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NOSE TO BRAIN DRUG DELIVERY SYSTEM

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Abstract:

Nose-to-Brain Drug Delivery System is an approach to deliver a drug directly in brain through the nose. Intranasal Drug delivery is very beneficial as it avoids first pass mechanism and can achieve greater concentration of drugs in Central Nervous System (CNS) at very low dose. Delivery of a drug through nasal route has been potentially explored as an alternative route for the administration of vaccines and biomolecules. Nose-to-Brain drug delivery system is most widely used for the treatment of Neurological disease such as Alzheimer's Disease, Parkinson's Disease, etc. Such Disease affecting CNS and the most difficult to cure due to the presence of Blood Brain Barrier (BBB) which refers as the highly selective semi-permeable border of the epithelium cells surrounded by astrocyte foot processes. The Main Objective of this review report is to study some essential characteristics and their possible obstacles related to Nose-to-Brain Drug Delivery System which includes anatomy and physiology of Nose-to-Brain drug delivery system and also transport of drugs in nose-to-brain via Olfactory Nerve and Trigeminal Nerve Pathways by passing BBB.

Keywords: *Nose-to-Brain, Intranasal Drug Delivery, Blood Brain Barrier, Olfactory Nerve Pathway, Trigeminal Nerve Pathway.*

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INTRODUCTION:

The history of nasal drug delivery dates back to long years to treat the disease using natural medications. This route of drug delivery was considered by Traditional systems of medicines such as Unani, Ayurvedic as well as Persian. Nasal Therapy also called as 'Nasya Karma' has been recognized form of treatment in Ayurveda system of Indian medicines [1]. Traditionally, the nasal route has been intended for delivery of the drug for the treatment of local diseases like- nasal allergy, sinusitis, nasal infections and nasal congestion. In recent times intranasal drug delivery is being considered as preferred route of drug delivery for systemic bioavailability [2,3]. Conventional drug delivery method fall short in delivering a number of therapeutic agents to the brain efficiently [4].

The brain is a delicate organ with many vital functions and formidable mechanisms isolate and protect it from the outside world. Unfortunately, the same mechanisms that prevent environmental chemicals accessing the brain also prevent the access of therapeutic chemicals. The delivery of drugs to the brain is a key test appropriate to the existence of two physiological limitations, restricting the drug delivery to Blood Cerebrospinal Fluid Barrier (BCSFB), Blood Brain Barrier(BBB), and Central Nervous System (CNS). Nose-to-Brain delivery of drugs allows the drug to directly enter the brain by by passing the BBB and avoids extensive hepatic and intestinal metabolism. This route has been convenient and reliable route. Several new formulations are used to deliver drugs to brain by olfactory, neuronal, and trigeminal pathways.

Nasal route is alternative to parenteral therapy and also useful for long term therapy[2]. Nasal administration is non-invasive approach that allows the rapid transport of the drug directly to the brain and minimizes its systemic exposures [3]. Nose-to-Brain drug delivery allows application of drugs at roof of nasal cavity, which are transported to the Central Nervous System (CNS) of Humans and Rodents [4]. Nose-to-Brain delivery of drug moieties have been tried by several researchers to explore the merits of this route, such as circumvention of BBB, avoidance of hepatic first pass metabolism, practicality, safety and convenience of administration and non-invasive nature. The Nose-to-Brain drug delivery system relies on the strategy in which the medication is delivered on nasal route for system impact[5].

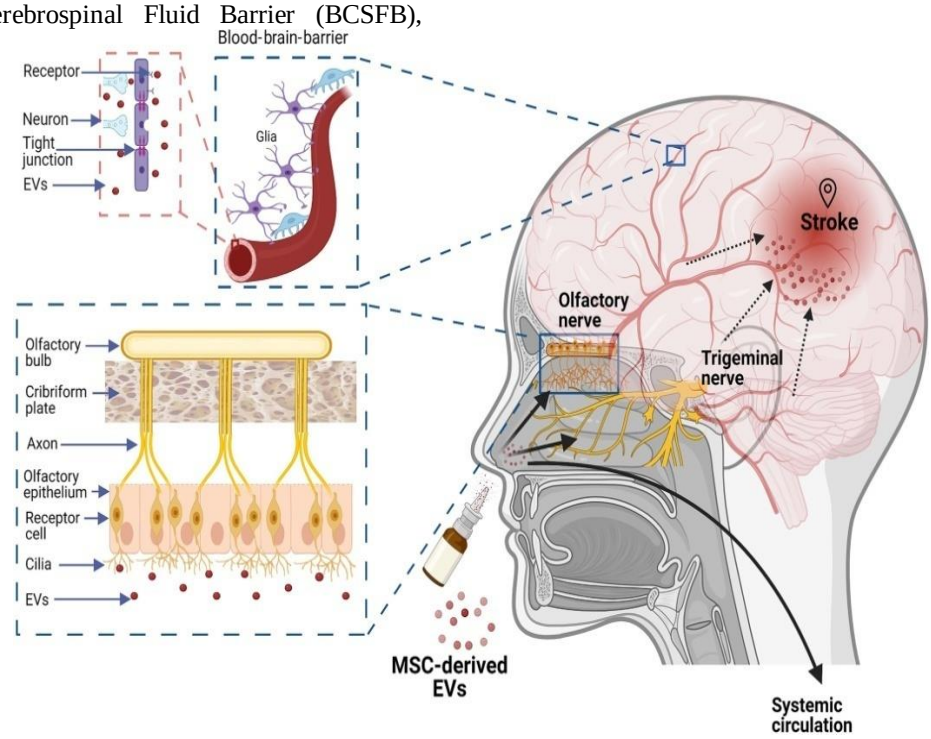

Figure 1: Nose-to-Brain Drug Delivery System *via* integrated Pathways bypassing the Blood Brain Barrier.

Advantages and Disadvantages of Nose-to-Brain Drug Delivery System:

Table 1: Advantages and Disadvantages of the Nose-to-Brain Drug Delivery system[6,7,8].

Advantages	Disadvantages
Absorption of a drug is rapid via highly vascularize mucosa	Frequent use of this nose to brain route may cause mucosal damage
Nasal Administration is non-invasive approach and is easy to administered	Decreased permeability across nasal mucosa and smaller absorption surface compared with GIT
Bioavailability for small drug molecule is very good	Cause irritation of nasal mucosa due to Budesonide, Azelastine drugs and due to this inconvenient compared with oral route
Improved Patient convenience and compliance as self-medication is possible	Rapid elimination of drug substances from nasal cavity due to mucociliary clearance
No consumption of ATP (energy)	Adversely affected by pathological condition
Reduced side effects by low dosing and alternate to parenteral route and so offer lower risk of overdose	High molecular weight compound cannot be delivered through this route
Convenient route of administration for patient on long term treatment	Delivery volume in nasal cavity is restricted to 25-200 microlitre (µl)

NASAL STRUCTURE AND PHYSIOLOGY

Structurally, the nose is divided into two nasal cavities via a midline spectrum called nasal passages. Air moves through these passages during breathing. The nasal cavity is about 12 cm long and the volume of each nasal cavity is 13ml and has a surface area of around 150cm^2[9]. The nasal cavity lies above the bone that forms the roof of the mouth and curves down at the back to join the throat. Within each nasal cavity there are three regions: Nasal vestibule, respiratory region, and olfactory region. The pH of nasal cavity secretion is 5.5-6.5 in adults and 5.0-6.7 in infants. Nasal secretions are secreted by goblet cells, nasal glands and transudate from plasma. It contains Sodium, Potassium, Calcium, Albumin, Enzymes like Leucine, CVP450, Transaminase, Lysozymes and Lactoferrins [10,11].

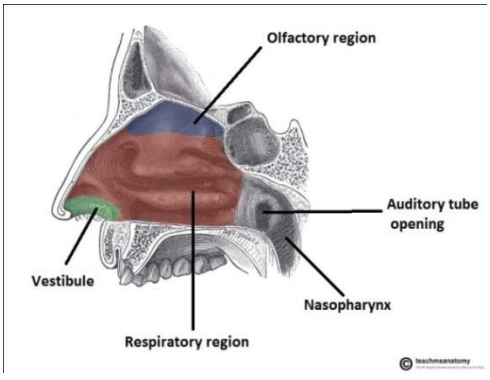

Figure 2. The three main region of Nasal Cavity

Functionally, the nasal cavity is most cephalic part of the respiratory tract. It communicates with the external environment via the anterior apertures, nares, and the nasopharynx via the posterior apertures, choanae. Both the nasal cavity consists of roof, floor, medial wall, and lateral wall[12]. The nasal vestibule is the first area encountered as you move posteriorly through the anterior nares and also called the nostrils or external nasal valve. The respiratory region covered in respiratory epithelium and mucous cells; this is the mostsubstantial part of the nasal cavity. The respiratory epithelium consists mainly of four types of cells, namely ciliated and non-ciliated columnar cells, mucus-containing goblet cells and basal cells[9]. Above the vestibular region,the respiratory region, which is the largest among all the three regions of the nasal cavity, can be found. The respiratory region also called as 'conchae'[12,13]. The olfactory region consists of three types of cells such as olfactory neural cells, the sustentacular or supporting cells and the basal cells. Olfaction requires oronasal or retro nasal airflow to transport odor-bearing particles up to the olfactory epithelium located at the apex of the nasal cavity. A unique feature of the olfactory receptors is that a single receptor cell can detect only one odorant type and cannot regenerate.

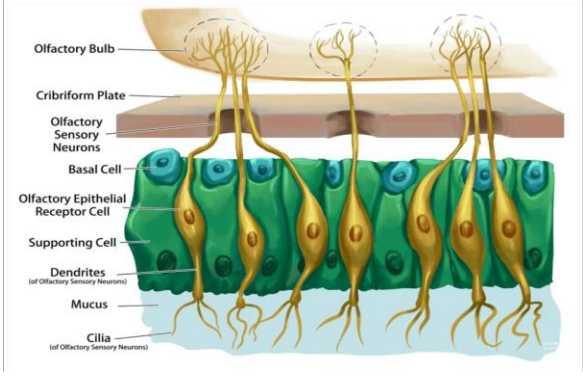

Figure 3. Schematic Representation of normal Olfactory epithelium and its cell types.

BLOOD BRAIN BARRIER

The Blood Brain Barrier (BBB) is the natural interface between the peripheral circulation and the central nervous system (CNS). Its function is to protect the brain tissue and to regulate the exchanges with blood circulation. Blood-Brain Barrier (BBB) is a selectively permeable membrane regulates the passage of a multitude of large and small molecules into the microenvironment of the neurons[14,15].

It achieves this feat by with the aid of multiple cellular transport channels scattered along the membrane. This includes:

- Amino acid transporters
- Glucose transporter1 (GLUT1)
- Nucleoside and nucleotide transporters
- Monocarboxylate transporters (MCT1 and MCT2)
- Ion transporters (Na+/K+-ATPase pumps) that facilitates the transport of essential molecules into the brain.

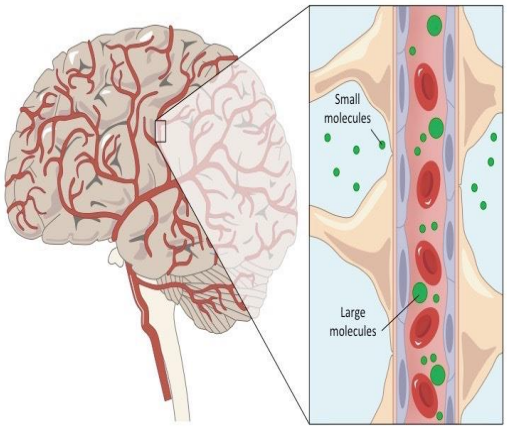

Figure 4. Blood Brain Barrier

The BBB represents a stringent barrier for delivery of the neurotherapeutics invivo. An attempt to overcome this barrier is represented by the direct transport of drugs from the nose-to-brain along with two pathways i.e. i) olfactory nerve pathways, ii) trigeminal nerve pathways[16]. The presence of BBB is essential as it protects the brain either infection or chemical circulating in the blood. On the other hand, it also hinders the passage of the therapeutic molecules that might be needed in the brain. It is estimated that the BBB excludes access to the brain of 98% of small molecules and the totality of large molecules endowed with therapeutic action. The BBB is highly selective allowing the passages through simple diffusion of only certain molecules such as water, carbon dioxide, and oxygen; Only highly selective drugs can cross this barrier. Water soluble drug with very less permeability can crosses. The Endothelial layer tightly bound with each other consist of astrocyte cell, pericyte cell, and capillary endothelial cell. All these three cells together form a solid barrier[16,17].

Pathways for Nose-to-Brain Delivery of Drug:

Drug Transport through the olfactory mucosa has been studied to deliver therapeutic substances to the brain to treat CNS Diseases. As described earlier, it has the significant advantage of bypassing BBB and reducing systemic exposure. The pathways for Nose-to-Brain delivery have not been fully understood, but many recent studies have suggested some major possible pathways. One way is the direct transport of drugs to the brain through neuronal pathways such as Olfactory Nerve Pathway and Trigeminal Nerve

Pathway. The other way is the indirect transport of drugs through the vasculature and lymphatic System, leading to the brain crossing BBB[18]. To overcome the Barriers nose-to-brain drug delivery used. Following Pathways are generally used.

a. Olfactory Nerve Pathway:

The olfactory nerve is sensory in nature and originates on the olfactory mucosa in the upper part of the nasal cavity. From the olfactory mucosa, the nerve travels up through the cribriform plate of the ethmoid bone to reach the surface of the brain. The olfactory nerve is the first and shortest cranial nerve[19]. The olfactory pathway begins when odorants, airborne chemicals, enter the nostrils and dissolve into the mucus lining covering olfactory nerves at the top of the nasal cavity in the olfactory epithelium. When odorants directly bind to the chemical receptor (chemoreceptors) on the cilia of olfactory neurons in the olfactory epithelium, it triggers a signaling cascade that transforms chemical signals into electrical signals.

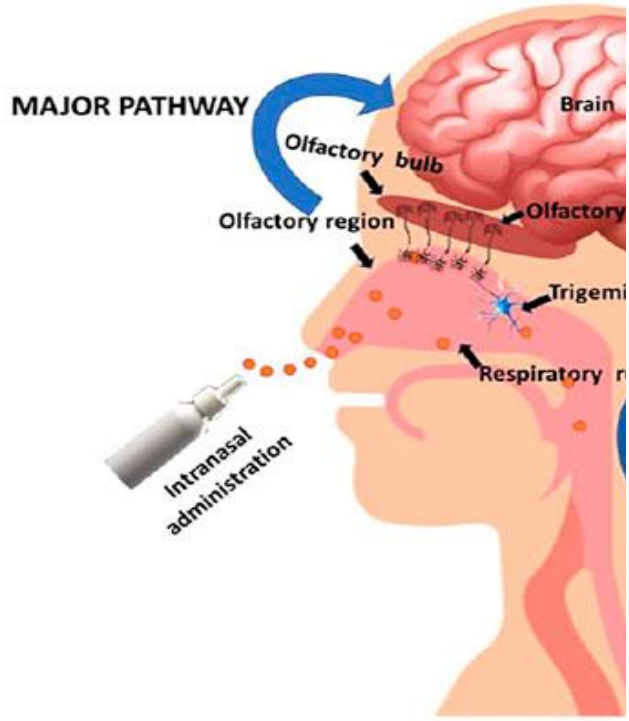

Figure 5. Pathway of drug distribution in nasal cavity and CNS, innervated by olfactory and trigeminal nerves.

b. Trigeminal Nerve Pathway:

Trigeminal nasal pathway is an important pathway connecting nasal passages to the CNS involves the trigeminal nerve, which innervates the respiratory and olfactory epithelium of nasal passages and enters the CNS in the pons. A small portion of trigeminal nerves also terminates in the olfactory bulbs[20]. The trigeminal nerve communicates sensory information from the nasal cavity, oral cavity, eyelids and cornea to the CNS via the ophthalmic division (V1), the maxillary division (V2) or the mandibular division (V3) of Trigeminal Nerve. The former two have only sensory function while later have both sensory as well as motor function. The ophthalmic and maxillary branches of the trigeminal nerves are important for nose-to-brain drug delivery as neurons from these branches pass directly through the nasal mucosa.

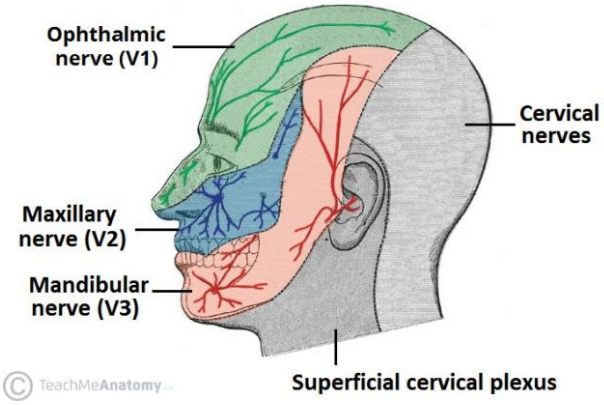

Figure 6. Trigeminal Nerves

The transport of the drugs to the brain follows different pathway, namely: (i) transport mediated by

trigeminal nerve, (ii) transport mediated by the olfactory nerves, and (iii) lymphatic and vascular transport. Among these, the trigeminal and olfactory pathways are certainly the best-known and most studied mechanisms for the transport of nose-to-brain drug[21].

Strategies to enhance Nose-to-Brain Drug Delivery System:

There are many barriers or obstacles present in nasal cavity which interrupt absorption of various drugs. The strategies could potentially dictate the ability of this nose-to-brain drug delivery route so that it would be more successful. This part was used to study the surface modifications or carrier system to enhanced drug delivery from Nose to Brain. There are some methods which are successfully used for improvement of nasal drug absorption such as[22]-

1. Structural modification
2. Nasal Enzymes inhibitors
3. Permeation enhancer
4. Particulate drug delivery
5. Prodrug approach
6. Penetration enhancer
7. Bio-adhesive polymer

Drug Formulations:

Nose to Brain delivery provides a great opportunity for fast and patient complaint drug applications. A major limiting factor for the treatment of CNS related disorders is the inability for drug substances to cross the blood-brain-barrier. Some medication may possess dose-limiting systemic side effects that hinder their ability to reach maximum effective concentrations in the CNS. Over the last several decades, scientists have studied the ability for drugs to be transported from the nose directly to the brain, and compared to intravenous injections, many studies have reported higher brain concentrations from the formulations administered intranasally[23,24].

Nanotechnology- Based nasal delivery systems have gained interest as a way of overcoming low drug bioavailability, limited brain exposure, fast metabolism, and elimination, high doses and unwanted side effects[25]. Many strategies have been developed to overcome the BBB, such as delivery systems, liposomes, polymeric and solid lipid NPs (SLNs), solid lipid carriers, liquid crystals (LCs), microemulsions, in-situ gels. Nanoparticles are defined as particles of matter that is between 1 and 1000 nanometers (nm) in diameter[26].

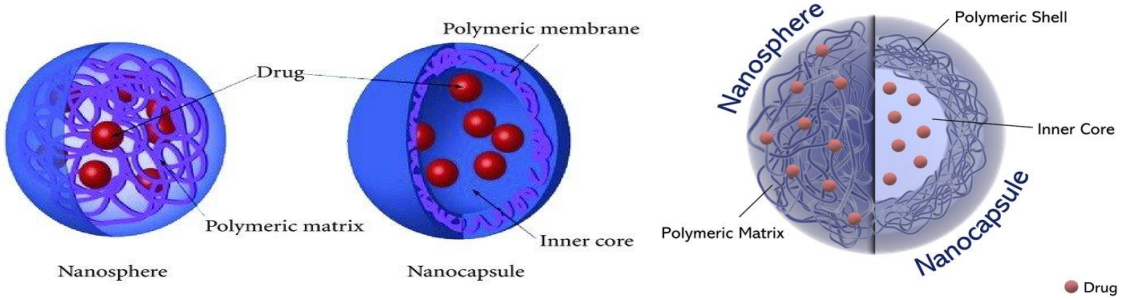

Figure 7. schematic different between the structure of nano capsules and nanospheres.

Microemulsions are stable transparent dispersions of water and oil and surfactant. They are prepared by simple mixing of the components and do not require specific preparation conditions. There are three kinds of microemulsions: oil dispersed in water (o/w), water dispersed in oil (w/o), and bicontinuous. The presence of o/w droplets is likely to be characteristics of microemulsions where the amount of oil is low in contrast, the existence of w/o droplets is characteristics of microemulsions where the water fraction is low.

In-situ gels is a soft, stable, or solid-like material which consist of at least two components, one of them being a liquid, present in substantial quantity[27]. In-situ gels are the solutions or suspensions that undergoes gelation after reaching the particular site due to contact with the body fluids or physicochemical changes such as pH, temperature, ionic concentration, UV radiation, presence of specific molecules, or ions, external triggers[28]. In-situ gel drug delivery system is a type of mucoadhesive drug delivery system. It is a process of gel formation at the site of action after the formulation has been applied at the site.

APPLICATIONS

1) Treatment of Alzheimer's Disease:

AD is characterized by cognitive degeneration and is a disease of ageing that is incurable disease with a long and progressive course. In AD plaque develops in the hippocampus, a structure deep in the brain that helps to encode memories, and in other areas of the cerebral cortex that are used in thinking and decision making. Approximately 5.8 million people in the US age 65 and older live with Alzheimer's disease. Of those, 80% are 75 years old and older. Out of the

approximately 50 million people worldwide with dementia, between 60% and 70% are estimated to have Alzheimer's Disease. This disease is the sixth leading cause of death in the US overall and the fifth leading cause of death for those aged65 years and older[29,30].

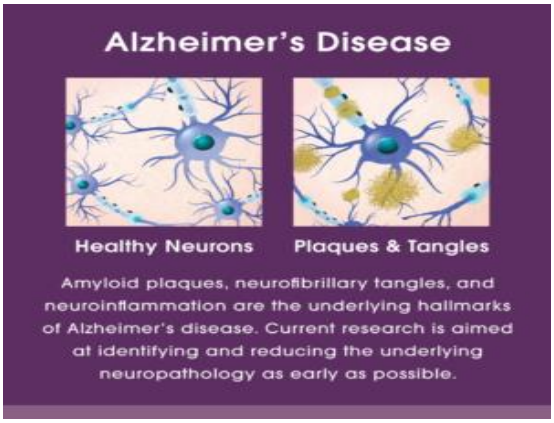

Figure 8. Comparison between Normal Healthy Brain and Alzheimer's Disease brain.

Reported histopathological characteristics of AD are extracellular aggregates of amyloid-β (Aβ) plagues and intracellular aggregation neurofibrillary tangles (NFTs). Aβ plagues develop initially in basal, temporal, and orbito frontal neocortex regions of the brain and in later stages progress throughout the neocortex, hippocampus, amygdale, diencephalon, and basal ganglia. In critical cases, Aβ is found throughout the mesencephalon, lower brain stem, and cerebellar cortex as well. The deposition of Aβ is increased in patient with AD when there are mutations in the amyloid precursor protein (APP) and presenilin (PS)[31]. When the concentration of Aβ is high, insoluble amyloid fibers are formed in the brain.

2) Treatment of Parkinson's Disease:

In the early stages of Parkinson's disease, your face may show little or no expression. Your arms may not swing when you walk. Your speech may become soft or slurred. Although Parkinson's disease can't be cured, medications might significantly improve your symptoms. Occasionally, your health care provider may suggest surgery to regulate certain regions of your brain and improves your symptoms. Globally, disability and death due to Parkinson's disease are increasing faster than for any other neurological disorder. Despite the significant impact, there is inequality in the availability of resources to manage the disease. The technical brief on PD is targeted to policy-makers, health programme managers and planners, health-care providers, researchers, people with PD and their careers and will support the implementation of the intersectoral action plan on epilepsy and other neurological disorders. Parkinson's disease is primarily associated with the gradual loss of cells in the substantia nigra of the brain. This area is responsible for the production of dopamine[32].

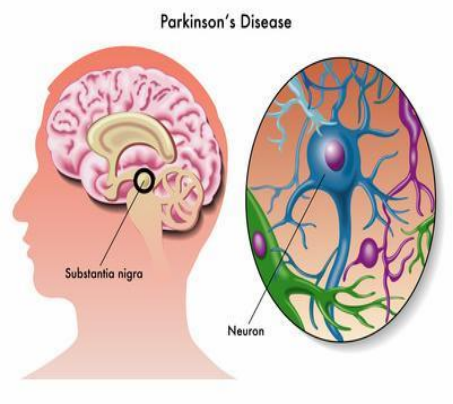

Figure 9.Parkinson's Disease

3) Treatment of migraine:

Through many trials and studies, it has been demonstrated and proved that Nasal route of administration provide optimal result for migraine treatment which has better drug concentration in the brain and give better Bioavailability of drug to the brain. These approaches may be associated with limiting the adverse effects of drug therapeutics. Migraine treatment differ in opinion whether migraine is primarily a vascular or a neurological dysfunction. Sumatriptan is a drug which is administered orally and absorbed rapidly but incompletely, and undergoes first-pass metabolism, resulting in a low absolute BA of 14% in humans. The transport of Sumatriptan across the BBB is very poor. Thus, intranasal route of administration offers a practical, noninvasive, alternative and effective route of administration for drug delivery to the brain[33,34].

4) Treatment of Amnesia:

To improve memory and faster regain of memory loss, study on mice has been done. Microemulsion and mucoadhesive microemulsion of tacrine, assessed its pharmacokinetic-pharmacodynamic performances for brain targeted and for improvement of memory in scopolamine induced amnesic mice. The results demonstrated greater extent of tacrine into the mice brain and faster regain of memory loss in scopolamine induced amnesic mice. Microemulsion is administered through intranasal route[35].

5) Treatment of epilepsy:

Various types of researches have been done to provide drug delivery through nose in these diseases. Intranasal administration allows transport of the drug to the brain circumventing the BBB, thus providing the better option to target drug to the brain with quick

onset of action in case of emergency in epilepsy[36]. Mucoadhesive microemulsion for the antiepileptic drug clonazepam has been formulated[37]. The aim was to provide rapid delivery to the rat brain. Brain/blood ratio at all sampling points up to 8 hours following intranasal administration of clonazepam mucoadhesive microemulsion compared to i.v. was found to be 2-fold higher, indicating larger extent of distribution of the drug in the brain. Microemulsion containing valproic acid resulted in fractional diffusion efficiency and better brain bioavailability efficiency[38]. Hence microemulsions are the promising approach for delivery of valproic acid for treatment of epilepsy. This study showed high brain targeting efficiency of prepared clobazam microemulsion and delayed onset of seizures induced by pentylene tetrazole in mice after intranasal administration of developed formulation. Further clinical evaluation of the developed formulation may result in a product suitable for the treatment of acute seizures due to status epileptics and patients suffering from drug tolerance and hepatic impairment on chronic use in the treatment of epileptics, schizophrenia and anxiety.

6) Treatment of antidepressant:

Administration through intranasal route of Microemulsions of eucalyptus oil has been formulated. It was demonstrated that the microemulsion of eucalyptus oil provides the rapid onset in soothing stimulant and antidepressant action. It was also cost effective[39].

7) Treatment of angina pectoris and Neurological deficit:

To improve the solubilityand enhance the brain uptake of nimodipine, Microemulsions has been prepared which was suitable for intranasal delivery. The uptake of nimodipine in the olfactory bulb from the nasal route was three folds, compared with intravenous injection. The ratios of AUC in brain tissues and cerebrospinal fluid to that in plasma obtained after nasal administration were significantly higher than those after IV administration. Thus, for the treatment and prevention of neurodegenerative disease, microemulsion system is a promising approach for intranasal delivery of Nimodipine[40].

8) Delivery of genes:

A major clinical challenge for delivery of genes to the CNS results from the limitations of the currently available vectors. Most of the viral vectors are too big, and have to be injected directly into the brain tissues. Therefore, nasal administration for delivery of plasmid DNA encoding therapeutic or antigenic genes is gaining attention in recent years as an effectiveness of nasal products we here to pay Attention to basic research in sasal drug delivery.

alternative method due to its non-invasive administration. One study investigated the intranasal delivery of Calcitonin gene-related peptide (CGRP), a potent vasodilator, to the brain. The data suggested that intranasal CGRP significantly relieved vasospasm, improved cerebral blood flow, and reduced cortical and endothelial cell death. Intranasal route was shown to be an effective way to deliver CGRP for brain targeting[41]. The beta-galactosidase protein encoded by the recombinant plasmids was significantly expressed in brain tissues following intranasal administration. Over 1 hour after dosing, the brain targeting efficiencies were shown consistently higher for plasmid DNA administered intranasally than that administered intravenously[42].

9) Delivery of proteins and peptides:

Oral administration of peptides is impossible because of gastrointestinal enzymatic degradation and hepatic first-pass effects. Increasing evidence suggests that the intranasal route of administration may be an attractive and convenient option for the delivery of certain compounds to the brain. In fact, several peptides including luteinizing-hormone-releasing hormones, oxytocin, calcitonin, and vasopressin, are routinely administered intranasally in clinical practice, and other peptides, including insulin, glucagon, growth hormones, growth hormone-releasing hormone, and somatostatin, are currently under investigation[43,44].

CONCLUSION:

Based on the various studies out lined in this review report- a successful drug delivery system is one which offers commercial applicability to pharmaceutical industries for large scale production. CNS drug delivery is complex due to limitations imposed by the BBB. Over a decade ago, the nasal cavity became one of the promising and conceivably adaptable routes for drug delivery. Direct nose-to-brain delivery system is a potential strategy to overcome the obstacles presented by BBB. Nasal drug delivery is a novel platform and it is promising alternative to injectable route of administration. There is a possibility in the near future that more drugs will come in the market in the form of nasal formulations and nasal devices intended for systemic treatment. For the treatment of long illness such as diabetes, osteoporosis, fertility treatment novel nasal products are also expected to be marketed. Bioavailability of the nasal drug products is one of the major challenges in the nasal product development. And also for the avoidance of the limitations and side effect and also to improve the

Although the BBB limits the delivery of certain drugs to the brain and deals with the treatment of certain

CNS disorders, accessing the brain via the nose-to-brain route has been demonstrated by scores of pre clinical studies and clinical trails results.

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