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Nose to Brain Drug Delivery System of Antipsychotic Drug: A Review

Miss. Shweta Prakash Jadhav, Pratiksha R.Sudrik, Dr.A.H.Hosmani

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ABSTRACT
Antipsychotic medications are used to treat psychotic disorders, which affect millions of people worldwide and place a heavy financial, emotional, and healthcare burden on society. Intranasal administration has the potential to enhance brain-specific targeting, although this promise has not yet been fully realized. In this article, we examine the mechanisms and procedures employed for intranasal (IN) brain targeting as well as the novel drug carriers developed for the same. A number of antipsychotic drugs have been studied for intranasal administration using cutting-edge delivery systems, such as nanoemulsions, nanoparticles, nanosuspensions, liposomes, polymeric micelles, and so on.A brief discussion predicts that the limited aqueous solubility of antipsychotic medications can be overcome and non-toxic formulations are adopted.Given the inherent advantages of IN delivery over other techniques, it will become more important in the future especially when targeting specific brain areas.

Keywords
Brain Targeting, Antipsychotic Drug, Schizophrenia, Nose to Brain Delivery

I. INTRODUCTION

One of the most intricate and important organs, the brain receives signals from the sense organs and controls the majority of bodily functions. In addition to numerous other organs' operations, it regulates hormone secretion, memory encoding, and both voluntary and involuntary motions [1].

The structure and physiology of the brain or spinal cord, which together make up the CNS, are affected by diseases of the CNS, also referred to as CNS disorders. Because of the blood-brain barrier's (BBB) imperviousness, neurological disorders like Alzheimer's disease (AD), Parkinson's disease (PD), psychosis, Huntington's disease (HD), head trauma, brain tumors, and epilepsy are challenging to identify and treat[2].

The most difficult challenge is delivering a medicine to the brain because of its anatomy and physiological barriers like the blood-brain barrier (BBB) [3].Currently, a variety of treatments are available, including surgery, deep brain stimulation, intravenous (IV), oral, and topical dose forms.Conventional therapies, however, have some restrictions that help the medicine enter general blood circulation after passing through various physiological barriers like the blood-brain barrier (BBB), which is a portion of the apparent blood distribution volume [4].Once the drug's payload has just a minimally effective therapeutic effect in the brain. In contrast, surgical methods and brain implants are regarded as risky, transient, and extremely invasive therapy modalities [5].Several procedures, including intraparenchymal or intracerebra-ventricular injections, catheter infusions, mini-pump-assisted intracranial administration, precise ultrasound technologies, or electromagnetic force-field techniques, are being used for the local delivery of active medicines to the brain. However, many of these techniques are inappropriate for long-term therapy because they are intrusive, dangerous, and have neurotoxic side effects at the delivery site [6].

A persistent psychotic condition, schizophrenia,Schizophrenia symptoms frequently start to appear in maturity and last the rest of a person's life. There are three primary categories of etiological factors. These include genetic, brain abnormalities, and environmental influences [7].One percent of people worldwide experience schizophrenia, both the positive (delusions, auditory illusions) and negative (social disengagement, severe disorganization, inability to pay attention) symptoms of schizophrenia can be successfully reduced by antipsychotic drugs, especially atypical antipsychotic medications [8].

The intranasal pathway for medication delivery from the nose to the brain has undergone substantial research. The intranasal route can deliver therapeutic substances to the brain without passing through the BBB because of the special connection between the nose and the CNS. The ability to target medications to the brain through olfactory area of the nose is a special characteristic and superior choice [9].

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Advantages and disadvantages associated with intranasal delivery-

Advantages

1. Rapid absorption produces a plasma profile for lipophilic medicines with 1000 Da molecular weight that is identical to intravenous delivery [10].
2. Enhanced bioavailability compared to oral administration due to avoidance of hepatic or gastrointestinal metabolism [10].
3. Pharmacological effects start to take effect quickly compared to oral delivery [10].
4. Self-administration is non-invasive and simple; qualified medical staff is not necessary, unlike with parenteral administration [10].
5. Suitable for patients with gastrointestinal pathology, nausea, or vomiting as well as difficulty swallowing [11].
6. Suitable for people who are afraid of getting shots [11].
7. Affordable delivery methods which are safe for reusing [11].
8. Drugs can be directed to the brain and CSF by avoiding the BBB, making them appropriate for peptides and proteins that are directed to the brain [12].
9. The potential for lowering dosages given due to targeted or improved bioavailability, resulting in fewer side effects [12].

Disadvantages

1. Limited deliverable volumes(maximum up to 0.1 mL/nostril)[13]
2. Because most pharmaceuticals are insufficiently soluble, only powerful medications (requiring modest doses) can be administered [11].
3. Rapid mucociliary clearance leading to the removal of drugs form the site of absorption [14].
4. May not be suitable for hydrophilic drugs or drugs which are ionized at nasal pH (6.5–7.5) [11].
5. Extracellular and intracellular enzymatic degradation [15].
6. Attenuated transport of efflux transporter (e.g. P glycoprotein efflux transporter) substrates [16].
7. Drugs might have unpleasant odor or aftertaste if they diffuse to oral cavity [10].
8. Potential for irritation or toxicity to nasal mucosa [11].
9. Absorption might be affected in conditions like rhinitis, rhinorrhea, nasal congestion, etc. or by interaction with drugs like vasoactive agents [11].

Anatomy of Nose-

One of the five primary senses is housed in the nose, an organ that is both physically and functionally complex. In addition to filtration, humidification, and temperature regulation, the nose's ability to smell is crucial for humans as well as animals to locate food, predators, and partners [17].The external nose is a pyramidal structure, with the nostrils formed by cartilage and soft tissues that regulate airflow into the airways, and an upper bony section attached to the frontal bone of the skull. The internal nose is the functional component made up of two cavities that connect the base of the skull to the roof of the mouth and open up to the face through the nostrils [18].The nasal cavity measures 12 to 14 cm in length, 5 cm in height, 15-20 ml in volume, and 150 to 200 cm2 in surface area[19].The nasal vestibule, the respiratory portion, and the olfactory section are the three divisions of the nasal cavity [1].The nasal vestibule is a collection of sweat, sebaceous, and hair glands that is found in the most anterior section of the nasal cavity [20].The middle and inferior turbinates are the most prominent structures in the respiratory region, which acts as a route for air into the lungs. The superior turbinate contains the olfactory region, which is roughly 10 cm2 in size and contains olfactory receptors that are in charge of the sense of smell. The major locations of interest for intranasal medication administration are the respiratory and olfactory mucosa [21].

Olfactory Mucosa:

About 5–10% of the surface area of the human nasal cavity is taken up by the olfactory mucosa, which is situated on top of the nasal cavity[1].It is made up of the neurons that pick up smells in the air that is inhaled. The olfactory axons in the lamina propriety on their way to the olfactory bulb are sheathed in cells that either support the neurons in the epithelial layer or surround them [20].The first cranial nerve to transmit sensory data relating to scent is the olfactory nerve. A coating of mucus that coats the epithelium is secreted by tubular Bowman's glands, one of the several cell types that make up this tissue. Close to the lamina propriety, glucose basal cells (GBCs) and horizontal basal cells (HBCs) serve as progenitor cells for several cell types. Additionally, olfactory sensory neurons (OSNs), also known as olfactory

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receptor neurons (ORNs), are enclosed by the olfactory epithelium and are surrounded by supporting cells. The olfactory sensory neurons (OSNs) are unmyelinated, bipolar cells with a dendritic extension to the mucosal surface[22].In comparison to rodents, who have about 1000 olfactory receptors, humans have about 400 [23].OSN neurogenesis takes place in the nasal epithelium to replenish the neurons in order to preserve its functionality. The systemic apoptosis of OSNs is thought to occur to protect the brain from infections, and a few studies have revealed that OSNs have a life span of 30 to 60 days. A delay in tight junction creation occurs during neural regeneration, creating a gap that permits some substance penetration [24].Similar to respiratory epithelium, the olfactory epithelium is made up of ciliated columnar cells that are covered in a mucus layer. However, compared to the respiratory epithelium, the cilia in the olfactory epithelium are longer and non-motile [25].Two different types of basal cells, globose basal cells and horizontal basal cells make up the olfactory epithelium. Globose basal cells, which are OSN progenitor cells, are responsible for maintaining the homeostasis of healthy tissue in the olfactory mucosa[26].The olfactory epithelium contains supporting cells in addition to basal cells. Supporting cells called sustentacular cells (SUS) surround the OSNs in the olfactory epithelium region. Their main job is to maintain OSNs' structural and ionic integrity [27].

Respiratory Mucosa

A significant site for systemic drug absorption, respiratory mucosa accounts for 80–90% of the surface area of the human nasal cavity. It is also highly vascularized [28].Basal cells, goblet cells, ciliated epithelial cells, and serous glands are only a few of the different cell types and glands that make up respiratory mucosa[20]. In addition to helping to affix ciliated and goblet cells to the basal lamina, basal cells are progenitor cells within the epithelium that can develop into various cell types [29].Mucus is secreted by goblet cells and is made up of mucin (high molecular weight glycoproteins), water, salts, a few proteins, and lipids[30].The respiratory epithelium forms a coating of mucus, which acts as a first line of defense by trapping any irritants or foreign objects that are inhaled. Mucociliary clearance is achieved by the removal of this mucus by ciliated cells in the direction of the nasopharynx (MCC)[31].

Pathways for Nose to Brain Drug Delivery-

Although the mechanisms of Nose to Brain delivery are not entirely known, a number of recent researches have offered some significant hypotheses. The direct delivery of medications to the brain via neural routes, such as the trigeminal or olfactory nerves, is one method. The other method involves medication delivery indirectly via the lymphatic and vascular systems, which allows the brain to pass the blood-brain barrier [32].The various pathways for nose to brain absorption of drug are as follows:

1) Olfactory pathway-

Major drug delivery mechanisms from the olfactory system can be categorized into four categories: intra neuronal, extra neuronal, Trans cellular, and Para cellular pathways. The Nose to Brain delivery system heavily depends on olfactory neurons. Therapeutic molecules may be engulfed by OSN and form vesicles, which then permit intracellular axonal transport down the neurons, across the cribriform plate, and to the olfactory bulb. When they get to the brain, they will travel via exocytosis and be dispersed throughout the CNS [33]. One of the tiniest axons in the CNS, the human olfactory axon has a diameter of between 0.1 and 0.7 m. Due to their tiny dimensions, small molecules only in this range may be transported via intracellular axonal transport [34]. The delayed-release is another drawback of intracellular axonal transport. Since the average rate of axonal transport is 25 mm per day, it could take hours or even days for active molecules to reach the brain [35]. Molecules go over an extra-neuronal pathway by spanning the space between the OSN and the SUS in the epithelial layer. Once there, they are integrated into the lamina propria in the space between the axons and the OECs. The olfactory epithelium's neuronal turnover creates a gap that the active compounds must pass through in order to enter the cleft, allowing drug transport to take place even for bigger moieties [1]. Through the opening along the SUS and a Para cellular channel, the olfactory epithelium and basement membrane are crossed. Therapeutic compounds can pass the blood-CSF barrier in the subarachnoid space and then be delivered to the brain without integrating in the cleft. This pathway is best suited for hydrophilic and tiny molecules because it does not require medications to attach to receptors [21]. The passage of inhaled chemicals through the SUS membrane via passive diffusion or receptor-

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mediated endocytosis creates a Trans cellular route. Hydrophobic compounds can use this route [36].

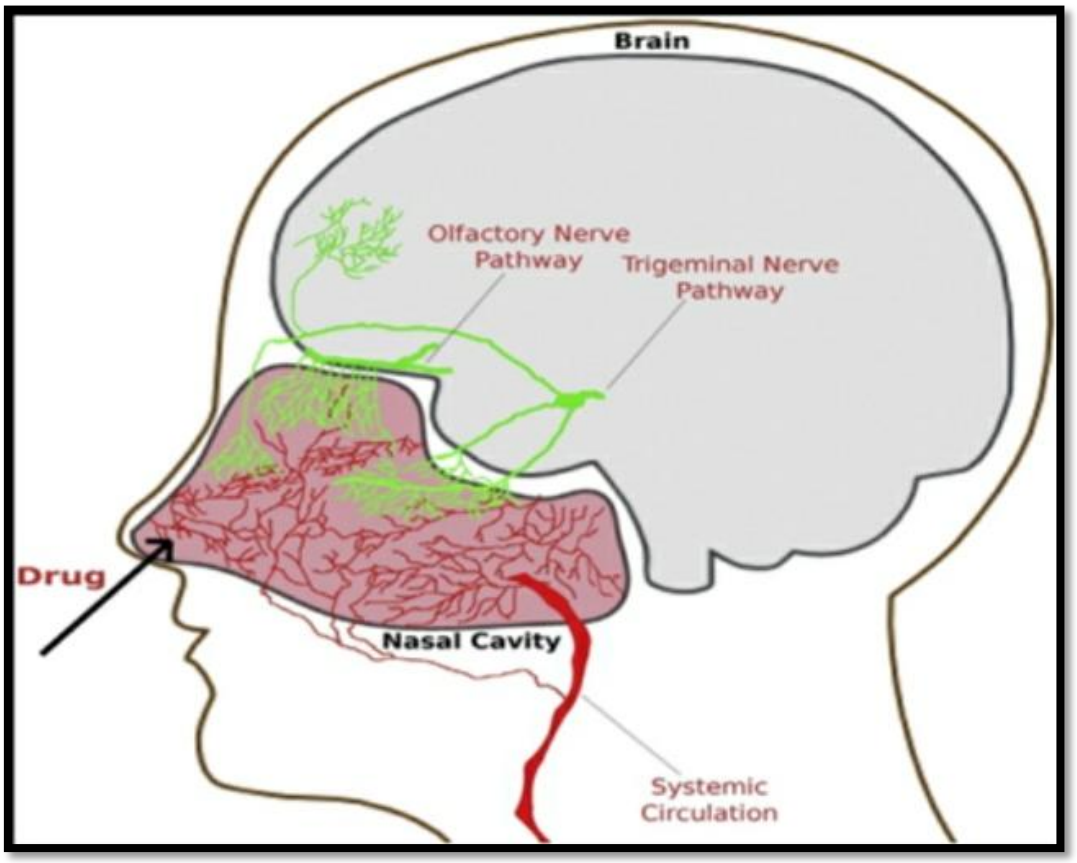

Fig 1: Pathways for transport of drug from the nasal cavity to the brain and systemiccirculation.

2) Trigeminal Pathway:

The fifth cranial nerve, the trigeminal nerve, is the biggest cranial nerve and innervates the respiratory and olfactory mucosa. The ocular, maxillary, and mandibular nerves are its three separate branches, and they are in charge of carrying sensory and motor information from these regions to the spinal cord, the medulla, and the pons [37].The nasal, ocular and oral mucosa receives chemosensory and thermosensory signals from the trigeminal nerve as its primary function.Drug transport via the trigeminal nerve happens via several paths, much to the olfactory nerve system. Drug molecules will combine in the trigeminal ganglion and enter the brain close to the pons when they get to the trigeminal nerve branches. Additionally, certain trigeminal nerve fibers are located close to the olfactory bulb which enables drug molecules to pass through the cribriform plate and reach both the caudal and rostral regions of the brain[38].

3) Systemic Pathway:

For lipophilic medicines with low molecular weight, the systemic pathway, an indirect transport mechanism that runs from the nose to the brain, can be a potential strategy [39].Drugs are subsequently transferred to the systemic circulation after being absorbed via the lymphatic system and vascular sections of the nasal mucosa's epithelial membrane, evading the first-pass metabolism [37, 39].

4) Lymphatic Pathway:

From the sub mucosal portion of the olfactory region, drugs can be delivered by a number of extracellular pathways, including perineural, perivascularand lymphatic channels [37]. These extracellular routes connect to olfactory nerves that emerge from the lamina propria and travel to the brain's olfactory bulb [28].

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Recent Advances in the delivery of Antipsychotic Drugs:

Intranasal antipsychotic drug delivery has received a lot of attention in recent years due to a number of difficulties that it presents over other more traditional routes. Among the many different delivery methods, a few focused on the delivery of drugs specifically. A number of antipsychotic medications, including aripiprazole, asenapine, olanzapine, zotepine, clozapine, amisulpride, paliperidone, quetiapine, and haloperidol, have been investigated for intranasal administration using cutting-edge delivery systems, including nanoemulsions, lipid nanoparticles (SLNs and NLCs), nanosuspensions, liposomes, polymeric micelles & so on.

Nanoemulsion based drug delivery system-

The term "nano emulsion" refers to the dispersion of two immiscible liquids (often water and oil) into droplets with a diameter of 20–200 nm. This dispersion system's superior physical stability, biodegradability, nano-range droplets, and biocompatibility enable it to effectively distribute lipophilic medicines across the BBB [40].The small droplet size of NEs prevents destabilizing phenomena including coalescence, creaming, and sedimentation, and as a result, they have a higher surface area than other formulations and exhibit long-term physical stability. Different approaches that fall into two major categories—high-energy procedures and low-energy methods—can be used to prepare NEs. In the case of high-energy procedures, such as ultra-sonication and high pressure homogenization, the formation of the small droplets comprises a mechanical device that produces disruptive forces breaking up the oil and water phases to produce the droplets, a process that uses a lot of energy. Microfluidic, ultrasonic, or high pressure homogenizers are the tools employed[41].To create small droplets without using a lot of energy, low-energy technologies use specialized physico-chemical processes including phase inversion temperature and emulsion inversion points. The droplets are formed in the low-energy methods when the system experiences a phase inversion in response to changes, such as those in composition or temperature, and then moves through a low interfacial tension state [42].The nanoemulsion was found efficient for intranasal delivery with targeting efficiency of the drug.

Micro Emulsion based drug delivery system-

As second-generation colloidal carrier systems, micro emulsions have developed and are now frequently chosen over emulsions. Micro emulsions are colloidal dispersions that are transparent,low viscous, isotropic, and thermodynamically stable. They are maintained by an interfacial coating of alternating molecules of cosurfactant and surfactant. They consist of bicontinuous, reverse micellar (W/O), and swelling micellar structures (O/W) [43].Micro emulsion globule diameters are under 150 nm. They have an advantage over traditional emulsions due to a number of benefits such spontaneous creation, optical transparency, long-term physical stability, and self-preserving nature [44]. Incorporation of mucoadhesive agent into ME prevents rapid nasal clearance of formulation by overcoming MCC. Such mucoadhesivemicro emulsion(MME) systems have been reported by variousscientistswho help in enhancing the residence time at the site of absorption therebyimproving bioavailability.

Overview of Emulsion based drug delivery of antipsychotic drug:

Name of API	Formulation	Composition	Pharmacological Effect	Reference
Risperidone	Nanoemulsions	CapmulMCM, Tween 80, polyethylene glycol 400, ethanol, transcutol, propylene glycol, Distilled Water	Significant quantity of risperidone was quickly and effectivelydelivered to the brain by intranasal administration of formulatedmucoadhesivenanoemulsion.	[45]
Olanzapine	Nanoemulsion	Capmul MCM,Tween 80, polyethylene glycol 400, ethanol, Propyleneglycol,	rapid and larger extent of selective olanzapine nose-to-brain transport	[46]

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		Distilled Water		
Risperidone	Nanoemulsion	Capmul MCM, Tween 80, Propylene Glycol, Transcutol, Water, Chitosan	Mucoadhesive NE containing Chitosan displayed highest diffusion coefficient.	[47]
Ziprasidone HCl	Nanoemulsion	CapmulMCM,Labrasol, Transcutol,Phosphate buffer pH-8.0	Higher drug diffusion of ziprasidone NE than the solution was found.Pharmacodynamic study revealed the superiority of mucoadhesive NE than NE in the locomotors activity and paw test. Formulation was devoid of acute nasal ciliotoxicity.	[48]
Olanzapine	Micro emulsion	cis-9-octadecenoic acid,Caprylocaproylpolyoxylglycerides, polyoxyl40 hydrogenated castor oil ,diethylene glycol monoethylether,Water	Intranasal delivery of the olanzapine mucoadhesive Micro emulsion shown higher drug concentration in brain.	[49]
Quetiapine	Nanoemulsion	Capmul MCM, Tween 80, Transcutol P , propylene glycol	Higher drug transport effciency (DTE%) via intranasal NE.	[50]
Quetiapine Fumarate	Nanoemulsion	Capmul MCM, Polyethylene glycol, Tween 80, Ethanol	14 folds increase in relative bioavailability of Quetiapine Fumarate as compared with oral & Formulation was free from nasal ciliotoxicity.	[51]
Quetiapine Fumarate(QF)	Micro emulsion	Capmul MCM EP, Labrasol, Tween 80, Transcutol P, Chitosan	Enhanced transport of QF with improved bio availability	[52]
Haloperidol	Miniemulsion	Capmul® MCM EP, Capryol™ 90,Transcutol, Ethanol, Span 20, Tween 80, Water	Stable formulation free from nasal ciliotoxicity with potential for nose to brain transport of drug	[53]
Asenapine Maleate	Nanoemulsion	Capmul PG-8, Kolliphore RH40, TranscutolHP,Carbopol 971.	Higher AUC and Cmax values of the drug in the animal brains when treated with intranasal Asenapinemucoadhesive NE	[54]
Lurasidone	Nanoemulsion	Capmul MCM EP, Capmul MCM C8 EP, Cremophor® EL,Water	Higher concentration of LurasidoneHCl in brain when administered through intranasal route.	[55]

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Aripiprazole (ARP)	Nanoemulsion	Capmul PG-8,D-a tocopheryl polyethylene glycol 1000 succinate, Transcutol-HP, carbopol 971	The drug-loaded Mucoadhesive NE was found to possess higher AUC and Cmax values were observed in the brain.Non-existence of extrapyramidal side effect.	[56]
Clozapine	Nanoemulsion	peppermint oil, tween 80, transcutol P	Enhanced permeation of drug when incorporated into in situ gel	[57]
Amisulpiride	Nanoemulgel	Gellan gum, Labrasol, Maisine CC, Transcutol HP, poloxamers 407.	The presence of stimuli-responsive polymers facilitated mucoadhesion and enhanced localization time in the nasal cavity. The presence of polymers improved the in vitro release profile and ex vivo permeation of Amisulpiride.	[58]

Nanoparticle based drug delivery system:

Lipid Nanoparticles:

Lipid nanoparticles, also referred to as solid lipid nanoparticles, are made up of a lipid core stabilized by a surfactant. They differ from oil-in-water emulsions in that they are made by melting a lipid, then reducing its size, and then stabilizing the resulting particles with a surfactant in an aqueous disperse phase. These formulations may have a high concentration of hydrophobic medications, and when applied nasally, have been demonstrated to transport medications to the brain [59].For drug delivery, SLNs provide a number of benefits, including the capacity to be made without the use of organic solvents, a high level of physical stability, and increased, controlled release of loaded medicines. Due to their rigid form, SLNs have a restricted ability to load drugs, especially for hydrophilic molecules. They also suffer from undesirable particle development by agglomeration, which might result in the drug being released in a burst [60].

Polymer-based Nanoparticles:

Polymer NPs have a polymer core that usually has medication that is dispersed into the matrix between 60 and 200 nm in diameter. Poly (L-lactideco- glycolide) (PLGA) is a polymer approved for human use in the world's largest markets. It is approved for use in drug delivery systems, and this means that it is the polymer of choice for preparing medicinal products as it is biodegradable and demonstrates no toxicity concerns when used in humans. PLGAmay be used to protect drugs from degradation in the nasal cavity and may be loaded with hydrophobic drugs [61].

Nanoparticles Containing Chitosan and Chitosan Derivatives:

Chitosan has been incorporated into a number of nose-to-brain nanoformulations as chitosan solution, and chitosan nanoparticles (prepared by physical crosslinking of chitosan with tripolyphosphate) have been shown to act as penetration enhancers by temporarilyopening intercellular tight junctions.

Name of the API	**Type of Nanoparticles**	**Composition**	**Pharmacological Effect**	**Reference**
Risperidone	SLN	Compritol 888 ATO, Pluronic F-127	Intranasal SLNs have demonstrated superior brain targeting and higher levels of drug absorption.	[62]

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Olanzapine	Polymer-based NP	Poly-lactic-glycolic acid	Higher drug concentration in the brain and sustained drug delivery.	[63]
Haloperidol	Polymer-based NP	poly(ethylene glycol), Poly(D,L)-lactic-co-glycolic acid,Lectin	The amount of drug transported to the brain via nanoparticles is substantially greater.	[64]
Haloperidol	SLN	Glyceryl Monostearate, Tween 80	In vitro drug release indicates controlled and sustained release profile of HP-SLNs with property to bypass BBB.	[65]
Olanzapine	Chitosan NP	chitosan,pentasodiumtripolyphosphate	Enhanced systemic absorption	[66]
Olanzapine	SLN	Tripalmitate, Stearyl amine, Tween 80	Sustained release of the OLZ, Enhanced drug delivery potential in the brain.	[67]

Liposomes

These are concentric vesicles in which a membranous lipid bilayer confines an aqueous volume. Phospholipids, either natural or manufactured, can build this bilayer. The size, surface charge, and number of bilayers of these liposomes are distinguishing features [68]. They are categorized as unilamellar vesicles (ULVs) or multi lamellar vesicles (MLVs), depending on the method of synthesis and post-formation processing. ULVs have a large aqueous core and are suitable for encapsulating drugs with hydrophilic structures, but MLVs are better for encapsulating pharmaceuticals that are lipid-soluble [69].

Because they can deliver both hydrophilic and hydrophobic medications and are biocompatible and nontoxic, liposomes have become one of the most popular nano-based delivery systems [70].Because they are smaller than cells, liposomes have a higher intracellular absorption capacity than other particulate systems. Nano-sized drug loaded systems can be administered via the nasal route in addition to other methods. Due to the formulation's strong vascularization, it bypasses the blood-brain barrier and is immediately delivered to the brain after nasal administration [32].Liposome administration through the nasal cavity has better brain penetration [71]. For improved systemic availability and targeting, liposomes are increasingly being investigated for the intranasal delivery of medications and vaccinations. The following are some instances of medications that have been administered via intranasal liposomes:

Name of the API	**Composition**	**Pharmacological Effect**	**Reference**
Olanzapine	l- _-phosphatidylcholine , acetonitrile, methanol, ethanol, Poloxamer 188 (Plx 188) , Poloxamer 407 (Plx 407).	Developed vesicles enhanced the brain delivery of olanzapine via the noninvasive intranasal route with 37.9% absolute bioavailability and 100% brain targeting efficiency.	[72]
Quetiapine Fumarate	Egg Phosphatidylcholine,Cholesterol	Prepared liposomes have better diffusivity & better potential to deliver drug to the brain. Higher brain uptake and distribution of QTF from liposomes.	[73]

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Risperidone	Soya phosphatidylcholine (SPC), cholesterol, stearylamine (SA), distearylphosphatidylethanolamine-mPEG- 2000	High absolute bio availability, Less clearance rate & High mean residential time.	[74]
Olanzapine	phosphatidylcholine (PC), Cholesterol	Controlled drug release	[75]

Polymeric Micelles Based Drug Delivery System-

Hydrophobic medications can be encapsulated within the micellar core of polymeric micelles, which are spherical nanostructures made of a hydrophobic core and a hydrophilic shell generated by the self-aggregation of polymeric amphiphiles in aqueous medium above the critical micelle concentration (CMC) [76].Due to their intriguing properties, such as biocompatibility, low toxicity, core shell organization, micellar association, shape, nano size, and relatively high stability, polymeric micelles are employed in drug delivery [76]. Different mucosal administration methods, such as intranasal administration, have been examined to boost the bioavailability of hydrophobic medicines using polymeric micelles [77].The incorporation of significantly larger medication levels, longer blood circulation times, and thermodynamic stability are all benefits of mixed polymeric micelles. The polymeric micelle core has been engineered to have the greatest drug loading capacity and longevity.Depending on the polymer's chain size, different nanomicelle preparation methods may be used.For the creation of nanomicelles, two techniques can be used: (1) direct dissolution (2) Solvent casting.There are three different types of solvent casting techniques: Dialysis, oil in water (o/w) emulsion, and solution casting are the first three methods. The ability of polymeric micelles to load drugs is primarily influenced by the length of hydrophobic blocks and the type of substituents present in the core [78].By blocking multidrug transporters like Pglycoprotein, polymeric micelles made of pluronic 123 (P123) and TPGS have the potential to increase cargo movement across the BBB (P-gp). Additionally, poloxamers like Kolliphor®P407 (P407) have the capacity to speed up the dissolution of hydrophobic drugs even in distilled water [79].

Overview of Polymeric Micelles Based Drug Delivery of Antipsychotic drug:

Name of the API	Composition	Pharmacological Effect	Reference
Clozapine	Pluronic L 121, pluronic P 123	Formation of Kinetically & Thermodynamically stable micelles with ability to transport significant fraction of Clozapine directly to the brain	[80]
Lurasidone hydrochloride (LH)	Gelucire 44/14, Pluronic F127, Carbapol-940	Mixed micelles improved the brain distribution as well as kinetics of lurasidone via intranasal route.The developed micelles shown better permeability and brain bioavailability.	[81]
Clozapine	Tetronic 904, Tetronic 701, Synperonic PE/F127	Formation of stable micelles with good nasal tolerability & have the ability to increase CLZ solubility. It also shown good permeation behavior with fivefold higher flux when compared to CLZ suspension	[82]
Clozapine	Poloxamer P 407, HPMC, Glycerin, Carbopol	BinaryPS80-P407 mixed micelles were more thermodynamically stable and rigid due to the higher synergismof both surfactants. However, binary mixed PS20-P407 micelles showed better drug permeation acrossthe nasal mucosa tissue.	[83]
Olanzapine	Pluronic 123, Kolliphor P	Current study demonstrates the feasibility of theproposed PM to improve the	[84]

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	407,Tween 80, d-_-tocopheryl polyethylene glycol 1000 succinate (TPGS) ,Kolliphor TPGS	therapeutic outcome of OZ in schizophrenic rats compared toIV drug solution. In addition, the OZ–PM showed less extrapyramidal side effects due tothe lower systemic biodistribution than the OZ–IV solution.	

Nanosuspension

Nano suspensions are biphasic dispersion systems made up of a medication dispersed in an aqueous medium with particles no larger than 1 m in size. For improving the solubility and bioavailability of pharmaceuticals manufactured using a number of techniques, including melt-emulsification, precipitation, micro emulsion, milling processes, and high pressure homogenization, nano suspension is a particularly effective strategy. Due to their capacity to increase the absorption and bioavailability of numerous poorly soluble medicines by intranasal administration, nano suspensions (NS) hold significant potential for nose-to-brain medications[85, 86].Because of their wide surface area and small particle size, NS have certain advantages for improving the solubility and dissolving rate of pharmaceuticals that aren't easily soluble. However, due to accelerated mucociliary clearance, liquid suspensions have short retention periods in the nasal cavity. The use of intelligent stimuli-responsive systems can solve this issue [87].

Name of the API	Composition	Therapeutic Activity	Reference
Zotepine	Pluronic F-68, Pluronic F-127 and Vitamin E-TPGS,Hydroxypropyl methyl cellulose (HPMC)-E15 and Soya lecithin (SL),Tween 80	NS prepared by combination technique was physically more stable than sono precipitation method with increased drug concentration in the brain	[88]
Clozapine	Alpha-Tocopherol Polyethylene Glycol 1000 Succinate (TPGS), Polyvinylpyrrolidone (PVP) K-30	Enhanced drug absorption &increased Clozapine concentration in the brain.	[89]

Dendrimers

Branching macromolecules known as dendrimers have precisely regulated size and shape. These are created through polymerization from monomers, either through convergent or divergent growth [68].These hyper branched polymers are viewed as desirable drug carriers due to their ordered three-dimensional architecture and wide surface functionalities [90, 91].Drug molecules may be affixed to the surface groups of dendrimers or incorporated therein. On the dendrimer surface, several functional groups can accommodate medicinal compounds and medicines [92, 93].Cascade molecules and arborols are other names for dendrimers.Haloperidol has been demonstrated to be more widely distributed in the brain and plasma after the synthesis of PAMAM dendrimers of the water-insoluble medication. Furthermore, 6.7 times lower doses of the dendrimer-haloperidol formulation given intravenously caused behavioral reactions similar to those brought on by haloperidol formulations given intraperitoneally [94].

II. CONCLUSION:

The advantages of IN delivery in experimental animals employing specialized delivery methods such nanoparticles, liposomes, polymeric micelles, dendrimers, mucoadhesivenanoemulsions etc. are strongly

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supported by evidence, notwithstanding the paucity of investigations on the IN delivery of conventional antipsychotic drugs in people. Following the administration of PLGA and solid lipid nanoparticles with diameters < 150 nm, drug concentrations in the CNS were sustained. The direct nose-to-brain transfer that occurs after IN administration has been related to the advantages of such persistent concentrations. Numerous investigations found significant behavioral effects, and pharmacokinetic data suggested that direct nose-to-brain transfer is the most plausible mechanism for the delivery of antipsychotic drug.

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