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Intranasal Drug Delivery: Novel Delivery Route for Management of Parkinson's and Depression Neurological Disorders

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Abstract: Neurological disorders are increasing worldwide due to the rapidly aging population, which increases healthcare costs. Drug delivery to the brain is challenging because of the brain's anatomy, and orally administered drugsare mostly unable to cross BBB. Intranasal (Nose to Brain) administration of drugs is one novel approach to address this challenge. Intranasal delivery has appeared to evade the blood-brain barrier (BBB) and deliver the drug into the CNS at a higher rate and degree than another traditional route. Transport of drugs from the nasal cavity to the brain along with olfactory and trigeminal nerves. The purpose of this review is drug delivery by the intranasal route for treating neurological disorders like Parkinson's and depression because drug delivery by other routes is unable to cross BBB. Still, delivery through the intranasal route by using the nanotechnology approach is possible to deliver the drug directly to CNS.

Keywords: intranasal; Parkinson's; depression; nanocarrier; nose to the brain.

1. Introduction

The nasal pathway is a non-invasive administration route of active pharmaceutical ingredients for local, systemic, and CNS action. Intranasal drug delivery is a very conventional route for drug delivery from nose to the brain to treat neurological disorders [1]. Neurodegenerative disorder (ND) is a term used for conditions that affect the nervous system. ND results in damage to nerve cells of the nervous system, and damage causes chronic, progressive loss of neurons which causes decreasing cognitive abilities of the brain [2]. Nerve cells regulate our bodies with a response. Most degenerative nerve diseases are like Parkinson's, Alzheimer's disease, Depression, Huntington's disease are the most propagated diseases in the elderly population of developed and developing countries, and most are not easily cure. All of these have similar cellular progression; they present with different clinical features. For example, Huntington disease the main cause of this disease is a genetic modification that leads to severe motor restriction and eventually death [3]. Another one is Parkinson's disease due to the depletion of dopamine at the brain's basal ganglia, which is

responsible for stiffness, rigidity, and tremors in the body's major muscles [4]. It is challenging for drug delivery to the central nervous system (CNS) because of the brain's anatomy [5]. The various types are drugs discovered for the treatment of CNS disease, but the clinical potency of any therapeutic agent is not only dependent on its bioavailability its depend on its ability to penetrate the protective layer, i.e., cerebrospinal fluid (CSF) and blood-brain barrier (BBB) which are the major obstacles for therapeutic agents which are used in the treatment of CNS because they restrict the entry of hydrophilic and large lipophilic molecules to the brain [6]. Therefore, the physicochemical properties of active therapeutic molecules and formulation for brain drug delivery are considered while designing any drug-delivering mode. Various techniques like intravenous, intrathecal, intraparenchymal are used and chemical modification, prodrug approach or antibody are used to increase drug targeting to CNS. Nose to Brain drug delivery has gained the interest of researchers as a potential delivery route for targeting the brain because of the Linkage between brain and nose by the olfactory route and by peripheral circulation [7]. The nose is the only organ for direct contact with the brain. Absorption of the molecules through the trigeminal and olfactory pathways from the nasal cavity provides a direct entrance to the brain, which executes the therapeutic effect of CNS-acting drugs [8]. This enhances therapeutic efficacy by circumventing hepatic circulation and reduces the systematic toxicity of centrally acting drugs. The nasal route has several advantages over oral or intravenous routes, including self-administration, shorter time onset of action, avoidance of hepatic first-pass metabolism, and bypassing the BBB may potentially increase the central nervous system (CNS) availability of the drug [9].

1.1. Anatomy of the nasal cavity.

In humans and animals function of the nasal cavity is not only breathing but also offers a protective function by filtering the air before reaching terminal alveoli; the other function is greater permeation from nasal mucosa [10]. The oral cavity and nasal cavity are separated from each other by the palatine bone. The total area of both nasal cavities is ~150–160 cm^2 [11]. The respiratory, olfactory, and vestibular regions are different parts of the nasal cavity involved in the different delivery routes of drug molecules. The first region is vestibular; it is most anterior and located immediately at the nostril opening; its surface area is around 0.6 cm^2 and contains nasal hairs that filter inhaled particles. This region has the largest area at ~130 cm^2. The respiratory region covers the lateral walls of the nasal cavities, including the three projecting turbinates (lower, middle, and upper nasal turbinates). The other is the olfactory region; in the olfactory region, the olfactory bulb and nerves are responsible for olfaction function through neuroepithelium cells [12].

1.2. Pathways for intranasal drug delivery.

Based on current research, the pathways for the nose to brain drug delivery are olfactory neuronal pathways and trigeminal nerve pathways; the other is pathways involving CSF, vasculature, or lymphatic system [13]. Intranasal drug delivery may occur by either one or combined pathways (Figure 1).

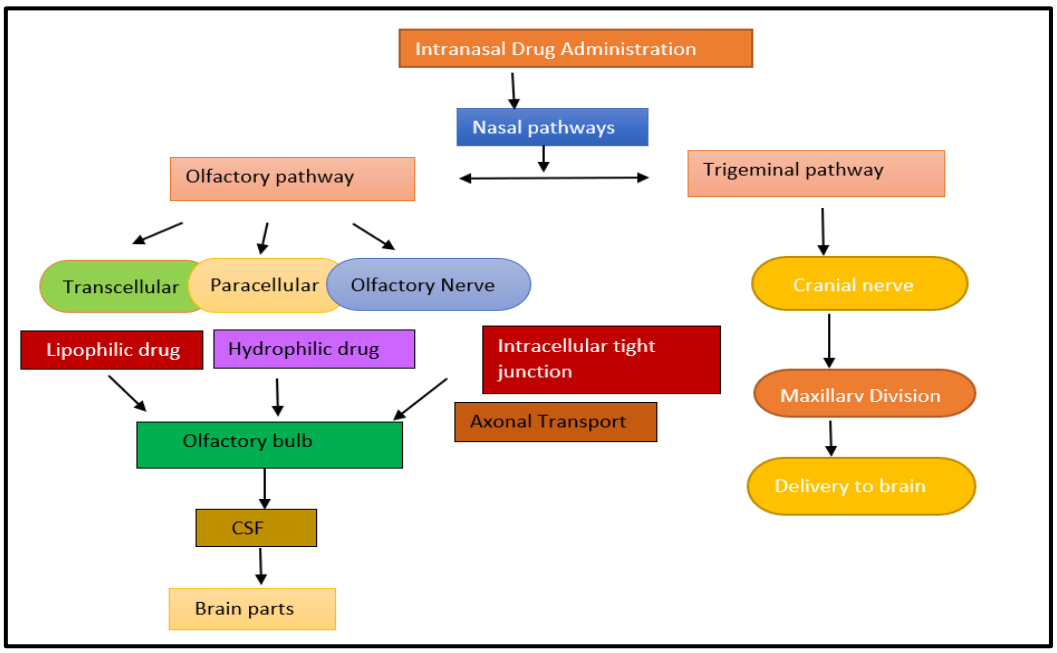

Figure 1. Pathways for intranasal drug delivery.

1.2.1. Olfactory neuronal pathways.

These are the most prevailing pathways of intranasal drug absorption to the brain; the delivered drug needs to cross the olfactory epithelium consumed by olfactory neurons. The movement is managed in three ways, paracellular movement or endocytosis and passive diffusion by neuronal cells. Lipophilic drugs are transported by passive diffusion, where paracellular movement is liable for the transportation of hydrophilic drugs. In this mechanism, the molecular weight and lipophilicity of the drug are important [14].

1.2.2. Trigeminal nerves pathways.

The trigeminal nerve is the largest cranial nerve, the trigeminal nerve passes on tactile data from the nasal cavity, the oral hole, the eyelids, and the cornea, to the CNS using the ophthalmic division (V1), the maxillary division (V2), or the mandibular division (V3) of the nerve [12,15]. It innervates the nasal olfactory epithelium toward one side, while the opposite end arrives at the cerebrum by two various destinations, close to the pons and cerebrum of the mind, just as to the frontal mind and olfactory bulb less significantly [9]. Accordingly, possible locales of medication conveyance to the cerebrum can likewise be benefited through trigeminal nerve pathways. Investigates indicated proof on the transport of insulin-like- growth factor-I to the CNS through intranasal organization through the olfactory and trigeminal pathways [16,17].

1.2.3. Cerebrospinal fluid and lymphatic pathways.

This CSF and lymphatic pathways are connected from the CSF of subarachnoid space in the brain to the nasal lymphatic framework using olfactory nerves enveloped into perineurial space[18]. These pathways can transport a drug into the nasal cavity to the CSF and perivascular part to distribute to the other parts of the brain. The transport and distribution of drugs into CSF is depended on lipophilicity, molecular weight, and degree of ionization of the drug [19].

2. Nanocarrier for Intranasal Drug Delivery

2.1. Lipid nanoparticles.

Lipid NPs included solid lipid NPs (SLNs), nanostructured lipid carriers (NLCs), and liposomes. Lipid NPs can be utilized as a vehicle for drug delivery systems [20,21]. They have numerous focal points, contrasted with other colloidal carrier systems like drug entrapment, delayed medication discharge, improved physical and chemical stability, and effective fuse of lipophilic medications in the lipid core of the SLNs and NLCs [22]. Encapsulation of drugs in lipid NPs [23]. Prolonging the medication delivery time in the circulation system diminishes the medicine symptoms and builds its remedial consequences for CNS issues. These attributes make lipid NPs truly valuable for drug delivery to the CNS [24,25].

2.2. Polymeric micelles.

Polymeric micelles have been produced for sedate conveyance as of late [26,27]. These micelles structure precipitously in amphiphilic copolymer solution and show shell-core structures, which comprise hydrophobic block polymers (e.g., L, D-lactine polycaprolactone) as a core and hydrophilic square polymer (normally PEGs) as a shell [28]. The polymeric micelles are described to have a molecule size of 10–100 nm. The core could be stacked with a water-insoluble drug. These structures improve drug bioavailability [26]. The micelle shell shields drug from collaborating with serum proteins and non-target cells. The stacked drug discharges through the diffusion mechanism after reaching the target· The straightforward structure of the pharmaceutical system with no surface changes is the principal property, making this system valuable for drug delivery to the brain and CNS [29].

2.3. Dendrimers.

Dendrimers are atoms with an exceptionally stretched and three-dimensional structure, comprising an underlying core, a few inside layers, redundant units, and a few terminal dynamic surface groups [30]. The parts of dendrimers and surface groups are expanded with upgrading the quantity of dendrimer generation[31]. Dendrimers have low dispersion and superior performance [31,32]. Dendrimers are known as one of the perfect particles with a controlled nanoscale structure for drug delivery [33,34]. Dendrimers encourage the vehicle of drugs in different cell membranes or natural boundaries by endocytosis through cell disguise [35,36]. Dendrimers are a potent carrier in intranasal drug delivery [37].

2.4. Nanoparticles.

Pharmaceutical NPs have been created to control the drug release and shield it from enzymatic or synthetic debasement to improve its therapeutic efficacy [38,39]. A few sorts of NPs can be utilized to convey drugs and gens to the CNS. The NPs drugs have been incredibly evolved to encourage the productive delivery of insoluble drugs to the CNS to cure neurogenerative disorders [40]. Likewise, the outside of the NPs is regularly adjusted by PEG to upgrade the stability of the colloidal solution and draw out its support in the body [41]. The nanoparticles are a potent carrier for intranasal drug delivery [42], as illustrated in Table 1.

3. Neurological Disorders (Parkinson's and Depression)

Neurodegenerative illnesses (NDs) are problems that occur due to innovative loss of particular important neuronal populations or, in a few instances, related to protein aggregates [43]. The semis folded proteins are chargeable for neuronal degradation and essentially neuronal death. Oxidative stress, generation of loose radicals/reactive oxygen species, mitochondrial dysfunctions, impaired bioenergetics and DNA damage, neuro-inflammatory techniques, and disruption of mobile/axonal transport are linked to the formation of toxic varieties NDP (nucleoid disruption protein)-related proteins. The leading purpose for ND is complicated; however, normally is related to an age-associated decline of neuronal and behavioral functions[44]. Parkinson's and depression are chronic and progressive disorders of CNS.

3.1. Parkinson's disease.

Parkinson's disease (PD) is the most widely recognized age-related neurodegenerative disorder with an around-the-world commonness in the millions. The main source of PD is to decrease dopamine levels because of the degradation of dopaminergic neurons in the substantia nigra pars compacta (SNc)[45]. This inhibitory abatement impact of dopamine while increments excitatory impact of acetylcholine and at last produce challenges in controlling and commencement of deliberate development of muscle [44]. Side effects are characterized by tremors very still, rigidity, a shortcoming of wilful development, postural precariousness, and freezing. Now, there is evaluated 7 to 10 million individuals worldwide live with Parkinson's disease [46]. The frequency of Parkinson's is increasingly inclined with age; however, an expected 4% of individuals with PD are analyzed previously at the age of 50. Men are more defenseless than ladies [47]—the spread and scenes of PD increment with age. PD rates are expanding increasingly around worldwide. Neurons are transmitted with the assistance of DA and are fundamental for daily physical movement. In this way, a decline in DA level for neurotransmission in corpus striatum characterized PD and prompts irregular developments [48]. Pathogenesis of PD is very convoluted and observing more than one mechanism like expanding oxidative pressure, an imperfection in mitochondrial capacities, arrangement of plaque-like α-synuclein, unevenness of calcium homeostasis, and some hereditary components. These all might be liable for the extreme demise of neurons [49].

3.2. Current drug therapy by intranasal route for Parkinson's disease.

The choice of drug treatment is based on different factors like symptoms, age factors, and health issues, also depend on patient needs and stage of PD and metabolism. Different classes of drugs are available for the treatment of PD and classes are cholinesterase inhibitors, dopamine agonists, and monoamine oxidase type B inhibitors but from all of this levodopa is mostly used medication to treat PD [50]. Levodopa is normally utilized, which gives symptomatic relief and creates resilience, and has some unsafe reactions, such as reaction variances and levodopa-initiated dyskinesia(LID) [51]. Because of all these conditions, creating a controlled-release delivery technique is important to lighten the rate of side effects and build a dopamine stimulant effect. Furthermore, researchers are followed by novel methodologies for rewarding PD. Furthermore, among these, the intranasal drug delivery route creates a consideration of specialists for improving a patient's way of life. The following area

talks about the medications used to treat PD and their patent-related distribution through the intranasal course. The following section talks about the drug used to treat PD and their patent-related distribution through the intranasal route.

3.3. Ropinirole.

Ropinirole following under the class of DA agonist is a non-ergot subsidiary showing high selectivity toward D2 receptors [52]. This kind of DA agonist can be administrated alone or alongside another mix of drugs like levodopa to treat PD [53]. The various formulations are formulated by using nanotechnology. Nanoformulation has the greatest chances for intranasal drug delivery to explain the limitation related to customary ropinirole and increment of uptake of the drug in the brain [54]. Ropinirole has relativity low oral bioavailability due to its extensive hepatic first-pass metabolism. It uses various forms of nanocarrier ropinirole delivered to the brain by intranasal route; one example of ropinirole intranasal drug delivery formulation is spray-dried microparticles by using sodium alginate for ropinirole intranasal delivery [55]. Various kinds of nanoformulation are accessible for intranasal drug delivery of ropinirole.

3.4. Rotigotine.

Rotigotine, another class of non-ergoline DA agonists used in treating PD and off-mark treatment of Willis-Ekbom Disease (moreover known as Restless Leg Syndrome) presents agonistic movement on DA receptors giving more inclination to D3 receptor than some other. The mechanism of action of this class of drugs is undetermined however induced to have the capacity to stimulate DA in caudate-putamen, explicitly D2 receptor [56]. A few nano carrier-based drug delivery probes Rotigotine have been led by scientists to upgrade the delivery of Rotigotine to CNS, for example, intranasal approach with micro emulsion-based gel, microspheres, nanoemulsion [57]. For instance, advanced pharmaceutical utilization of nanoemulsion in a mix with intranasal drug delivery approach through mucoadhesive specialist has captivated the interest of many researchers because of the benefits related to fastly drug transport to brain from nasal route [58]. One example of Rotigotine mucoadhesive Nanoemulsion by intranasal route to brain is one alternative approach to solve the oral drug delivery problem [59]. Mucoadhesive nanoemulsion is a good Nano formulation for intranasal drug delivery [60]. Therefore, nanotechnology is a great tool for direct drug delivery to the brain.

3.5. Pramipexole.

Pramipexole is a non-ergot derivative that displays natural movement with DA receptors explicitly at the D2 subfamily, indicating greater proclivity towards D3 than different subtypes like D2 or D4 receptors [61]. The activity of Pramipexole being undefined depends on the stimulating capacity of DA receptors inside striatum, which is upheld up by physiologic creature contemplates that clarifies activating of DA receptors at the site of neurons in substantia nigra and striatum [62]. Researchers carried out several studies on Pramipexole. one example of Pramipexole intranasal drug delivery is the preparation of polymeric nanoparticles for brain-to-nose drug delivery; as a result, nanoformulation shows better effect [63].

3.6. Depression.

Depression is a typical mental disorder, influencing >300 million individuals of any age all around, and this number is ascending at a quick pace. Depression is the main source of incapacity worldwide, a significant supporter of the overall global burden of disease. Depression is mostly found in adult age people, but more than 50% of patients are unable to give a response to the first-line pharmacological treatment of antidepressant drugs because of BBB [64]. The BBB is complex that contains cerebral endothelial cells that express efflux transmembrane proteins, mainly from the ATB-binding cassette family, which mainly include P-glycoprotein (P-gp) and breast-cancer-resistant protein (BCRP) [65]. These transporters limit the entrance of lipophilic drugs to the brain, and they have been seen as overexpressed in the brain of hard-headed patients. Because of the good therapy of antidepressant drugs based on drug concentration in the brain, oral and parenteral therapy have limitations because they cannot cross BBB. Therefore, there is a rising requirement for new successful doses form that controllably release of the drug straightforwardly into the brain for decreasing adverse effect, drug interaction, and systemic exposure but intranasal drug delivery proved that have the potential to pass blood-brain barrier by enhancing target ability and decrease systemic adverse effect [66]. The nasal route protects the drug from chemical and metabolic degradation, enhances solubility, drug nasal residence time, and delivers the drug exactly at the point of absorption, bypassing the biological membrane [67]. The following section discusses current intranasal drug therapy for depression.

4. Current Drug Therapy by Intranasal Route for Depression

4.1. Venlafaxine hydrochloride.

Venlafaxine hydrochloride (VLF) is a double-action antidepressant drug that belongs to the serotonin-norepinephrine reuptake inhibitor (SNRI) pharmacotherapeutic class[68]. VLF is a broadly utilized antidepressant, being commercially accessible as quick and controlled-release tablets and capsules. VLF is a hydrophilic compound that presents a restricted BBB permeability, short half-life (4–5 h), broad hepatic impact, and low oral bioavailability (45%), in this way requiring frequent administration to ensure a blood level for therapeutic concentration. Besides, oral treatment gives a moderate beginning of the activity, and clinical symptoms like tachycardia, increase blood pressure, fatigue, cerebral pain, unsteadiness, sexual dysfunction, dry mouth [69], so the nasal route is an alternative to oral administration of different nanoparticles, nanostructured lipid carrier by using chitosan [70] or alginate chitosan nanoparticle [71].

4.2. Desvenlafaxine.

Desvenlafaxine (DVF), a second-generation SNRI, was chosen as the drug for the nose to brain delivery. Desvenlafaxine is a functioning metabolite of venlafaxine with an oral bioavailability of 80% and half plasma existence of 11 h. Even though desvenlafaxine has better serotonin: norepinephrine proportion (10:1) than venlafaxine (30:1), oral treatment is related to various symptoms, for example, expanded circulatory strain and pulse, constipation, tremor, perspiring, queasiness, migraine, and sleep disturbance [72]. Therefore, nasal formulation for desvenlafaxine delivery is an alternative way for delivery bypassing BBB.

Various types of nanoparticles are formulated using suitable polymers such as chitosan and polylactide-co-glycolide (PLGA) for the delivery of desvenlafaxine [73].

4.3. Ketamine and esketamine.

Ketamine and esketamine is a fast, significant stimulant effect and the plausible against a self-destructive effect that was transient when restricted to single administration [74]. Aside from the clinical results, the inborn difficulties of intravenous (from a coordination's perspective, medical clinic confirmation, and consultation with an anesthesiologist are required) or oral (decreased bioavailability) esketamine administration have provoked its intranasal delivery as a liked and progressively advantageous route for quiet self-administration. Surely, intranasal esketamine has been accounted for to create a pharmacokinetic profile like that got with higher dosages that were intravenously administrated generally rapid activity and expanded bioavailability of the drug once intranasally administered are inferable from the rich vasculature and moderately high systemic absorption of esketamine by the nasal mucosa [75]. The clinical proof preferring an antidepressant effect and better decency profile related to intranasal esketamine led the FDA to assign this drug an advancement treatment assignment [76]. That justifies the help in the clinical trial in progress with intranasal esketamine since, if the results recovered are sure, approval will be allowed for esketamine nasal splash (Spravato1) new drug application for the treatment of depression in adults. Therefore, it proved that esketamine is a rapid-acting antidepressant.

Table 1. Different Nasal Delivery System for Parkinson's and Depression targeted Drug Delivery.

Delivery platform	Incorporated Drug	Target	Source
Polymer-Lipid microparticle	Ropinirole	Anti-Parkinson's	[77]
Gel (thermoresponsive/in situ)	Ropinirole	Anti-Parkinson's	[78]
	Venlafaxine	Anti-depressant	[79]
Nanoparticle	Pramipexole dihydrochloride	Anti-Parkinson's	[63]
	Desvenlafaxine	Antidepressant	[73]
Microparticle	Resveratrol	Anti-Parkinson's	[80]
Niosomes	Bromocriptine	Anti-Parkinson's	[81]

5. Conclusion

Effective treatment of Neurological disorders is limited because of the BBB barrier, so drug delivery to CNS is challenging, but intranasal drug delivery is a novel delivery route that overcomes disturbance by Blood-Brain Barrier and delivers the drug to CNS, and protects the drug from systemic exposure and increases bioavailability. Different types of drugs are delivering to the CNS by using various nanocarriers, which are helpful to treat neurological disorders. It can be concluded that an intranasal route is a non-invasive approach for drug delivery to the brain.

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Conflicts of Interest

The authors declare no conflict of interest.

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