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MINI REVIEW ON NASAL – TO – BRAIN DRUG DELIVERY

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ABSTRACT

There are different type of dosage form which are administered orally, by parenteral, by topical etc. But the patient having trouble in swallowing tablets are preferred to parenteral injection. Thus, alternate to parenteral nasal drug delivery was developed. This drug delivery system is used to produced high concentration. The nasal drug delivery system has many dis advantages such as stability, physiochemical properties Blood brain barrier (this barrier restricts the transport of potential moieties to the brain), increases drug uptake, need to improve bioavailability. Nasal drug delivery system is used for both local and systemic circulation. In last five decades nasal to brain drug delivery system has gain numerous progresses, and development with numerous advantages. In this system there is direct targeting to brain via olfactory and trigeminal pathway, and gives wide range of neurotherapeutics to brain. The nasal route of administration directly delivers the drug to brain without systemic drug absorption This review is based on nasal drug delivery system, structure and function of the nose, novel drug delivery system, as nanoparticle, liposomes etc.

KEYWORDS: Mechanism of Absorption, Factors, nose to brain, olfactory pathway, Trigeminal Pathway, Systemic Pathway, Current Approaches.

INTRODUCTION

Nose to brain drug delivery system is the challenging and risk task due to its physiological trouble such as (BBB) blood – brain barrier it acts as a major obstacle for the transport of active molecule into central nervous system. It is estimated that more that 98% of CNS active drug are unable to cross the barrier because of its physiological properties. The blood brain barrier separates the brain intestinal fluid from circulating blood which act as a major barrier and reason for the diffusion of most drug from the blood to receptors present in central nervous system.[1] The blood brain barrier contains number of transporters such as P-glycoprotein (efflux transporter). The P-glycoprotein limits the transport of drug to CNS. From last several year many invasive and non-invasive strategies have been studied and developed to target CNS. But in recent years interest has been grown in the uses of nasal route (Non-invasive) to administer drug to brain, exploiting the trigeminal/olfactory pathway.[2]

To overcome on the major drawback of nose to brain drug delivery system i.e., Blood-brain barrier many research has been done. The olfactory region I only the region connected to peripheral environment in whole body. Olfactory region is a region from where active moieties can be absorbed directly in to the brain. The drug formulation when administered it comes in contact with mucosa and transports drug directly to brain bypassing the BBB, due to which it achieves excellence bioavailability, reduces the side effects, increases stability. Overcomes on drawback arises some limitation such as nasal enzymatic barriers, limited dose of administration, mucociliary clearance.[3] The researcher developed advanced drug delivery system to overcome on limitation. Through, applications of nanoparticles in nose to brain drug delivery system. However, nanoparticle has special properties that it can bypass the BBB,[4] the toxicity of nanoparticle may occur, after the nanoparticle enters in to brain may causes neurotoxicity. In brain some amount of neurotoxicity can be neutralized by systemic circulation.[5]

Anatomy and Physiology of Nose

The nose is made of complex structure and physiological properties. The nasal cavity (Nose) is divided into two halves i.e., nasal septum and extend posterior nasopharynx, and the anterior parts of nasal cavity, nasal vestibule, opens through nostril. The nasal cavity of nose generally divided in to three regions namely olfactory region, vestibule region and respiratory region. The olfactory region consists of olfactory receptor cells, basal cell, sustentacular cells etc., it has a surface area of 10

cm2.[6] The olfactory neurons are the bipolar neuron, this neuron involves in transduction of information from epithelium receptor to olfactory bulb. Vestibule region are present in nasal cavity, this region is not involved in absorption. Respiratory region has major role in drug absorption and is surface area is about 160 cm2 in human. Respiratory region is composed of ciliated and non-ciliated columnar cells, basal cells, mucus secreting cells etc. The purpose of mucus secretion is to protect against inhaled bacteria and viruses. Mucus secretion contain large amount of water approximately 92-95%, 1%salts, 1-2%mucin, and 1-2% other proteins.[7]

Advantages of Nose-to-Brain Drug Delivery System[8,9]

1. Drug degradation observed in the gastrointestinal tract is absent in nose-to-brain drug delivery.
2. The hepatic first pass metabolism is avoided in nasal cavity.
3. The rapid drug absorption found with quick onset of action can be achieved.
4. The bioavailability of larger drug molecules is improved with the help absorption enhancer and approach.
5. The nasal bioavailability for smaller drug molecules is fund to be good.
6. Drugs which are not absorbed orally can be delivered to the systemic circulation by nasal drug delivery system.
7. Studies indicate that the nasal route of administration is an alternate to parenteral route, especially, for protein and peptide drugs.
8. It is convenient to patients, those on long term therapy, when compared with parenteral medication.
9. Drugs possessing poor stability in gastrointestinal fluids are given by nasal route.

Factor Inflecting Nasal Drug Absorption[10,11]

Numerus factors affect the systemic bioavailability of drugs which are administered through the nasal cavity. The factors affecting to the physiochemical properties of the drugs, and the anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drugs delivery system nose to brain targeting. These factors play an important role for most of the drugs in order to reach therapeutic effective blood levels after nasal administration i.e., in nasal cavity. The factors influencing nasal drug delivery absorption are described as follows: -

1) Nasal effects
- Membrane Permeability
- Environmental pH
- Clearance
- Cold
- Rhinitis
- Mucociliary

2) Delivery Effects
- Drug Distribution and Deposition
- Viscosity
- Concentration
- pH
- osmolarity

3) Physiochemical Properties
- Molecular Size
- Lipophilic-Hydrophilic balance
- Enzymatic Degradation in Nasal Cavity

Mechanism of Absorption

The drug formulation absorbed from nasal cavity and passes through mucus layer it is also the first step of drug absorption. Small particles easily pass through this layer but large drug particles are difficult to cross the layer. The mucus secretion contains mucin protein which has the ability to binds drug particle, solutes, hindering diffusion. The mucus secretion varies or varies in mucus layer are possible as the environment changes i.e., temperature, pH etc. Different more absorption mechanism was developed by the researcher but only two mechanisms have been used such as:[12]

➢ 1st Mechanism Method: - In the first method there is involment of aqueous route transport, this is also called as paracellular route which is slow and passive. In this method there is correlation between intranasal absorption and the molecular weight of water-soluble compound. The molecular weight of drug is greater than 1000 daltons shows poor bioavailability.

➢ 2nd Mechanism Method: - In the second method there is involvement of lipoidal route, which is also called as transcellular process. The transcellular process is responsible for the transport of lipophilic drug this show rate dependency on their lipophilicity. In this method the drug formulation also cross cell membranes by an active transport route via carrier-mediated.

Transport of active moieties and nanocarriers from nose to brain

According to recent research and development in nose to brain drug delivery system, the nose to brain pathway is the potential pathway for the transport of therapeutic moieties/nanocarriers directly into the brain by bypassing the blood-brain barrier. In this transport mechanism there is involvement of three different ways that are olfactory pathway, trigeminal nerve pathway, and systemic pathway.

Olfactory Pathway

In olfactory pathway once the therapeutic moieties are administered via nose it travels through olfactory mucosa. The olfactory mucosa consists of olfactory receptors, neurons that are responsible for transduction. The transduction process occurs in cilia of olfactory receptor. The molecules move toward olfactory receptor neuron by transcellular and paracellular mechanism. In nasal cavity the nasal epithelium cells, and space between epithelium cell, along with its narrow tight junction allows the entry of compounds by paracellular transport. This pathway is considered as a determining step to nasal to brain administration. In olfactory pathway there is presence of olfactory nerve which are responsible for entering of therapeutic moieties in

olfactory bulbs and cerebrospinal fluid.[13] This moiety travels axon via nerve bundle crosses the cribriform layer and reach to the olfactory bulb which appears on the surface of brain. The drug gets distributed from cerebrospinal fluid to brain with the help of intestinal fluid present in the brain. As the drug reaches it just take few minutes to reach brain via olfactory transport. The olfactory neuron pathway divided in to external-neuronal and intra-neuronal pathway into brain. Intra-neuronal pathway consists of axonal pathway transport which requires hours or days for transport of active moiety to different region of the brain, whereas extra-neuronal pathway consist of perineural channel pathway which requires only few min to transport active moiety directly to brain. In the olfactory pathway system, it involves the deeper areas of brain such as cerebellum, cerebrum, and cortex etc.[14]

Trigeminal Pathway

The trigeminal pathway is the connecting pathway between tail part of the brain such as medulla, spinal cord, and pons etc. The drug is administered through nose transport via trigeminal nerve pathway by intracellular transport process also called as axonal transport or endocytosis. The trigeminal nerve composed of 3 branches such as ophthalmic, mandibular, and maxillary, it is also a largest fifth cranial nerve. Out of those three branches mainly ophthalmic and maxillary plays an important role in nasal to brain drug delivery system, the drug directly passes through neurons of nasal mucosa, it's some part ended in olfactory bulbs[15] The ophthalmic part of the trigeminal pathway, nerves get innervate to the dorsal part of anterior nose and nasal mucosa. As the drug passes through the mucosa of nasal cavity, the drug reaches to trigeminal nerve in olfactory respiratory region via axonal route or by brain steam transporter. The parts of trigeminal nerve which passes through cribriform region may get involved in delivering the therapeutic moiety from nasal cavity to forebrain. R G Thorne report an intranasal administration of drug in rat of insulin growth factor-l which rapidly reached brain via trigeminal neuronal pathway. The drug that administered by intranasal route get absorbed from nasal cavity and passes through the mucus, this is the first step of absorption. As the drug passes through mucus several mechanisms such as transcytosis, transcellular, carrier-mediated transport, receptor mediated transport, paracellular etc., gets involved in transportation of mucosa. Where transcellular route is transport of drug across the cells, by carrier mediated transport. In transcellular route adsorptive transcytosis mechanism there is involvement of macromolecules. This mechanism involved an interaction between cell surface and ligand (present in blood stream). This type of interaction may occur due to the electrostatic interaction involved between ligand which are positively charged and negatively charge membrane. The paracellular route transport occur between cells.[16]

Systemic Pathway

Drug administered into the brain from nasal cavity transmit through blood circulation. As the vasculature are rich the respiratory epithelium than olfactory mucosa fraction of the drug gets absorbed into the systemic circulation. The respiratory segment comprises of combination of the continuous and fenestrated endothelium which allows the passage of both small and large molecules into the blood circulation subsequently transport across the BBB to the CNS. As small as lipophilic molecules easily get enter into the blood and cross the Blood Brain Barrier as compared to the high molecular weight and hydrophilic molecules. The active moiety gets distributed throughout the systemic circulation blood and it enters into the nasal blood vessels and they were rapidly within few second transferred to the carotid arterial blood supply to the brain and spinal cord, this process is called counter current exchange, it is the rapid process of drug transport in to brain.[17]

Current development in Nasal to brain drug delivery system

1. Artemether-loaded nanostructured carriers was design for the treatment cerebral malaria. cerebral malaria is a type of malaria in which blood vessel of brain are blocked and causes heavy headache. To cure cerebral malaria Artemether-NLCs were developed by micro emulsion method and optimized by central-composite design. The particle size was found to be 123.4 nm and zeta potential were found to be 34.4 mV. In vitro cytotoxicity was performed on the SVGp12 cell line. The nasal ciliotoxicity (cilia) studies resulted as the formulations were safe and non-toxic for intranasal administration of drug artemether-NLCs. The pharmacokinetic parameter of the brain were studies and demonstrated and found higher concentration of drug in brain in case of intranasal administration of artemether-loaded NLCs. Brain-to-blood ratio for different routes of administration were determined 2.619 artemether-NLCs intranasal route, 1.642 for artemether–solution intranasal route and artemether-solution by intravenous route at 0.5 h. As a result, higher drug targeting efficiency was found and drug transport percentage to the brain via intranasal route was observed in artemether-NLCs high as compared to artemether-solution[18]

2. The current developed of the valproic acid-NLCs for the nasal to brain delivery route for the treatment of epilepsy. epilepsy is the neurological disease in which there is excessive firing of neuron occur in brain. there by valproic acid-NLCs were prepared by solvent diffusion followed by ultrasonication method. The valproic acid NLCs were characterized for the particle size, zeta potential, drug loading and huge entrapment efficiency. The valproic acid–loaded NLCs with the particle size of ranges from 154 ± 16 nm and drug loading percentage as 47 ± 0.8% was observed. In vivo pharmacodynamics study was performed via administering the valproic acid-NLCs and drug solution

by intra-peritoneal or intranasal route on rats by maximal electroshock method. The experiment results that brain plasma concentration level ratio was higher in case of intranasal administration of valproic acid-NLCs as compared to the intra peritoneal administered on control group rats. the result found that the administration of valproic acid-NLC provide a better protection for the seizure therapy.[19]

3. Temozolomide nanostructured lipid carriers (TMZ-NLCs) formulation was investigated to enhance brain targeting via nasal route of administration. The formulation was formulated by using a four-factor, three-level Box–Behnke design. The formulated TMZ-NLCs was evaluated for their surface morphology and ex-vivo permeation and in-vivo studies. All TMZ-NLCs drug formulations showed sizes in the nanometer (nm) range, with high drug loading capacity and prolonged drug release (sustain drug release). The optimized formulation of TMZ-NLCs displayed a drug entrapment efficiency of 81.64 ± 3.71%, zeta potential of drug was found to be 15.21 ± 3.11 mV, and polydispersity index found to be less than 0.2. The drug dose enhancement ratio was found to be 2.32-fold that control the formulation TMZ-NLCs. In vivo studies were demonstrated in mice, the brain/ blood ratio of TMZ-NLCs and found to be significantly higher compared to that of TMZ-dispersion (intranasal, intravenous). The scintigraphy images of mice brain displayed the presence of a high concentration of TMZ-NLCs in brain. As a result, the study substantiates the existence of a direct nose-to-brain delivery route for TMZ-NLC.[20]

4. The duloxetine-NLCs is evaluated for the treatment of depression through intranasal route. The duloxetine-NLCs were prepared by homogenization process followed ultrasonication method. The in vivo nasal infusion experimental study was performed on rat to estimate the known amount of duloxetine permeated or the amount of dose necessary to penetrate into the brain. The drug absorption rate of nanocarriers and drug solution was administered for nose to brain and blood permeation. Duloxetine-NLCs drug was found to be more permeable through nose to brain as compared to the drug solution. The duloxetine-NLCs drug was 2-2.5 times more permeable than drug solution. As a result, higher amount of drug was observed in brain in case of duloxetine-NLCs. This experimental study resulted that intranasal infusion of duloxetine- NLCs were found to be the potential route for the delivery of drugs to the brain for the treatment of depression.[21]

5. Asenapine-loaded NLCs were develop for the treatment of schizophrenia and mania it also treated for bipolar disorders via intranasal route i.e., nose to brain drug delivery system. The asenapine-NLCs particle size was found to be 167.30 ± 7.52 nm, zeta potential was found to be 4.33 ± 1.27 mV and entrapment efficiency were found to be 83.50 ± 2.48%. The surface morphology of asenapine was smooth surface and in spherical shape. The biological distribution study of asenapine revealed that higher drug concentration of asenapine-loaded NLCs Cmax peak of 74.13 ± 6.73 ng/mL, AUC0–24 h of 560.93 ± 27.85 ng/mL and the mean residence time (MRT) of 7.1 ± 0.13 h as compared to the asenapine via intranasal route. The behavioral study of Asenapine-NLCs results founded that the decrease in extra-pyramidal side effects with increasing anti-psychotic effect was observed after the treatment of 1–2 weeks. the drug was administered through nasal cavity. As a result, NLCs could be a better drug delivery system for the delivery of asenapine to the brain via intranasal route of administration for the treatment of schizophrenia or mania associated with bipolar disorder.[22]

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