has been used by various researchers [64,65,133] to increase the mucoadhesion of formulation in order to increase the residence time of the therapeutic agent in the nasal cavity. Poor physicochemical properties of the drugs and formulations may be another issue that needs to be addressed to achieve successful intranasal drug delivery. The use of novel and specialized approaches such as nanoparticles, microspheres, liposomes mucoadhesive polymers to encapsulate and protect the drugs has been a way to enhance the bioavailability of drugs in the brain and CNS. Mechanisms of transport and absorption of drugs in the nasal epithelium is another issue to be considered, for example some of the solutes introduced to the nasal cavity follow the trigeminal route and major part of the solutes may be distributed to the orofacial tissues which may reduce bioavailability of drugs in the brain and the CNS as evidenced by the work of Johnson et al. Trigeminally innervated structures were found to have up to 20-fold higher tissue concentrations of lidocaine than the brain and blood following intranasal administration of lidocaine to rats [169]. In addition, the nasal vasculature is undeniably another limiting factor to direct nasal mucosa delivery to the CNS and brain to treat neurogenerative diseases as it clears applied therapeutic agents into the system circulation for possible systemic delivery or elimination. This may be overcome by ensuring rapid movement of therapeutic agents to the olfactory region for onward delivery to the brain via the olfactory pathway.

Considering the mechanism involved in transporting the drug directly to the brain which depends on passive diffusion of the drugs to the olfactory epithelium before being transported to the brain, substantial part of the drugs may have found their way into the blood and then follow the systemic pathway thereby limiting the amount of drug that will follow the olfactory pathway for onward delivery to the CNS. This action ultimately reduces bioavailability to the brain and CNS. A formidable strategy is therefore desirable which will not only enhance the bioavailability of the drugs in brain and CNS (by the drugs going through the olfactory pathway) but ultimately ensuring timely and sustainable delivery to the brain and CNS within the shortest possible time in order to prevent drugs passing through the systemic pathway. Researchers are thus challenged to find an improved and better method of getting the drugs into the brain via the nasal mucosa in order to increase bioavailability of drugs in the brain by transportation and absorption going via the olfactory pathway instead of the systemic pathway.
Conclusion

This chapter shows evidence of direct nasal mucosa to brain and CNS delivery, the importance of the intranasal route of administration and its great potential as a means of delivering therapeutic agents to the brain for the management of brain diseases that may not have been possible due to the BBB and other barriers. The nasal mucosa is very rich in blood vessels and capillaries for systemic delivery, the probability of the drugs administered intranasally getting absorbed into the systemic pathway is very high, even though, only molecules permeable through BBB will eventually reach the brain.

All the researches enumerated in this chapter have employed the mechanism of passive diffusion that relies mainly on instillation of drug deep in the nasal cavity, physicochemical properties of the nasal and neuro-epithelia as well as gravity to penetrate the brain and CNS via the olfactory pathway. However, substantial quantities of drugs still go through the systemic pathway thereby reducing the quantity via the olfactory pathway. This is a challenge in the intranasal delivery of drugs as this action reduces the bioavailability of the drugs in the brain. Application of a ‘driving force’ that can propel the therapeutic agents directly to the brain after being administered through the nasal mucosa may be a promising way of increasing bioavailability and decrease the time drugs reach the CNS and brain for the treatment of neurogenerative diseases. This method could be achieved by employing the use of electroactive polymers in formulating intranasal drug delivery system with the aid of external stimuli such as electric or magnetic force to propel non-invasively the drugs directly from the nose to CNS within shortest time in a sustainable manner. This could be proffered as a future advancement in intranasal drug delivery in the management of CNS diseases and brain disorder.

References


