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Innovative approach for nasal drug delivery system for brain target

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Abstract

The goal of brain drug targeting technology is the delivery of therapeutics across the blood brain barrier (BBB), including the human BBB. Nose to brain drug delivery has received a great deal of attention as a non- invasive, convenient and reliable drug delivery system. For the systemic and targetedadministration of drug. The various drug deliveries through some drug transport pathways, Factor influencing nasal drug absorption, formulation strategies nose to brain, colloidal carriers in nose to brain drug delivery system and nasal delivery systems. Physiological barriers (BBB) that restricts the delivery of drug to CNS. Thus intranasal route has attracted a wide attention of convenient, non-invasive, reliable, and safe route to achieve faster and higher level of drug in the brain through olfactory region by passing blood brain barrier. Intranasal administration rapid onset of action, no first –pass effect , no gastrointestinal degradation lungs toxicity and non-invasiveness application and also improves bioavailability.

Keywords: Nose; Brain; Blood-brain barrier; Brain target; Nasal drug delivery

1. Introduction

The delivery of drug to the brain still remains problematic because of poor bioavailability due to the impervious nature of the endothelial membrane separating the central intestinal fluid and the systemic circulation from blood (termed as Blood Brain Barrier-BBB). The absorption and permeation of drug for desired therapeutic action in brain is restricted by the blood brain barrier (BBB). Thus the nasal route facilitates direct targeting the brain via olfactory and trigeminal neural pathway by passing the BBB. Intranasal brain targeting drug delivery system is a system which provides direct delivery of drug in brain via nasal route. Drugs those are susceptible to enzymatic or acidic degradation and first-pass hepatic metabolism e.g. Vaccines and biomolecules such as proteins, peptides and non- peptides can be administered via nasal route for their better permeation and absorption for desired therapeutic action targeting the drug delivery to the brain. One of the most permeable and highly vascularized sites for drug administration ensuring rapid absorption and onset of therapeutic action is the nasal mucosa. In addition it minimizes the lag time associate with oral drug delivery and offers non-invasiveness, self-medication, patient comfort and patient compliance which are hurdled in intravenous drug therapy. Scientists have focused their research toward intranasal administration for drug delivery to the brain especially for the treatment of CNS diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, depression, anxiety, autism spectrum disorders, seizures, drug addiction, eating disorders, and stroke such as epilepsy, migraine, emesis, angina pectoris and erectile dysfunction.[1,2,3]. This is all the possible pathways for drug can reach brain after nasal administration is predominately either by the olfactory or trigeminal region or through systemic circulation as shown in-[4].

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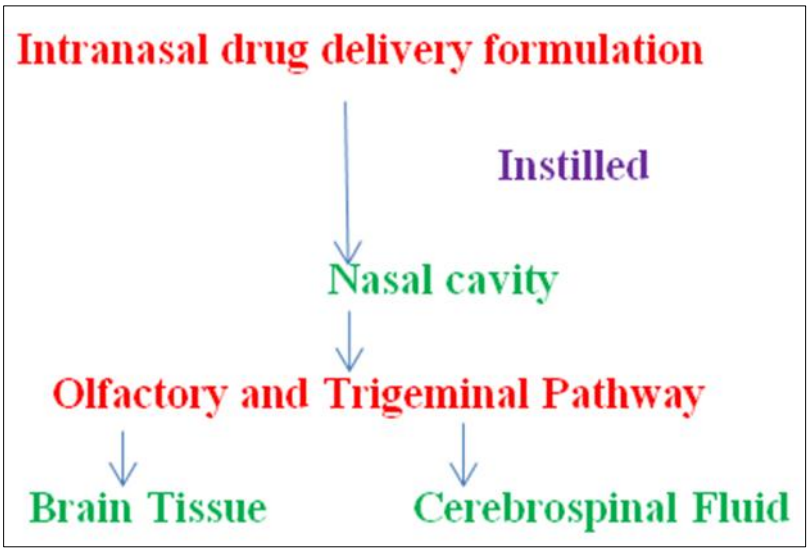

Figure 1 Drug Instillation to the Nasal cavity

1.1. Nasal Cavity Anatomy, Physiology and Histology

The major functions of the nasal cavity are breathing and olfaction. It also affords an important protective activity once it filters, heat and humidity the inhaled air before reaching the lowest Nasal cavity contains lining with mucus layer and hairs which are involved in functions like, trapping inhaled particles and pathogens [5]. Moreover, resonance of produced sounds, mucociliary clearance MMC, immunological activities and metabolism of endogenous substances are also essential functions of nasal structures. Anatomic and histological characteristics of the different areas of nasal cavity are allowing these functions to be performed optimally. Anatomically, human nasal cavity fills the space between the base of the skull and the roof of the mouth, above it is supported by the ethmoid bones and, laterally, by the ethmoid, maxillary and inferior conchae bones. Total volume of the human nasal cavity is 15-20mL and the total surface area is approximately150 cm2. It is divided by middle or nasal septum into two symmetrical halves, each at the face through nostrils and extending posterior to the nasopharynx [6].

1.1.1. Nasal to brain delivery

The sensory system region may be a little patch of tissue containing little receptor and is found at the terribly prime of the cavity close to the inner finish of the higher throat. The patch features a chromatic tinge in distinction to its close pink tissue and consists of many million small endings of the cranial nerve whose bundle passes through the cribriform plate and enters the quickest forward extension of brain. Sensory system epithelial tissue is thought to be a portal of entry of the substance into the central system nervous and peripheral circulation. The transport of the drug across the nasal membrane and into the blood could involve the passive diffusion of drug through the pores within the nasal mucous membrane and a few from non-transport.

1.1.2. Mechanism of Nasal absorption

The absorbed drug from the nasal cavity passes through the mucus layer. It is the first step in Absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs find difficulty to cross it. The principle protein of the mucus is mucin. It has the tendency to bind to the solutes and hinders diffusion of drug molecules. Structural changes in the mucus layer are possible as a result of environmental changes like change in pH, temperature. Many absorption Mechanisms were proposed earlier but only two mechanisms have been predominantly used, such as [7]

First mechanism

It is also known as the Para cellular transport. It involves an aqueous Route of transport but slow and passive. There is an inverse correlation between intranasal Absorption and the molecular weight of water soluble compounds. Drugs having molecular Weight greater than 1000 Daltons shows poor bioavailability.

Second mechanism

It involves transport through a lipoid route. It is also known as the Trans cellular process. It is responsible for the transport of route via carrier mediated means. For example: chitosan, a natural biopolymer from shellfish is known to

open the tight junctions between epithelial cell and facilitate drug transport. Dependency on their lipophilicity. Drug also crosses the cell membranes by an active transport route via carrier-mediated means. [7]

1.2. Drug delivery strategies for brain targeting

1.2.1. Invasive Strategies

- Disruption of the BBB.
- Intracerebral Implants.
- Intra ventricular Delivery.
- Intrathecal delivery (Intra-CSF drug delivery).
- Focus ultrasound enhanced delivery.
- Craniotomy based drug delivery.
- Convection enhanced delivery (CED).
- Polymeric wafers and microchip technology II.

1.2.2. Non- invasive Strategies

- Efflux pumps inhibitor.
- Prodrug approach.
- Cell based therapy.
- Nano carriers as drug delivery system.
- Intranasal drug delivery.

1.2.3. Physiological Strategies

- Pseudo nutrient Approach.
- Ligand Binding Proteins.
- Chimeric Peptides.

1.2.4. Pharmacological Strategies

- Prodrug based brain targeting.
- Nanoparticles.
- Liposomes.
- Nano conjugates

1.2.5. Recent advancements in brain targeted drug delivery

- Antibodies mediated drug delivery.
- Mfsd 2a- based drug delivery strategy.
- Facial intradermal injection.
- Laser light based technology. [8, 9].

1.3. Invasive Strategies

1.3.1. Disruption of the BBB

The thought behind this approach is the shrinkage of BBB momentarily by injecting mannitol solution into arteries in the neck. The resulting high sugar concentration in brain leads to the following step.

- Capillaries take up water out of the endothelial cells.
- Shrinkage of endothelial cells.
- Thus opening tight junction.

The effect lasts for 20 to 30 minutes, which is sufficient for the drugs to diffuse freely, that would not normally cross the BBB. In addition to opening of junction complexes and formation of inter endothelial gaps, trans- endothelial opening

and tracer passage through the cytoplasm of injured endothelial cells were also observed in response to the hypertonic barrier disruption [10,11]

1.3.2. Intracerebral Implants

Intracerebral chemotherapeutic implants are the controlled release systems which increases the survival of human with recurrent malignant gliomas and of animals with transplanted gliomas. Drug added to polymer pellet implants intracranially bypass the BBB and release drug molecules locally in the brain in a sustained fashion. Malignant gliomas are located deeply in the brain and thus the effectiveness of the drug delivered by the polymer is dependent on whether drug molecule can be transported a sufficient distance from the implanted site to reach malignant gliomas. Intracerebral delivery involves delivery of drug directly into parenchymal space of the brain. Drugs can be injected directly (bolus or infusion) via intrathecal catheters, by controlled release matrices, microencapsulated chemicals16 or recombinant cells. The major problem with bolus injection is slower movement of compounds within the brain due to the limited diffusion coefficient. The reason behind this is, due to the closely packed arrangement of cells in both gray as well as white matter microenvironment and due to the concentration dependent diffusion phenomena in brain. Hence a large amount of dose is required for an appropriate drug concentration in parenchyma. Alternatively the continuous infusion method can be used which uses convection enhanced diffusion (CED) phenomena to drive the drugs to a larger tissue region

1.3.3. Intra ventricular vascular

Intra ventricular route also act as an approach to bypass BBB by neurosurgical means where therapeutic agents are instilled directly into cerebral ventricle. This route is best suited for meninginoma treatment and metastatic cells of CSF as it distribute drugs mainly into ventricles and sub arachnoidal area of brain. Major advantage of this route is that, its lack of interconnection with interstitial fluid of brain unlike intra cerebral delivery. Thus the drug achieves higher concentration in brain in comparison to that of its extra vascular distribution but the major disadvantages are the chance of causing sub ependymal astrogliatic reaction due to high drug exposure at the ependymal surface of brain.

1.3.4. Intrathecal delivery

(Intra-CSF drug delivery): Intrathecal route involves delivery of neuro therapeutic agents to brain by direct administration of drugs through intrathecal route into cisterna magna of brain. Though it is substantially less invasive than intra ventricular administration, but this method fails to results in drug accumulation in parenchymal structures of the deep brain which is highly essential for sustained drug release20. The major disadvantage of this route is the chance of understood when etoposide administered through this route into the dogs led to ataxia and loss of muscle coordination. Due to this, intra thecal route is best suited for drug delivery for treatment of spinal diseases and disseminated meningeal diseases but not for large parenchymal diseases like parenchymal tumors such as glioblastoma.

1.4. Physiological Strategies

1.4.1. Pseudo nutrient Approach

Pseudo nutrient approach Peptide drug design incorporates a specific molecular characteristic that facilitates the drug to be transported by one or more of the inwardly directed nutrient carriers. The BBB expresses several systems for the transport of nutrients and endogenous compounds. Utilization of these transport systems is a potential strategy for controlling the delivery of drugs into the brain. These drugs must have a molecular structure that mimic the endogenous nutrient. The hexoses, large nutrient amino acid carrier have the highest capacity and are best suited for the delivery of substrates to the brain [12].

1.4.2. Ligand Binding Proteins

Protein ligands possess various properties such as high affinity to receptors and selectivity for targeting, which increases the interest towards the use of proteins as a delivery tool for targeting drugs to the brain. Central ligand binding component such as lectins act as a ligand binding protein for brain targeting of glucose triggered glycosylated insulin and bi specific antibodies. Cationized albumin appears to be useful for the Delivery of the active agents across the BBB to the brain. Other ligand binding protein classes Include biotin-binding proteins, lipid binding proteins and avidin binding proteins. Like avidin biotin conjugates immunoglobins occupy a special place in the field of ligand binding proteins because of their ability to recognize almost infinite number of ligand molecules [12].

1.4.3. Chimeric peptide

Synthesized chimeric peptides are another possibility for the drug delivery to the brain. Chimeric peptides are generated by linking of a drug which lacks transport at BBB to a vector at the luminal membrane of brain capillary endothelial cells. The vector initiates receptor -mediated or adsorption - mediated trancytosis.

1.5. Pharmacological Strategies

1.5.1. Pro-drug Based Brain Targeting

Brain uptake of drugs can be improved by pro drug formation. Pro drugs are pharmacologically inactive compounds that result from chemical modifications of biologically active species. The chemical change is designed to improve some deficient physicochemical property, like membrane permeability and water solubility. After administration, the pro drug, by virtue of its improved characteristics, is brought closer to the receptor site and is maintained therefore longer periods of time. Here it gets converted to the active form. Once in the CNS, hydrolysis of the modifying group will release the active compound and is ready to show therapeutic activity [13].

1.5.2. Nanoparticles

Nanoparticles are solid colloidal carrier particles ranging 1 to 1000 nm in size. They consist of macromolecular materials in which the active principle is dissolved, entrapped or encapsulated or to which the active principle is adsorbed or attached.

- Enhancement of the drug transport across the BBB by means of nanoparticles:
- Nanoparticles are preferably absorbed on the wall of the brain blood vessels without transport of particles across the endothelium.
- The fluidization of the endothelium by the surface activity of the surfactant polysorbate 80 is known to enhance the drug transport across the brain.
- Opening of the tight junction between the endothelial cells lining the brain.
- Endocytic uptake by the endothelial cells
- Lining of the brain blood vessels with or without degradation of the nanoparticle.
- Trancytosis across the brain endothelial cells. After the uptake of the nanoparticle by the endothelial cells, the nanoparticles and adsorbed drug may be delivered to the brain cells by trancytosis.
- The inactivation of p-glycoprotein flux pump has been reported to enhance the brain transport of nanoparticles.

1.5.3. Liposomes

A liposome consists of a region of aqueous solution inside a hydrophobic membrane. Hydrophobic chemicals can be easily dissolved into the lipid membranes; in this way liposomes are able to carry both hydrophilic and hydrophobic molecules.

1.5.4. Steps involved in liposome action of drug delivery

Adsorption

Adsorption of liposomes to cell membranes causes its contact on the cell member delivery.

Endocytosis

Adsorption of liposomes on the cell surface membrane followed by engulfment and internalization into the liposomes.

Fusion

Fusion of lipid bilayers of liposomes with the lipoid cell membrane by lateral diffusion and intermingling of lipids results in direct delivery of liposomal contents in the cytoplasm.

Lipid exchange

Due to the similarity of liposomal lipid membrane with cell membrane phospholipids, lipid transfer proteins in the cell membrane easily recognize liposomes and cause lipid exchange. For example, in case of cancer cells; they consume large

amounts of fats to fill the requirement of rapid growth; they recognize the liposomes (loaded with anti-cancer drug) as a potential source of nutrition. When they are targeted by liposome, they get absorbed. Once the anti-cancer drugs are released from the liposome into the site, cancer cells are killed by the drug [14].

1.6. Recent advancements in brain targeted drug delivery

1.6.1. Antibodies mediated drug delivery

Passive and active targeted Nano particulate delivery systems show promise to compensate for lacking properties of conventional therapy such as side effects, insufficient efficiency and accumulation of the drug at target site, poor pharmacokinetic properties etc. For active targeting, physically or covalently conjugated ligands, including monoclonal antibodies and their fragments, are consistently used and researched for targeting delivery systems or drugs to their target site [15].

1.6.2. Mfsd 2a- based drug delivery strategy

The blood-brain barrier (BBB) keeps the central nervous system (CNS) safe from various brain diseases, while the BBB makes it difficult for effective drugs to enter the CNS. Mfsd2a is specifically expressed on the cell membrane of brain-microvascular endothelial cell (BMEC) and is implicated in the delivery of some substances across the BBB. Mfsd2a is the first inhibitor of the transcytosis and the first transporter for lysophosphatidylcholine-docosahexaenoic acid (LPC-DHA) in BMECs. The crucial dual function of Mfsd2a puts forward two kinds of Mfsd2a-based strategies for carrying drugs from blood to the CNS [16].

1.6.3. Facial intradermal injection

This study assessed selective dermal rejuvenation using sequential intradermal injections of carbon dioxide and hyaluronic acid as a treatment of facial wrinkles. An injection device was designed. After topical anaesthesia, 0.1-mL carbon dioxide was gently injected intradermal so as to spread diffusely. A volume of 0.01- to 0.02-mL diluted hyaluronic acid was sequentially injected until the skin rose slightly [17].

1.6.4. Laser light based technology

The development of high power GaN based blue laser devices allows the development of remote phosphor converted laser based light source, where blue radiation emitted from a laser diode (or laser diodes array) is optically collimated (or focused according to the specific application) and excites a phosphor layer deposited over a transparent or reflective substrate, these systems are also known as LARP (Laser Activated Remote Phosphors). The combination of visible blue (450 nm) light and remote phosphor is a technology well known for LEDs, but finds application also for laser diodes lighting systems [18].

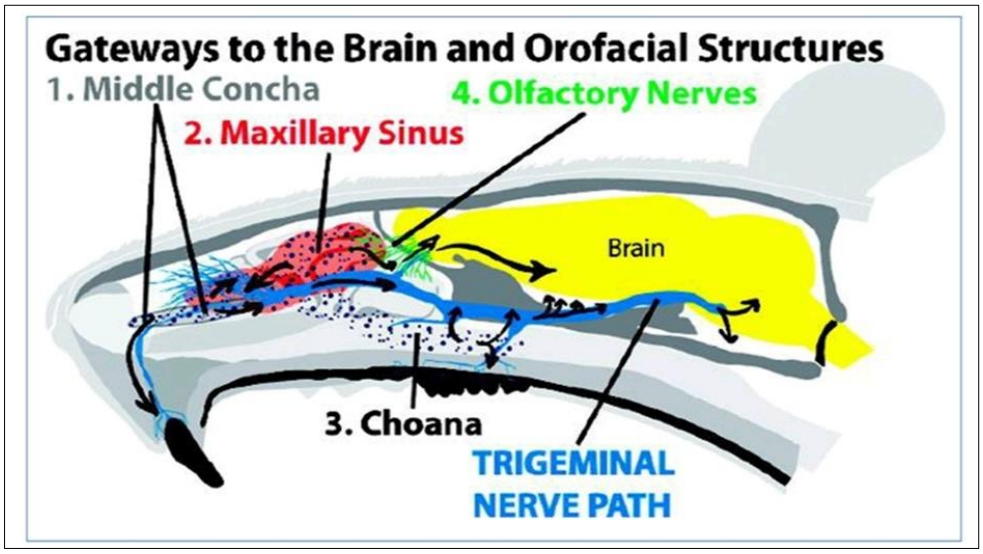

Figure 2 Gateway to the brain and orofacial structure

1.7. Nasal drug delivery systems

Nasal Drug Delivery Route The nasal route has gained attention as it is a direct noninvasive way to transport drugs to the brain which cannot be transferred via the oral route. To date, olfactory and trigeminal nerves have been shown to be safe and effective pathways to deliver therapeutic agents to brain. The olfactory pathway is composed of the olfactory epithelium, lamina propria, and olfactory bulb. Three types of cells, neuronal cells, progenitor cells, and supporting cells belong to the olfactory epithelium and are connected by tight junctions. An information pathway to the brain is built by neuronal cells which start from the olfactory bulb in the CNS to the olfactory epithelium in the nasal cavity. Due to the constant motion between basal cells and neural cells, the delivery ability of drugs to the brain was enhanced. Lamina propria, which consists of blood vessels, mucus secreting glands, olfactory axons, and a maxillary branch of trigeminal nerve, lies on the nasal epithelium. The olfactory bulb is used for direct nasal delivery of drugs for its distribution in different regions of the brain, such as the piriform cortex, amygdala, and hypothalamus. The trigeminal pathway is another important route for delivery of therapeutic agents to the brain. The trigeminal nerve with three branches, including the ophthalmic nerve, maxillary nerve, and mandibular nerve, control the respiratory region of the nasal cavity and sensation of the nasal cavity. Among them, ophthalmic and maxillary nerves bring the information from the nasal cavity to the CNS by controlling the nasal mucosa. So, numerous drug delivery systems for the brain or nerves usually use these two branches as a target for the delivery of drugs. Drugs enter the brainstem through pons by the trigeminal nerve controlling the nasal cavity and then travel to caudal and rostral parts of brain so that transport of drugs to the brain is achieved. Because not only the olfactory pathway but also the trigeminal pathway could deliver drugs to the rostal area of the brain, it difficult to distinguish when drugs are intra nasally

Cerebrospinal fluid (CSF) in the subarachnoid space and nasal lymphatics provide a pathway for therapeutics to both CSF and other areas of the CNS. Some radiolabeled tracers were injected into the CSF in cerebral ventricles or subarachnoid space drain to olfactory bulbs, which then travelled into channels and entered the nasal lymphatic system and cervical lymph nodes which demonstrated the reach of drugs to the CNS after intra nasal drugs moved from the nasal cavity to the CSF, the brain interstitial spaces, and perivascular spaces.

The distribution of neuro therapeutics in CSF also proves the mechanism of nose-to brain drugs The general rapid clearance of the administered formulation from the nasal cavity because of the mucociliary clearance mechanism is another issue of importance low membrane transport, this can be particularly the case once the drug isn't absorbed enough across the nasal membrane it's been shown that for each liquid and powder formulations, that don't seem to be bioadhesive, the life for clearance is of the order of 15-30 min. The employment of bio adhesive excipients within the formulations is an approach to beat the fast mucociliary clearance. The clearance may additionally be reduced by depositing the formulation within the anterior, less ciliate a part of the cavity so resulting in improved absorption.

1.7.1. Low bioavailability

Bioavailability of polar medicine is mostly low, regarding 100% for low mass medicine and not on top of Chronicles for peptides like thyrocalcitonin and insulin. The foremost issue limiting the nasal absorption of polar medicine and particularly massive mass polar medicine like peptides and proteins square measure the low membrane porosity. Drugs will cross the epithelial cell membrane either by the transcellular route or vascular transport mechanisms or by the paracellular route. Polar medicine with molecular weights below a thousand public prosecutors can usually pass the membrane victimization the latter route. Nasal absorption of such polar drugs is improved by co administration of absorption enhancing agents. Commonly used dosage form for transnasal absorption include surfactants (laureth-9, Na laurylsulfate), bile salts, bile salt derivatives (sodium glycocholate, Na deoxycholate, Na taurodihydrofusidate), fatty acids, fatty acid derivatives (linoleic acid), phospholipids (lysophosphatidyl choline), numerous cyclodextrins and ion compounds like chitosan and its derivatives, poly-L-arginine, poly-L- essential amino acid. A spread of mechanisms however usually they act by fixing the porosity of the vegetative cell layer by modifying the lipid bilayers, activity of proteins from the membrane or maybe uncovering off the outer layer of the mucous membrane.

1.7.2. Membrane permeability

Nasal membrane permeability is the essential factor which has an effect on the absorption of the drug through the nasal route. The water soluble drugs and particularly large molecular weight drugs like peptides and proteins are having the low membrane permeability are mainly absorbed through the endocytosis transport and by passive diffusion through the aqueous pores (i.e. tight junctions).

Drug concentration, dose and dose volume these three interrelated parameters affect the performance of nasal drug delivery. Some drugs tend to show increase in nasal absorption with increased drug concentration. Approximately the

maximum concentration of drug for nasal administration can be 20mg/dose. Increased volume or excess volume of dose administered may lead to draining of formulation from nasal cavity. Volume maximally 100 µl/ spray administration.

1.7.3. Viscosity

Higher the viscosity of the pharmaceutical formulation greater is the contact time between the drug and the nasal mucosa thus increases the time for permeation. At an equivalent time, extremely viscous formulations could interfere with the traditional functions like ciliary beating, mucociliary clearance and so alter the porousness of medication.

1.7.4. Lipophilic-hydrophilic balance

The HLB nature of the medication affects the absorption mechanism. By increasing lipophilicity, the permeation of the compound commonly will increase through nasal membrane. Beating, mucociliary clearance and so alter the porousness of medication. Lipophilichydrophilic balance The HLB nature of the medication affects the absorption mechanism. By increasing lipophilicity, the permeation of the compound commonly will increase through nasal membrane. Through the nasal membrane was found to possess some deliquescent character, it seems that these mucosa area unit primarily oleophilic in nature and therefore the macromolecule domain plays a very important role within the barrier perform of those membranes. Oleophilic medication like narcotic antagonist, buprenorphine, androgenic hormone and 17a-ethinyl- oestrogen area unit nearly utterly absorbed once administered intranasal route [1, 19].

1.8. Barriers in nasal drug product development

1.8.1. Physiological barrier Nasal mucus

Viscosity, pH of mucus and interaction of drug/dosage form and mucus Nasal epithelial barrier -Molecular weight, mode of transport and ionization constant Mucociliary clearance -Nasal residential time and properties of dosage form Pathophysiology – Nasal secretion volume and mode of epithelium transport Efflux transport system -Nature of drug molecule and time period of therapy.

1.8.2. Formulation factors

High concentration for better bioavailability and maximum dose in minimum volume vehicle (less than 200µl). Drug concentration and dose volume. Osmolality Isotonic solution prevents epithelial damage and toxicity Site of deposition based on viscosity, molecular weight and size of drug, position of head, volume, delivery device, the nasal residential time prolongs by deposition at anterior chamber of cavity.

1.8.3. Physiochemical Properties of Drugs

Chemical forms

The chemical form of a drug is an important factor in determining absorption. For example, conversion of the drug into a salt forms can also alter its absorption. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of Tyrosine.

Polymorphism

Polymorphic nature of drug molecules is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological member Tyrosine.

Molecular weight

A linear inverse correlation exists between the absorption of drugs and molecular weight up to 300 Da. Absorption decreases significantly if the molecular weight is greater than 1000 Daltons. Absorption can be enhanced with the use of absorption enhancers.

Partical size

It has been reported that particle sizes greater than 10µm are deposited in the nasal cavity. To Fine particles i.e., below 5µm should be avoided for nasal administration as there are chances of inhalation directly into the lungs.

1.8.4. Solubility and Dissolution rate

Drug solubility and dissolution rates are the predominant factor that governs nasal absorption from powders and suspensions [20]. The absorption profile is not only influenced by drugs solubility but also by the nature of pharmaceutical preparations. As the size of nasal cavity is small, the allowable volume of drug solution should below for intranasal drug administration. Therefore, drugs poorly soluble in water or requiring high doses may affect the dissolution rate. The particles deposited in the nasal cavity should get dissolved prior to absorption. If a drug remains as particles or is cleared away absorption of drug get hampered.

1.9. Nasal drug delivery devices

It should denoted that efficient and novel nasal drug delivery devices used for direct transport of drugs from nose to brain is another important strategy improvement of diagnosis and treatment effect, which help drugs to be transported to the brain via the olfactory/trigeminal pathway. Some devices, including droppers, syringes, pressurized meter dose inhalers, Breathe Powered Bi-directional nasal devices, and pressurized olfactory delivery devices, were adopted in clinical treatment and were also categorized into devices with liquid, powder, and semisolid formulations. The right delivery system depended on the type of drug formulation. Powder formulations with high stability often stick to the nasal mucosa before it is cleared. Liquid formulations are the oldest, cheapest, and simplest method. Popular nasal sprays spread easily and deposit in the olfactory region. The spray would distribute in the nasal cavity through nasal mucociliary clearance. But the limitation of nasal drops or spray devices depends on the self-administration technique [21].

1.9.1. Powder Devices

Compared with liquid (solution or suspension) and gel formulations of drugs, powder particles are stable and not easily dissolved so they can remain in the nasal mucosa for a long time. Moreover, because of free preservatives, powder dosages could be administrated in a large dose and prevent microbial contamination. Deposition and absorption of a powder formulation of drugs for nasal delivery depend on many factors, including size and shape of powder particle, flow characteristics, and solubility as shown in an insufflator composed of straw or tube with drugs could directly deliver drugs to the olfactory region, although usually local anesthetics or decongestants are needed before insufflations delivery. Dry powder inhalers are simple in design, cheap, can be operated without medical supervision, and doses range from μg to mg.

1.9.2. Liquid-Based Devices

This technique is usually accompanied with anaesthesia or a sedative to deliver the liquid. Because mucosa is sensitive to the deposition site, it is a major issue with this method of drug delivery. By blowing with the mouth, solution filled in the catheter enters into the nostril by the other end of the catheter in the nose cavity. Drops are another important method of nasal drug delivery for liquid formulations and have been used for decades due to their cost effectiveness and easy manufacture [22].

1.9.3. Sprays and Solution

The solutions of drug molecule are administered in nasal cavity is act as a nasal sprays and nasal solutions. It is most convenient approach for delivering the drug formulation for nose to brain delivery bypassing the BBB.

Figure 3 Sprays and Solution

1.9.4. Instillation and rhinylecather

Liquid formulation device is important to deliver the formulation by drop by drop in appropriate region of nasal cavity. Catheter dosing is measured by the filling prior to admin-iteration [23].

Figure 4 Instillation and rhinylecather

1.9.5. Compressed air nebulizers

They are the nasal administration devices in which the drug loaded formulation in the gases state deliver to the lungs. It is a compressed air filling devices for compressed air nebulizer's drug formulation to nasal cavity. This device is more applicable for targeting the drug formulation to respiratory tract to give rapid on-set of action and reduces the toxic effects[24].

Figure 5 Compressed air nebulizers

1.9.6. Squeezed bottle

This is important for delivering the decongestants. They are smooth plastic bottles with simple jet outlet by pressing the bottle air passes in inside the container is pressed out of the small nozzle, having the optimum volume. After minimizing the pressure the air again passes to inside the bottles. Dose concentration and deposition of liquid phase Squeezed bottle delivering via Squeezed bottles they are strongly dependent on mode of administration. Dose and droplet size of that formulation is mainly dependent on pressed application of that container.

Figure 6 Squeezed bottle

1.9.7. Metered-dose pump sprays

It is based on hand operated pump mechanism. It is important to give local effect such as topical decongestants, antihistamines. This container can be containing the pump, valve and the actuator. Dose of metered dose pump sprays depends upon the viscosity and surface tension of that formulation [25].

Figure 7 Metered-dose pump sprays

1.9.8. Single and duo dose spray devices

They are administered single dose of drug formulation to the intranasal pathway and duo dose device administered more than one dose of different or same formulation intranasal Figure 14: single and duo dose spray devices Cavity .It is simple convenient and non-invasive mode for delivering the drug into nasal cavity. It is used for treatment of chronic rhinosinusitis and in a vaccine study.

Figure 8 Single and duo dose spray devices

1.9.9. Vianase atomizer

This device atomizes liquids by producing a vertical flow on the droplets as exit the device. The induced vertical flow characteristics can be altered in circular velocity and direction to achieve different droplet trajectories [26].

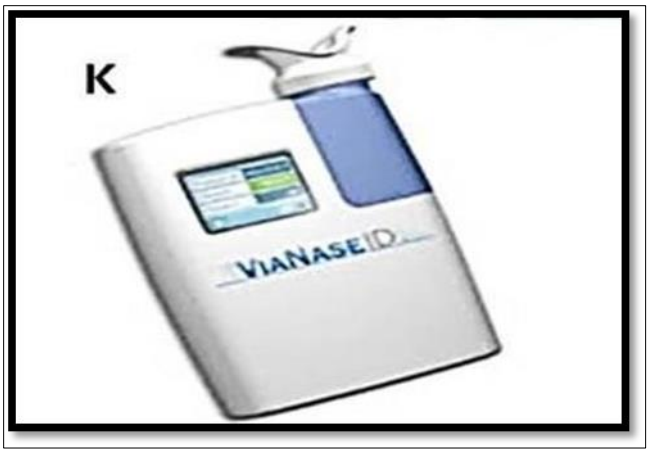

Figure 9 Vianase atomizer

1.10. Advantages

- Rapid drug absorption via highly vascularized mucous membrane.
- Easy administration, non-invasive.
- Rapid onset of action.
- Improved bioavailability.
- Improved convenience and compliance.
- Self-administration.
- Direct transport of drug into systemic circulation and CNS is possible.
- Massive nasal tissue layer area for dose absorption.
- Rejection of the digestive tube and first-pass metabolism.
- Fast onset of action.
- Lower facet effects medication that can't be absorbed orally is also delivered to the circulation through nasal drug delivery system.
- Convenient route when put next with duct route for future medical aid. Bioavailability of larger drug molecules may be improved by suggests that of absorption attention or alternative approach.

1.11. Disadvantages

- Volume which will be delivered into bodily cavity is restricted to 25-200 µl.
- Not possible for prime relative molecular mass quite 1k prosecuting attorney.
- Adversely stricken by pathological conditions.
- Drug porousness might alter due to ciliary movement.
- Drug porousness is also restricted due to catalyst inhibition.
- Nasal irritants medicine cannot be administered through this route.
- Actual mechanism isn't nonetheless clearly glorious; some medicine might cause irritation to the nasal membrane.
- Nasal congestion due to cold or allergies might interfere with absorption of drug.
- Drug delivery is predicted to decrease with increasing relative molecular mass.
- Frequent use of this route ends up in membrane injury.

2. Conclusion

Central nervous system (CNS) disorder (e.g., Multiple sclerosis, Alzheimer's disease) represents a glowing public health issue, primarily due to the increased life expectancy and the aging population. The treatment of such disorders is notably elaborate and requires the delivery of therapeutic to the brain in appropriate amounts to elicit a pharmacological response, However, despite the major advances both in neuroscience and drug delivery research, the administration of drug to the CNS still remains elusive .It is commonly accepted that effectiveness- related issues arise due to the inability of parenteral administered macromolecules to cross the Blood Brain Barrier (BBB)in order to access the CNS, thus impeding their successful delivery to brain tissues. As a result, the direct Nose- to – Brain delivery has emerged as a powerful strategy to circumvent the BBB and deliver drugs to the highlight the different experimental and computational approaches pursued so far to attain and enhance the direct delivery of therapeutic agents to the brain and shed some light in the underlying mechanisms involved in the pathogenesis and treatment of neurological disorders.

Compliance with ethical standards

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Disclosure of conflict of interest

There was no conflict of interest in this study.

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