

# Nose-to-Brain Drug Delivery: An Update on Clinical Challenges and Progress

Purushottam Gangane<sup>1,\*</sup>, Nikita Raulkar<sup>1</sup>, Nikita Wagh<sup>1</sup>, Vijaya Rabade<sup>2</sup>, Harigopal Sawarkar<sup>3</sup>

<sup>1</sup>Department of Pharmaceutics, Dadasaheb Balpande College of Pharmacy, Nagpur, Maharashtra, INDIA.

<sup>2</sup>Department of Pharmacognosy, Dadasaheb Balpande College of Pharmacy, Nagpur, Maharashtra, INDIA.

<sup>3</sup>Department of Pharmaceutical Chemistry, Dr. Rajendra Gode College of Pharmacy, Amravati, Maharashtra, INDIA.

## ABSTRACT

In 1987 James Parkinson first describes Parkinson's Disease (PD) as a neurological syndrome. Over ten million people worldwide suffer with PD. The exact quantity of people suffered with PD is difficult to calculate because many people are not diagnosed in the early stages of the disease. As people age, they are more probable to develop PD. After Alzheimer's disease, it's the second utmost common age-related neurodegenerative condition. PD is a common prevalent neurological illness that causes significant disability. Dopaminergic neuron malfunction in the substantia nigra compacta characterizes the diseased condition. The cardinal clinical symptoms of akinesia, stiffness, tremor and autonomic dysfunction distinguish it. Oral medications may lose their effectiveness in the treatment of PD because a number of factors such as dysphagia, impaired absorption from the gastrointestinal tract and delayed stomach emptying. Intranasal therapy may be considered to alleviate this problem. As a new approach to treating central nervous system disorders, the intranasal route of medication administration is being explored. It is a novel delivery method that may circumvent these issues, allowing Glial cell line-Derived Neurotrophic Factor (GDNF) to reach the brain and halt the progression of PD. Different nanocomposites can be delivered intranasally to treat PD.

**Keywords:** Parkinson's disease, Nasal cavity, Nose-to-brain drug delivery.

## Correspondence:

**Dr. Purushottam Gangane**

Associate Professor, Department of Pharmaceutics, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur, Maharashtra, INDIA.  
Email: p.gangane@gmail.com

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## INTRODUCTION

The second most frequent neurological disease is PD.<sup>1</sup> Dopaminergic neurons are damaged or lost in PD.<sup>2</sup> According to the PD Foundation, it affects around 7 to 10 million individuals worldwide. The percentage of PD cases is expected to increase significantly as the global problem of the aging population impacts most countries and regions at different phases of development.<sup>3-5</sup> Tremor, bradykinesia, stiffness and postural instability are the most common symptoms. PD is currently diagnosed using a clinical method that detects the presence of akinesia as well as at least one motor neuron symptom other than aftershock, toughness, or autonomic dysfunction.<sup>6-8</sup> Age is the single most reliable risk factor and the presence of PD will increase continuously in the future as the general aging population.<sup>9</sup> Both patients and healthcare providers have numerous obstacles when it comes to managing Parkinson's disease. Despite receiving

adequate pharmacological treatment, many people with PD are seeing an increase in motor and non-motor symptoms.<sup>10,11</sup>

## Nasal Cavity: Anatomy, Physiology and Histology

In humans and other animals, the nasal mucosa primarily helps in breathing and olfaction.<sup>12</sup> These tasks are performed by the mucus layer as well as the hairs that line the nasal passage which prevents intranasal molecules and microorganisms from entering inside. Apart from the resonant frequency of generated noises, inhaled structures also perform important functions such as mucosal cells, immune response actions and endogenous chemical respiration.<sup>13-17</sup> The surrounding bones, maxillary and inferior conche bones support the human nasal cavity above it and sideways, it is located between both the base of the spine and nasopharynx<sup>13</sup> shown in Figure 1.

The middle sternum divides the human nose into regularly spaced halves, each begins at the face via nasal passages and extends posterior aspect to the nasal cavity. The four areas nasal vestibule, atrium, respiratory region and olfactory region that include both symmetrical halves and are distinguished by their anatomical and histological characteristics. The respiratory system of a human has an overall amount of 15-20 mL as well as an increased surface area of around 150 cm<sup>2</sup>.<sup>18,19</sup>



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## Nasal Vestibule

It is found in the upper part of a nasal cavity, inside the nostrils. It has an area of approximately 0.6 cm<sup>2</sup>. It contains respiratory hairs located in the nasal vestibule, screen the intranasal particles. It has an epithelium and hypodermis epidermis, as well as sweat gland.<sup>15,17,20</sup> Substance absorption, including drug absorption, becomes extremely hard within that area.<sup>21</sup>

## Atrium

The space between the nasal vestibule and the respiratory region is known as the atrium. In the anterior section, it has a squamous cells epithelium and in the posterolateral portion, there are pseudostratified cells with microvilli.<sup>15,16</sup>

## Respiratory Region

The respiratory area occupies the majority of nasal cavity. To ensure that the inhaled air makes complete contact with the respiratory mucosal surface, there are spaces between them known as meatus, which are passageways where airflow is generated.<sup>22</sup> The epithelial tissue, the inner membrane and the stroma contain the nasal respiratory mucosa, pseudostratified epithelium cells, goblet cells, basal cells, mucus layer glands and serous glands that make up the nasal respiratory epithelium.<sup>13,15,18</sup> The large bulk of endothelial cells have microvilli on their anterior membrane, as well as fine projections known as cilia.<sup>16</sup> The thickness of the nasal mucus layer is only 5 micrometers and it is separated into 2 layers: one viscous and dense on the outside and fluid and serous on the inside. The mucus layer in the nose comprises 95% liquid, 25-35% mucus and 2% ions, proteins, fats, enzymes, antibody, sloughed epithelial cells and bacterial products.<sup>23-25</sup>

## Olfactory Region

It is located at the top of the nasal cavity and continues for a short distance along with the membrane and anterior part.<sup>16</sup> The olfactory epithelium is pseudostratified, it contains specific sensory receptors cells that are essential for scent detection.<sup>16,26</sup> Small serous glands (Bowman glands) are also present in this area.<sup>16,18</sup>

## Intranasal Drug Delivery

The peripheral route of medication administration is used in many of the known treatments for Parkinson's disease and other CNS illnesses (oral and intravenous route). A major disadvantage of peripheral drug delivery is the lack of availability of therapeutic agents or active ingredients from the blood supply to the brain.<sup>27-30</sup> It could be due to the influence of the BBB, which protects the brain from injury by preventing virtually all medication molecules, many phytochemical constituents, proteins, peptides and other big compounds from entering the brain, thereby protecting it from harm.<sup>31</sup> Simultaneously, the first pass effect and enzyme breakdown (internal delivery) as well as systemic clearance (oral and intravenous routes) limit

drug bioavailability significantly.<sup>29</sup> In the midst of all of these challenges, the intranasal route offers a pleasant and simple way to cross the Barrier and transport medications directly to the brain from nasal passage.<sup>16,32-35</sup> The intranasal route of brain medication administration, according to several hypotheses and research, overcomes the constraints of systemic delivery and speeds up a drug product delivery. Intranasal delivery, on either hand, is noninvasive and beneficial for treating CNS diseases.<sup>36-41</sup> Although intranasal drug delivery to the circulatory system and for topical therapy is favored, researchers are concerned around its use for direct brain medication delivery.<sup>42,43</sup> William H. Frey II advocate intranasal administration of therapeutic active ingredients directly into CNS in 1989.<sup>44-47</sup> Intranasal medication delivery is now established as a viable and effective alternative to oral and intravenous procedures.<sup>48</sup>

## Nose to Brain Drug Delivery Mechanism

Drug molecules must get to brain via two principle routes: a) the neural route (a major pathway) and b) systemically bloodstream via the BBB (minor pathway). Trigeminal sensory neurons are also found in the respiratory region, which is vascularized with blood vessels.<sup>16,49-55</sup> The blood vessels in the respiratory area boost absorption of the drug into the circulatory system, whereas trigeminal neurons transport the drug from nasal cavity to the cerebrum and to a lesser extent the olfactory and frontal brains.<sup>49,56,57</sup> The olfactory area is placed on the anterior surface of the nasal cavities and covers the inferior surface of the medial portion of the temporal bone. The area is little (10 cm<sup>2</sup>) but, its proportion is differed by species: for humans, it is only 10% of the total area, whereas in rats (a common model for nasal delivery study), it can be up to 50%.<sup>27,58</sup> The majority of the cells are supporting cells, microvilli cells, basal cell and olfactory receptor neurons with a small number of trigeminal neurons. The lamina propria contains blood veins, lymphatic network, Bowman's gland, perivascular spaces, axons and connective tissues beneath the olfactory and respiratory epithelium.<sup>59-61</sup>

The olfactory neural pathway is thought to be one of the most important intranasal medication absorption channels to the brain<sup>64</sup> shown in Figure 2. When drug enters the nasal cavity, it is cleared by the mucus system in the sensorimotor area.<sup>48</sup> The medication then enters the sinus cavity posterior portion, where it comes into contact with respiration and sensory areas. Drugs are delivered to a brain in this region via a number of pathways, including the sensory neurons pathway, the neurogenic pathway, the lymph and vascular pathways and CSF. The precise technique of delivering drugs from the nasal passage to the brain has sparked much debate among investigators. It can also have one drug carrier pathway or a combined effect of the drug transport pathways listed above. The type of drug transport pathway chosen is determined by the nature of drug, quantification criteria, physiological state, the type of delivery device and other. Irrespectively, the sensory neurons pathway and the trigeminal

nerve pathway continue to become the most essential pathways for delivery of drug from the nose to brain.<sup>62</sup> Medication reaches the lamina propria and the brain due to intra- and extracellular transport mechanisms. After reaching the submucosa, the drug crosses the lamina cribrosa of the ethmoid bone and needs to enter the interstitial fluid and sensory bulb via the nerve channel formed by olfaction enciphering molecules.

The drug combined with interstitial fluid and distributed throughout the brain by bulk flow after it enters in the cerebrospinal fluid as shown in Figure 3. The medication quickly spreads all across the central nervous system via periventricular regions once it enters the brain. This is also known as perivascular transport. It also happens in the nasal mucosa for medication delivery to the brain. Furthermore, the same mechanism is used to remove medications and other soluble compounds from the CNS to a peripheral system in the opposite manner. Furthermore, medication molecules absorbed by the nasal capillaries enter the pulmonary circulation where they cross the BBB (small lipophilic drug compounds) to reach the brain area.<sup>63-65</sup>

### Cellular Transport

As a result of drug transfer from the pulmonary epithelial and sensory region via trigeminal nerve and olfactory nerve, drug molecules are delivered to several parts of the brain, including the cerebral lobe, nucleus accumbens, cerebrum and cerebral cortex.<sup>66-68</sup> Intracellular and extracellular drug transport are two types of cellular drug transport systems. The intracellular mechanism includes the internalization of molecules by a sensory neuron, transportation of the endocytosis vesicles inside the membrane to the photoreceptor discharge region and eventually release through secretory vesicles. The drug enters the extracellular pathway by passing through the nasal mucosa and reaching the lamina propria, where bulk flow mechanisms transfer it external running the length of the neuronal axons. The axon penetrates the Central nervous system, in which the medicine is even further distributed by liquid flow.<sup>62</sup>

### Barriers to Clinical Application

To enhance permeation and absorption of drug, the addition of permeation enhancers, regulated delivery methods, dispersion of drug in carrier and other innovative strategies have been applied.<sup>69-73</sup> Nasal mucosa irritation is unpleasant. As a result, the selected medications are used in intranasal drug delivery formulations. It is possible to evaluate the inhaled toxic effects of treatments and inactive ingredients, particularly for drugs used to treat chronic conditions.<sup>74-76</sup>

### Drug particles for PD therapy: Towards therapeutic application

Researchers are working in this approach to develop a unique strategy for successful administration of neurotherapeutics

because the obstacles associated with intranasal medication delivery intrigue them.<sup>77,78</sup> Nanotechnology is the most appropriate and useful approach for this. As fresh study discoveries emerge, it is obvious that nanotechnology will improve the health-care system by delivering simple and effective diagnostic and treatment approaches. Because of their small size, low toxicity, biodegradability and soluble nature, nanoparticle-based medicines have emerged as a viable therapy for brain disease and disorder. When compared to traditional therapy, nanoparticles cause substantially less brain toxicity.<sup>79</sup> Nanoparticles can cross the BBB via transcytosis pathway by binding the surface of endothelial cells through two different mechanisms. One of which is adsorptive transcytosis, in this, drug loaded nanoparticles binds to the luminal plasma membrane of endothelial cells due to its modified surface properties. As compared nanoparticle with the non-ionic and anionic charge, nanoparticles bearing cationic charge are more prone to transcytosis, because the endothelial cell plasma membrane is negatively charged. Another mechanism is receptor-mediated transcytosis, where nanoparticles attached with different ligands on their surface are able to bind specific receptors and thus promote endocytosis. Apart from this nano size of this type drug delivery also promote the entry of the drug via BBB.<sup>79</sup>

### Intranasal drug delivery systems used to treat Parkinson's disease

#### Ropinirole-containing nanoparticles

Ropinirole is a dopamine agonist. It works by replacing dopamine, a natural molecule found in the brain that regulates movement. Omidreza Jafari *et al.* developed ropinirole-loaded mucoadhesive nanoparticles for intranasal administration to the brain. The goal of this investigation was to see the efficacy of polymeric nanoparticles to target ropinirole to the brain.<sup>80</sup> The ionic gelation approach was used to prepare ropinirole-loaded chitosan nanoparticle.<sup>81</sup> The researcher concluded that when nanoparticulate ropinirole hydrochloride was administered intranasally, it showed a sustained release effect up to 18 hr when compared to the intranasal administration of ropinirole hydrochloride solution. It was concluded that chitosan nanoparticles deliver more drug to the target site, resulting in higher absorption.<sup>80</sup>

#### Ropinirole loaded polyelectrolyte complex

Kulkarni A. *et al.*, used N,N,N trimethyl chitosan and dextran sulphate to prepare a polyelectrolyte complex of ropinirole hydrochloride.<sup>82</sup> They prepared a polyelectrolyte complex by irradiation charged structural features of previous mucopolysaccharides at various pH levels (pH 5,8,10,12).<sup>83</sup> They found that in alkaline circumstances (pH 10) the trimethyl chitosan and dextran sulphate produced more persistent polyelectrolyte complexes.

### PLGA nanoparticles with ropinirole

Patil Ganesh, *et al.*, prepared and statistically optimized surface modified PLGA-nano molecules for nose to brain delivery of ropinirole hydrochloride.<sup>84</sup> The ropinirole-loaded nanoparticles were made using a modified nanoprecipitation process.<sup>85</sup> Which was then optimized by using 2<sup>3</sup> factorial design. The ropinirole-loaded nanoparticles showed sustained drug release over 24hr, which could help to reduce the number of recommended daily dosage, improving conformance and correcting peak-to-valley variations associated with the traditional treatment.

Aikaterini-Theodora Chatzitaki *et al.*, were synthesized a ropinirole hydrochloride loaded PLGA nanoparticles with chitosan coatings for nasal administration in order to maximize drug concentration at the site of action, in neurologic diseases such as PD. Mucoadhesive PLGA and PLGA/chitosan nanoparticles were prepared to transport ropinirole hydrochloride through the mucus layer and to avoid first pass degradation. Nanoprecipitation approach was used to formulate the PLGA nanoparticles. Over a 24 hr period, 100% drug release was achieved from ropinirole nanocarrier in a simulated nasal electrolyte solution and chitosan coated PLGA nanoparticles of ropinirole hydrochloride permeated into sheep nasal mucosa 3.22 times faster than uncoated PLGA NPs.<sup>86-88</sup>

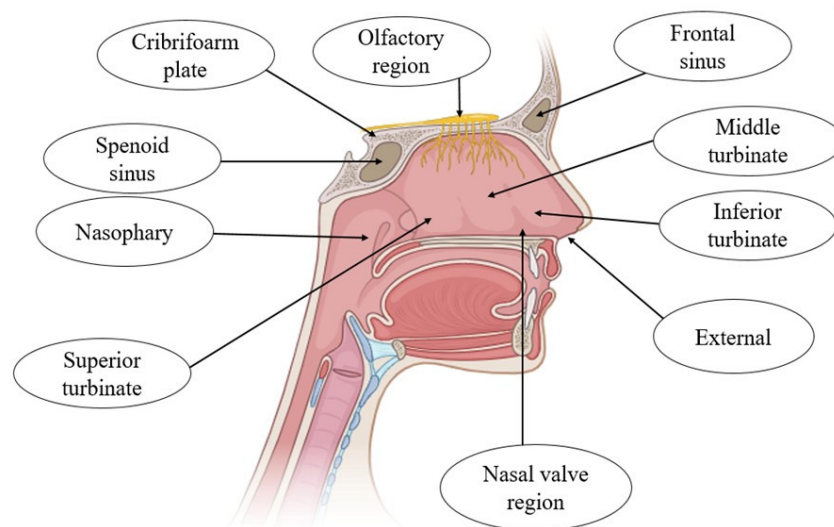
### Rasagiline-loaded chitosan nanoparticle

Rasagiline used to treat PD symptoms (stiffness, tremors, spasms). Rasagiline and levodopa might be used together on occasion. Deepti Mittal *et al.*, used chitosan glutamate with Tripolyphosphate

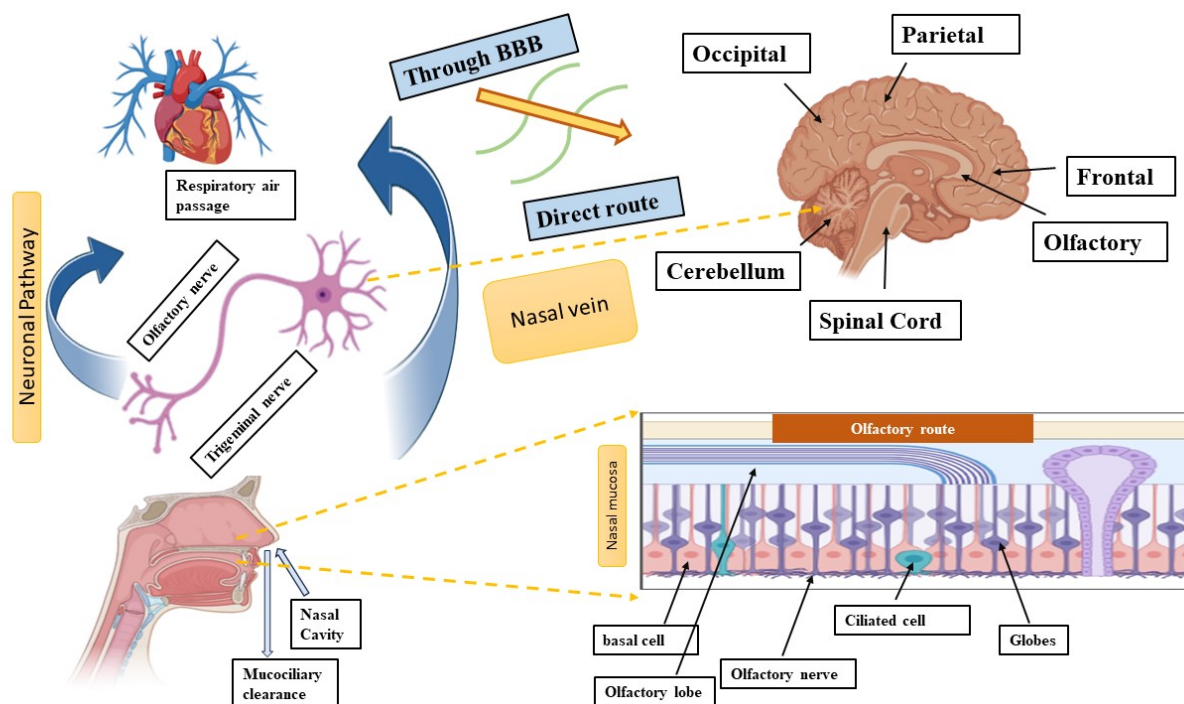
anions (TPP) to create Rasagiline-loaded Chitosan Glutamate nanoparticles (RAS-CG-NPs). Rasagiline-loaded nanoparticles were studied for *in vivo* biodistribution experiments in mice, which demonstrate the superiority of the developed formulation for the brain targeting over parenteral and intranasal solutions of drug. The produced nanoparticles had better release profiles than the nasal *in situ* gel delivery outcomes seen during the *in vitro* release research. Based on these data, it was suggested that RAS-CG-NP's could be a promising intranasal delivered strategy for the treatment of Parkinson's disease.<sup>89-91</sup>

To determine the Antiparkinson's effects, Vinay Sridhar *et al.*, prepared a pramipexole thermosensitive nasal gel and compared with an oral pramipexole solution. Within 8 hr, 95% of the medication was released across the goat nasal mucosa. A stiff gel was produced with 16% poloxamer 407 and 0.15% guar gum at 32-33°C. Authors concluded that, intranasal administered pramipexole gels successfully replace locomotor activity ratings, eliminated catalepsy, increased brain GSH and levels of dopamine and replace enzymes activity to average levels.<sup>92</sup>

Ruhi Raj *et al.*, prepared pramipexole dihydrochloride based chitosan nanocarriers for nose to brain administration. Pramipexole nanocarriers were made using the ionic gelation technique.<sup>89</sup> In comparison to other formulations; the *in vivo* pharmacodynamic investigation confirmed its brain targeting ability. The author concluded that pramipexole-based chitosan nanocarriers can be used for effective targeting of the brain via non-invasive nasal route for the treatment of PD.<sup>92,93</sup>



**Figure 1:** Nasal anatomy. (Created using BioRender)



**Figure 2:** The neural pathway mechanism (olfactory and trigeminal nerve) transport drugs from the nasal mucosa to the brain, A pathway is used to describe the systemic circulation (through BBB). The anatomy of the respiratory epithelium and olfactory nerves in the nasal cavity. (Created using BioRender)

### Rotigotine loaded nanoparticles

The clinical symptoms of PD are routinely treated with rotigotine transdermal patches. Subrat K *et al.*, developed rotigotine-based chitosan nanocarriers for intranasal delivery.<sup>94</sup> They employed an ionic gelation approach using chitosan and Tri-Polyphosphate to make rotigotine-based nanocarriers (TPP).<sup>95</sup> Using cell-based research, the researchers assessed its cerebral absorption, anti-oxidant and neurological activities. In a PD animal model, the therapeutic properties of rotigotine based nanocarriers for nasal to brain treatment transport were examined. In an animal model of PD, intranasally delivered rotigotine nanoparticles improved brain targeting and absorption of drug.

### Thermosensitive hydrogels with rotigotine-loaded polymer micelles

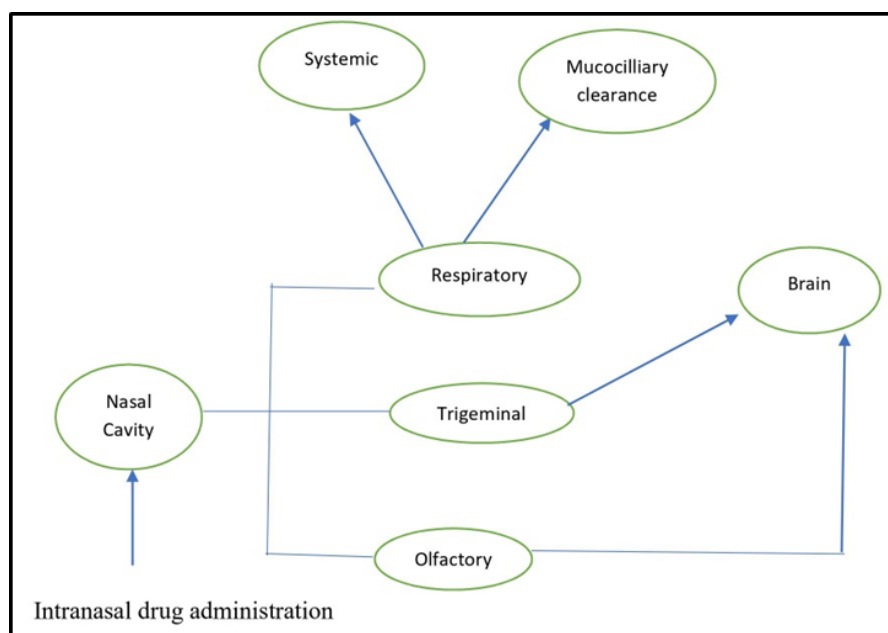
Fangyuan Wang *et al.*, developed a thermosensitive hydrogel with rotigotine-loaded polymeric micelles to improve drug solubility, prolong residence time and to increase drug concentration in brain tissue. This hydrogel formulation shows the sustained release properties and permeability analysis revealed that rotigotine could be delivered directly to the brain via nasal route. The nasal fibril and mucous membrane of rats showed no evident negative effects.<sup>96-98</sup> Levodopa nanoparticle incorporated thermo-reversible gel

In the therapy of PD, levodopa is a popular and successful medicine. Carbidopa is frequently used in conjunction with levodopa because it inhibits L-amino acid decarboxylase, the

enzymes that catalyses breakdown levodopa peripherally. It is co-administered with carbidopa because of its limited bioavailability and the fact that aromatic amino acid decarboxylase reduces it in peripheral motion. To address this issue, researchers looked into delivering levodopa to the brain via the trigeminal nerves and the olfactory system. Sumit Sharma *et al.*, prepared and characterized levodopa containing nanoparticles loaded in intranasal mucoadhesive thermo-reversible gel for delivery to the brain.<sup>99</sup> Ionic gelation approach was used for the preparation of levodopa-loaded chitosan nanoparticles, which was then incorporated into a Pluronic PF127 thermo-reversible gel. The cold method was used for gel preparation. *In vivo* studies showed a significant percentage of levodopa inside the brain. Also, the thermos-reversible gel system enhanced the residence time of the -drug delivery system in nasal cavity. Authors concluded that, if appropriately designed, the intranasal route may be considered a feasible option for nose to brain delivery.<sup>99,100</sup>

### Levodopa incorporated *in situ* nasal gel

Piyush Jangam *et al.*, developed and evaluated a pH induced *in vivo* nasal gel for levodopa brain targeting. To tackle the difficulty of mucociliary clearance, they created an *in situ* gel of levodopa with Carbopol 934 as a gelling agent to form a gel in the nasal pH and HPMC K4M as a Polymer with mucoadhesive properties. It was seen that pH-sensitive polymers Carbopol 934 and HPMC K4M increase drug residence time preventing drug draining and allowing the medication to be released for a longer period of time. As a result, it inhibits first-pass metabolism and acts as a



**Figure 3:** Nasal drug pathway.

**Table 1:** List of medication approved for treatment of Parkinson's disease in USA.

Sl. No.	Generic name	Trade name	Mode of action	Side effects
1.	Carbidopa-levodopa	Sinemet	DOPA decarboxylase inhibitor	Nausea, dizziness, orthostatic, hypotension, dyskinesia.
2.	Carbidopa-levodopa (controlled release)	Sinemet CR	DOPA decarboxylase inhibitor/DA precursor	Nausea, dizziness, orthostatic, hypotension, dyskinesia, hallucinations, somnolence.
3.	Carbidopa-levodopa (orallydisintegrating tablet)	Parcopa	DOPA decarboxylase inhibitor/DA precursor	Nausea, dizziness, orthostatic, hypotension, dyskinesia, hallucinations, somnolence.
4.	Carbidopa-levodopa (extended release capsules)	Rytary	DOPA decarboxylase inhibitor/DA precursor	Nausea, dizziness, orthostatic, hypotension, dyskinesia, hallucinations, somnolence.
5.	Carbidopa-levodopa (enteral suspension)	Duopa	DOPA decarboxylase inhibitor/DA precursor	Nausea, dizziness, orthostatic, hypotension, dyskinesia, hallucinations, somnolence.
6.	Levodopa inhalation powder	Inbrija	DA precursor	Nausea, dizziness, orthostatic, hypotension, dyskinesia, hallucinations, somnolence.
7.	Entacapone	Comtan	COMT inhibitor, inhibits breakdown of levodopa	Nausea, dizziness, orthostatic, hypotension, dyskinesia, hallucinations, somnolence, diarrhea, discoloration of body fluid.
8.	Tolcapone	Tasmar	COMT inhibitor, inhibits breakdown of levodopa	Nausea, dizziness, orthostatic, hypotension, dyskinesia, hallucinations, somnolence, diarrhea, discoloration of body fluid.
9.	Opicapone	Ongentys	COMT inhibitor, inhibits breakdown of levodopa	Nausea, dizziness, orthostatic, hypotension, dyskinesia.
10.	Carbidopa / levodopa entacapone	stalevo	DOPA decarboxylase inhibitor / DA	Nausea, dizziness, orthostatic, hypotension, dyskinesia, hallucinations.
11.	Pramipexole	Mirapex	DA agonist	Nausea, orthostatic, swelling of ankle, dyskinesia, confusion, somnolence, sleep attacks, control disorders.
12.	Pramipexole (extended release)	Mirapex ER	DA agonist	Nausea, orthostatic, swelling of ankle, dyskinesia, confusion, somnolence, sleep attacks, control disorders.

13.	Ropinirole	Requip	DA agonist	Nausea, orthostatic, swelling of ankle, dyskinesia, confusion, somnolence, sleep attacks, control disorders.
14.	Ropinirole (extended release)	Requip XL	DA agonist	Nausea, orthostatic, swelling of ankle, dyskinesia, confusion, somnolence, sleep attacks, control disorders.
15.	Apomorphine (injection)	Apokyn	DA agonist precursor/COMT inhibitor	Nausea, orthostatic, swelling of ankle, dyskinesia, confusion, somnolence, sleep attacks, control disorders. somnolence, diarrhea, discoloration of body fluid.
16.	Apomorphine (sublingual film)	Kynmobi	DA agonist	Mouth irritation, swelling, nausea, dizziness, sleepiness.
17.	Rotigotine (transdermal patch)	Neupro	DA agonist	Nausea, dizziness, orthostatic, hypotension, swelling of ankles.

**Table 2: The list of FDA approved drugs for Parkinson's disease.**

Sl. No.	Trade name	Dose	Side effects
1	Apokyn	Subcutaneous dose of 0.2-0.6 mL during acute hypomobility episodes via metered injection pen.	Yawning, dyskinesia, rhinorrhea, hallucination, inflammation.
2	Comtan	Not exceed 1600 mg/day	Dyskinesia, nausea, diarrhea, abdominal pain, urine discoloration.
3	Duopa (carbidopa and levodopa) enteral suspension	Maximum recommended daily dose of duopa is 2000 mg of levodopa administered over 16 hr.	Complication of device insertion, nausea, depression, peripheral edema, hypertension, upper respiratory tract infection, oropharyngeal pain.
4	Exelon (rivastigmine tartrate)	4.6 mg/24 hr or 9.5 mg patch designed for transdermal administration	Anorexia, weight loss, anxiety, headache, diarrhea, nausea.
5	Gocovri (amantadine)	137 mg-274 mg It is a sublingual film. It must be administered whole 10 mg-30 mg/per dose.	Hallucination, dizziness, dry mouth, peripheral edema, constipation, orthostatic hypotension.
6	Selegline tablets	10 mg/ day	Dizziness, lightheadedness, fainting, dry mouth, nausea, vomiting, stomach pain, difficulty swallowing.
7	Xadago (safinamide)	50-100 mg/day	Dyskinesia, sleep disorder, nausea, dystonia, anorexia, somnolence, excessive dreaming, muscle cramps

target drug delivery system, delivering drug to the brain via nasal mucosa and bypassing the BBB. It demonstrated its superiority over traditional dosage forms and increasing bioavailability with lower doses.<sup>101</sup>

### Bromocriptine-loaded chitosan nanoparticle

Bromocriptine is a dopamine receptor agonist prescribed for PD. Bromocriptine loaded chitosan nanoparticles were prepared by Shadab Md *et al.*, for direct nose to brain administration. Following oral administration, bromocriptine is expected to be easily absorbed but incompletely metabolized in the

liver. Pharmacodynamic, pharmacokinetic and scintigraphy studies were carried out using mice model. Ionic gelation was used to make bromocriptine-loaded nanoparticles. They concluded that the resultant nanoparticles improved brain uptake of bromocriptine-loaded nanoparticles and increased bromocriptine's antioxidant action after intranasal delivery.<sup>102</sup> The nano formulation of bromocriptine was optimised by Shadab *et al.*, for direct passage from nose to brain. They developed an analytical method for identifying bromocriptine and its nanoparticulate in brain plasma by using Ultra-High Performance Liquid Chromatography/Mass Spectrometry (UHPLC/MS).

Higher absorption of nanoparticulate formulation following intranasal delivery has been observed due to the olfactory and trigeminal nerve pathways.<sup>103</sup>

### Bromocriptine loaded niosomes

V.G. Sita *et al.*, prepared niosomes of bromocriptine mesylate and non-ionic surfactant from nose to brain transportation.<sup>104</sup> The ethanol injection method was used for the niosomes preparation.<sup>102</sup> The stable niosomes were tested for *in vitro* drug release study and compared with bromocriptine mesylate suspension for *ex vivo* mucosal penetration on goat nasal mucosa up to 24 hr. According to the pharmacokinetic findings, intranasal niosomes had superior brain relative bioavailability whereas oral niosomes had higher relative plasma bioavailability. This was accompanied by better pharmacodynamic effects and less decomposition stress. Niosomal formulations did not cause noticeable changes in morphological, haematological, or histological exams in a 28-day subclinical repeated dose trial in rats, demonstrating their safety and lack of toxicity.<sup>105</sup> Table 1 shows drugs approved for the treatment of Parkinson's disease in the USA and the Table 2 shows FDA approved drugs for Parkinson's disease.

### CONCLUSION

It's difficult to get a medicine into the brain through oral delivery. The quick metabolism, excretion and the first pass metabolism are the key causes for less oral bioavailability and limited the brain exposure. The limited brain penetration of the chemicals is due to the fact that they must pass across the BBB, which shields the brain from toxic compounds. Nasal medication delivery is one of the favorable options for crossing the BBB and avoiding hepatic first-pass metabolism to overcome this problem. The researchers are currently concentrating their efforts on building a viable IN drug delivery system, as an intranasal administration of medications typically has higher bioavailability, fewer adverse effect and results in advanced brain revelation than oral drugs. The majority of clinical trials are presently in the preliminary or initial clinical phases, with successful claims still dependent on rodent model responses. If clinical trials back up the preclinical findings, IN medication delivery could usher in a new era of Parkinson's disease treatment.

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### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

### ABBREVIATIONS

**PD:** Parkinson's disease; **GDNF:** Glial cell line-Derived Neurotrophic Factor; **%:** Percent; **BBB:** Blood Brain Barrier; **hr:** Hour; **mL:** Milliliter; **CNS:** Central Nervous System.

### SUMMARY

Parkinson's Disease (PD) is as a neurological syndrome and the present review focus on the formulation of various nanodrug delivery systems for the management and treatment of PD. This review mainly covered the study of various research work done on nose to brain drug delivery for the treatment of PD. In order to design nose to brain nano drug delivery system understanding of anatomy and physiology of the nasal cavity and the mechanism of transportation of drug to brain is important, so it included in this article. Olfactory neural pathway and trigeminal nerve pathway are more prominently involved in nose to brain drug delivery of drug. This review provided the information about the type of drug delivery systems developed and the techniques adapted for its preparations. This review also includes the examples of medications approved for the treatment of PD. So, this review will be helpful for the researchers.

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