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A Review on Nose to Brain Drug Delivery System

Miss. Vaishnavi Shankarpure[*1], Asst. Prof. Rajlaxmi Deolekar[2] and Miss Khushbu Mohurale[3]
Student B-PHARM, Independent Researcher, Maharashtra, India[1]
M-PHARM[2]
Student B-PHARM, Independent Researcher, Maharashtra, India[3]
New Montfort Institute of Pharmacy, Ashti.
Vaishnavishankarpure39@gmail.com[1] and khushbumohurale0@gmail.com[3]

Abstract: *Entering into the brain is always a big challenge for the drug moieties acting on of CNS disorder. Nose-to-brain drug delivery is a new and effective way to send medicines directly to the brain through the nasal cavity. This method helps drugs reach the brain faster and avoids the blood brain barrier. Nose to brain drug delivery system is a system in which nasal route provides a rapid and efficient pathway for drug transport directly to brain through olfactory and trigeminal nerves. It offers rapid onset of action improved patient compliance. It is a non-invasive, painless, and quick method that can be very helpful in treating brain diseases like Alzheimer's. Parkinson's, and brain tumors etc. The nose to brain drug delivery has proven its worth by the presence of many commercially successful product.*

Keywords: BBB (Blood Brain Barrier), Neurological Disease, Alzheimer's Disease Parkinson 's disease.

I. INTRODUCTION

The blood-brain barrier (BBB) separates the central nervous system (CNS) from the systemic circulation. The barrier characteristics of BBB depend on the properties of the brain endothelial cells that constitute the walls of the blood vessels. There are many neurological diseases such as neurological infections. Parkinson's disease, Alzheimer's disease, multiple sclerosis, age related neurodegenerative diseases, and cerebral ischemia. That require a therapy in which the drug must reach the brain. Further more many of these diseases need chronic therapies.[1]

The intranasal route exploits the unique neural connection that the olfactory and the trigeminal nerves provide between the nose and CSF to deliver drugs to the brain. This route can be exploited as a potential alternative drug delivery route for efficient delivery of challenging drugs such as low molecular weight polar compounds. Peptides, proteins and large proteins and polysaccharides like vaccines or DNA plasmids.[2]

This article presents discussion on physio-anatomical and pharmaceutical components of nasal drug delivery system, along with discussions on the efforts made by researchers in this field including discussion on patents. Nanoparticles are colloidal in nature with a size range of 101000mm. Nanoparticles are used as the drug delivery sys tem by entrapping, dissolving, or attaching the drug to the polymer matrix. [3]

The brain is one of the most complex, vital organs that accepts signals from sensory organs and regulates most body functions. It is protected by a skull with different membrane layers that prevent external damage and is internally protected by cerebrospinal fluid (CSF), the CSF blood barrier, and the blood-brain barrier (BBB). These barriers help maintain the homeostasis of the brain and prevent physical damage, infections, endotoxins, and any harmful effects. [4]

II. DRUG DISTRIBUTION OF INTRA-NASAL FORMULATION THROUGH DIFFERENT PATHWAYS

II.i) Olfactory Region (Minor Pathway):- The upper region of the nasal cavity (known as an olfactory region) remain directly connected to the brain, frontal cortex; especially olfactory bulb) via olfactory nerves. Major routes of drug transport fum the olfactor pathway can be subdivided into four different categories. intra and extra neuronal pathway and paracellula and trayecellular pathways (Fig: 1)[5]

II.ii) Trigeminal Nerver (minor pathway):- The trigeminal nerve boosts the respiratory and olfactory epitheliuin and reaches the brain. The functions of it is the transmission of sensory information from the nasal and oral cavities, the cornea, and the eyelids to the CNS through the ophthalmic division, the maxillary division, or the mandibular division.[6]

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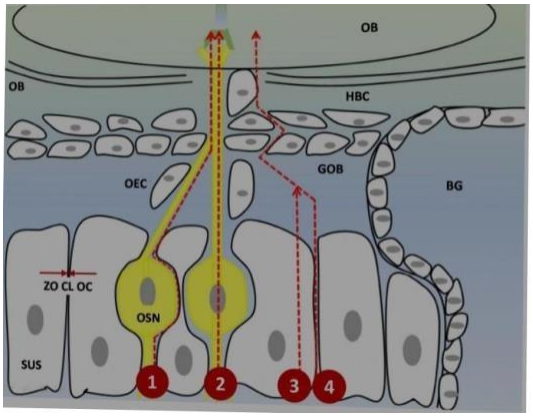

Fig no i. Olfactory Region[G]

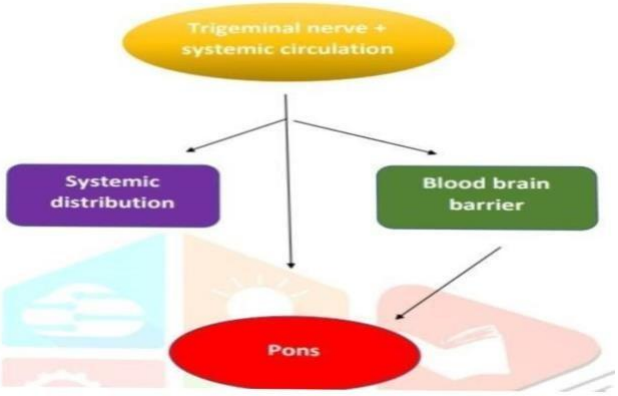

Fig no ii.Trigeminal Nerves [10]

II. iii). Lymphatic Pathway:- Lymphatic system is an important part of the body's immune system. It also play an important role in maintaining healthy fluid level in the body; The functional and anatomical connection between the extracranial lymphatics (nasal submucosa and cervical lymphatics) and subarachnoid spaces via the perineural spaces to the cribriform plate.[7]

II. iv). Vascular Pathways:-The vascular system is a network of vessels, including blood vessels and lymph vessels that transport fluids through out the body. The maxillary, facialand ophthalmic arteries and from the carotid nasal cavity. And this is very vascularized region.[8]

III. ADVANTAGES s DISADVANTAGES

III. i. Advantage of nose to brain drug delivery system

1. It is a rapid, safe, non-invasive and convenient method of drug delivery[11]
2. They provide biocompatibility, non-toxicity, and enhanced drug protection. St.Ns are produced from solid lipids stable at body temperature, whereas NLCs combine solid and liquid lipids for superior drug loading and stability[12]
3. It avoids hepatic first-pass metabolism.[13]
4. It is alternative route for parenteral administration[14]
5. Suitable for macromolecules and nanoparticles, enabling delivery of peptides, proteins, and gene therapies[15]
6. Bypasses the blood-brain barrier, allowing direct transport of drugs to the CNS [16]

III. ii. Disadvantage of nose to brain drug delivery system

1. There is a great deal of variability in the concentranoll attainable in different regions of brain and spinal cord [17]
2. High molecular weight of drugs may result in decreased permeability across nasal mucosa. [18]
3. Nose-to-brain drug delivery is limited by small dose size, nasal irritation, and poor drug absorption. [19]
4. Nose-to-brain drug delivery is limited by small dose capacity, rapid clearance, enzymatic degradation, and individual variability. [20]

IV. NEUROLOGICAL DISORDERS

Neurological diseases (NDs) are a fragment of human disorders that identify complications of the brain. Neurological illnesses, often known as brain, behaviour, or cognitive disorders, affect people's abilities to walk, speak, learn, and move. There are many neurological diseases such as neurological infections, Parkinson's disease. Alzheimer's disease, multiple sclerosis, age related, neurodegenerative diseases, and cerebral ischemia, that require a therapy in which the drug must reach the brain. [21]

IV.i. Causes:-

1. Genetic mulations (eg:- Huntington's Duchenne muscular dystrophy), [22]
2. Infection (eg:- Viral encephalitis) [23]

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3. Vascular Problem (eg: Stroke),[24]
4. Metabolic disorders (eg:- diabetics related neuropathy),[25]

IV. ii.Common systems :-

1. Chronic pain [26]
2. Vision problem[27]
3. Memory loss or confusion [28]
4. Sleep disturbances [29]
5. Muscle weakness or loss of co-ordination[30]

V. ALZHEIMER'S DISEASE AND PARKINSON DISEASE

V.i. Alzheimer's Disease

Age progression causes irreversible loss of nerve cells in the brain. This may result in difficulty remembering things, with slight confusion, thinking and responding slowly, etc. But severe memory loss, cognition and learning disability, difficulty in speech, abnormal behaviour, and disturbing daily activity are the common signs of Alzheimer disease (AD) Alzheimer is progressive, irreversible neurodegenerative disorder that slowly destroys this responsible for memory. [31] The Alzheimer Disease (AD) is a significant cause of dementia or memory loss throughout the world that mainly affects older adults, but in modern lifestyle, it seems to touch people at an early age which is known as younger stage AD. Alzheimer is a CNS dis-order characterized by progressive deterioration of neurons resulting in loss of cognitive behavior, memory impairment, and disturbance in a daily routine activity like brushing, bathing, cating, drinking, communications, reading, writing, etc. Overall disturbing the thinking ability and causes mental illness[32]

Dementia

Dementia is linked to the impairment of the elderly all over the world. Dementia affects almost 50 million individuals worldwide, with an estimated 10 million new cases. Diagnosed each year. Dementia is a
syndrome in which cognitive performance, such as thinking, remembering, and reasoning, deteriorates to the point where it conflicts with daily life and tasks. Many dementia patients lose emotional control, and even personality shifts occur. Memory loss, task difficulty, disorientation, language problems, behavioral abnormalities, and lost opportunities for initiative are the most common indications and symptoms of dementia. Dementi symptoms and signs were divided into three stages: early, middle, and late. [33]

V.ii. Causes of Alzheimer's disease

The causes of Alzheimer's disease can be explained with the help of three hypotheses.

a) Cholinergic hypothesis: The cholinergic hypothesis of Alzheimer's disease came about due to the combined observations of deficits in choline acetyltransferase and acetyl Cho-line (Ach) and the fact that Ach is important in memory and learning. It was thought that reduction in cholinergic neurons as well as cholinergic neuro transmission led to the decline in cognitive and non cognitive functions. Cholinergic function loss correlated to cognitive decline, but no causal relationship was established.[34]

b) Amyloid hypothesis: Amyloidosis is the abnormal deposition of amyloid proteins in tissues, with the altered amyloid proteins forming an insoluble B-pleated sheet. Reduced tissue and cellular clearance is observed in amyloid protein deposits. The membrane protein amyloid-ß precursor protein (APP) is proteolysis to form AB, and it is the amyloid form of A that makes up the amyloid plaques (neurotic plaques) found in the brains of Alzheimer's disease sufferers.[35]

c) Tau hypothesis: The Tau hypothesis revolves around the presence of neurofibrillary tangles (NFTs) in Alzheimer's disease. As a result of increased phosphorylation of Tau (originally bound to microtubules), there is an increase in free tau accompanied by loss of functioning microtubules. Phosphorylated Tau are subunits of paired helical filaments (PHFs), which form NFTs. [36]

V. II. Parkinson Disease :-

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by loss of nigrostriatal dopaminergic pathways Although the most commonly accepted criteria for the diagnosis of Parkinson's disease (PD)

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depend on motor symptoms, other signs and complaints related to the disease, such as a loss of sense of smell, constipation, depression, altered sleep patterns, and unexplained pain.[37]

V.II.i Causes of Parkinson Disease:

1. Genetic Mutations. [38]
2. Environmental Factors: Exposure to pesticides, herbicides, heavy metals, or rural living may increase risk.[39]
3. Oxidative Stress C Mitochondrial Dysfunction: Damage to neurons due to free radicals and impaired energy production in substantia nigra, [40]
4. Age-Related Degeneration:- Risk increases with age: Dopamine-producing neurons naturally decline over time.[41]
5. Other Causes:-Secondary Parkinsonism: Drug-induced (e.g.. antipsychotics), post-traumatic, vascular, or due to infections.[42]

VI. CURRENT SCENARIO OF NOSE TO BRAIN DRUG DELIVERY SYSTEMS

VI. i. Future prospective of intranasal delivery to the CNS

Effective non-invasive treatment of neurological diseases is often limited due to the presence of biochemical dynamic barriers: the BBB and blood-cerebrospinal fluid barrier (BCSFB) (Wong et al., 2012). BBB represents an insur-mountable obstacle for a large number of drugs including antibiotics, antineoplastic agents and various CNS-active drugs like neuropeptides. This creates a considerable threat for the therapy of cerebral diseases (Chakraborty et al., 2009). It is increasingly clear that crossing of BBB and drug delivery to CNS is a complex and challenging task requiring close collaboration and common efforts among researchers of several scientific areas including pharmaceutical sciences, biological chemistry, physiology and pharmacology (Denora et al., 2009). Therefore, treatment of neurological diseases has become one of the most significant challenges.[43]

Recent advances in nanotechnology have provided promising solutions to this challenge (Wong et al., 2012). From the works done in the last few years, we can conclude that nanotechnology is receiving increasing attention in an efficient manner. Several nanocarriers, for example, polymeric Nanoparticles, solid lipid nanoparticles, liposomes, micelles, dendrimers, nanogels, nanoemulsions and nanosuspensions have been studied for the delivery of CNS therapeutics (Wong et al., 2012). [44]

VI.ii. Recent drug delivery systems and applications

Significant progress has been made in recent years toward the successful development of drug delivery systems based on organic, inorganic, and hybrid nanoparticles as drug carriers for active targeting, particularly in chemotherapy. Recent drug delivery systems (DDS) are formulated with improved properties such as smaller particle size, increased permeability, increased solubility, efficacy, specific site targeting, stability, toxicity, and sustained delivery. [45]

Problems, and This would entail involving patients early in the development process, recognizing any ensuring they receive the most out of the device. Improving delivery systems that reduce toxicity while increasing efficacy. The different types of drug delivery systems are depicted in Fig.No. 3[46]

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Fig.iii Several types of recent drug delivery systems for different therapeutic purpose, [47]

VII. CONCLUSION

Nose to brain drug delivery system is a system in which nasal route provides a rapid and efficient pathway for drug transport directly to brain through olfactory and trigeminal nerves. It offers rapid onset of action improved patient compliance.It is a non-invasive, painless, and quick method that can be very helpful in treating brain diseases like Alzheimer's, Parkinson's, and brain tumors etc.The nose to brain drug delivery has proven its worth by the presence of many commercially successful product.

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