



A OVERVIEW OF NASAL TO BRAIN DRUG DELIVERY

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Article Received on 27/07/2020

Article Revised on 17/08/2020

Article Accepted on 06/09/2020

ABSTRACT

Use of the nasal route for the delivery of challenging drugs such as small polar molecules, vaccines, hormones, peptides and proteins has created much interest in nowadays. Due to the high permeability, high vasculature, low enzymatic environment of nasal cavity and avoidance of hepatic first pass metabolism are well suitable for systemic delivery of drug molecule via nose. The unique relationship between nasal cavity and cranial cavity tissues in anatomy and physiology makes intranasal delivery to the brain feasible. An intranasal delivery provides some drugs with short channels to bypass the blood–brain barrier (BBB), especially for those with fairly low brain concentrations after a routine delivery, thus greatly enhancing the therapeutic effect on brain diseases. In the past two decades, a good number of encouraging outcomes have been reported in the treatment of diseases of the brain or central nervous system (CNS) through nasal the paper also includes. The different types of barriers which affects the delivery and how to overcome it low bioavailability low membrane transport enzyme degradation etc physicochemical properties that overcome by prodrug innovative formulation absorption enhancer etc drug are delivered through the various type of devices to nose to reach brain.

INTRODUCTION

Routes encounter acidic or enzymatic degradation and Drugs are delivered to the systemic oral, parenteral (intravenous, intramuscular), and in most cases, drugs administered via these circulation via several routes, such as may undergo excessive first-pass effect (hepatic metabolism) following administration. Due to these factors, effective doses of drugs sometimes may not reach the systemic circulation, resulting in ineffective treatment. It is therefore required to explore either alternate routes or specialized delivery technologies that can result in improved and effective drug delivery options. The nasal route of drug delivery is one such alternate route that provides access to highly vascularized mucosa, which can be exploited as an interesting site for local drug delivery, systemic drug delivery, and targeted drug delivery.

Nose to Brain approach is a great area of interest for direct transport pathway of drugs in nose to brain through olfactory and trigeminal nerve cells through nose they can bypassing the BBB and enter brain directly. Olfactory region of the nasal mucosa is direct connection between nose and brain explored for CNS acting drugs. Improvement in bioavailability of some drugs and therapeutic proteins and peptides was reported). For nose to brain delivery, drugs need to permeate the BBB from the circulation. To achieve this, drug or Prodrug is absorbed through active and passive transport to cross the tight junctions of the BBB. Drug applied in nasal

pathway is directly reaches to the brain either by direct transport from olfactory region to the brain and from blood to brain or CSF).

The olfactory region, next to the respiratory region in which, drug is directly absorbed into the brain by different mechanisms including transcellular, paracellular, olfactory and trigeminal neural pathways. The olfactory region of nasal mucosa contains olfactory cells, which extend up to cranial cavity. In nose to brain approach drug formulation on nasal instillation comes in contact with nasal mucosa and it is rapidly transported directly into the brain. Bypassing the BBB and achieving very rapid CSF levels. Some amount of administered drug is reaches to systemic circulation by respiratory region and some amount of drug is lost to nasal associated lymphoid tissue. The hydrophobic (lipid soluble) molecules is rapidly enter to the blood stream from nasal mucosa and subsequently reach the CNS by crossing the BBB. But, Maximum pharmaceutical drug is hydrophilic (water soluble), this drug is a rate limiting barrier for targeting and highly lipid soluble drug molecules show better targeting ability due to higher partition coefficient (higher lipophilicity). Hydrophilic drug molecules is also cross the nasal mucosa when, nasal mucosa is break down due to local injury). In the recent years, most of drugs and Proteins and Peptides is delivered efficiently by using Nose to Brain Delivery. This strategy is useful to treat variety of CNS disorders including, Brain tumors, Parkinson disorder, Multiple

Sclerosis, Alzheimer disorder, Epilepsy and Psychiatric disorders). This is all the possible pathways for drug can reach brain after nasal administration are predominately either by the olfactory or trigeminal region or through systemic circulation.

ADVANTAGES

- 1) The nasal bioavailability for smaller drug molecules is good.
- 2) Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
- 3) Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
- 4) Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
- 5) Drug degradation that is observed in the gastrointestinal tract is absent.
- 6) Hepatic first pass metabolism is avoided.
- 7) Rapid drug absorption and quick onset of action can be achieved.
- 8) The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.

LIMITATIONS

- 1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.

- 2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
- 3) Nasal cavity provides smaller absorption surface area when compared to GIT.
- 4) There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
- 5) Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.

ANATOMY

The nasal septum divides the human nose into two equal symmetrical halves. The posterior part of the nasal cavity is called the nasopharynx, and each symmetrical half opens to the environment. Both halves of the nasal cavity consist of the following four regions.^[1,2]

Vestibule: Is not very highly vascularized and permeability of the drugs via this region is very poor.

Atrium: Vascularization in this part of the nasal cavity is low, which results in moderate permeability of drugs.

Respiratory Region: This part of the nasal cavity is highly vascularized and therefore the permeability of drugs from this region is good.

Olfactory Region: Is highly vascularized, which results in high permeability of drug. This region is also reported as a potential site for nose-brain transport of drugs.

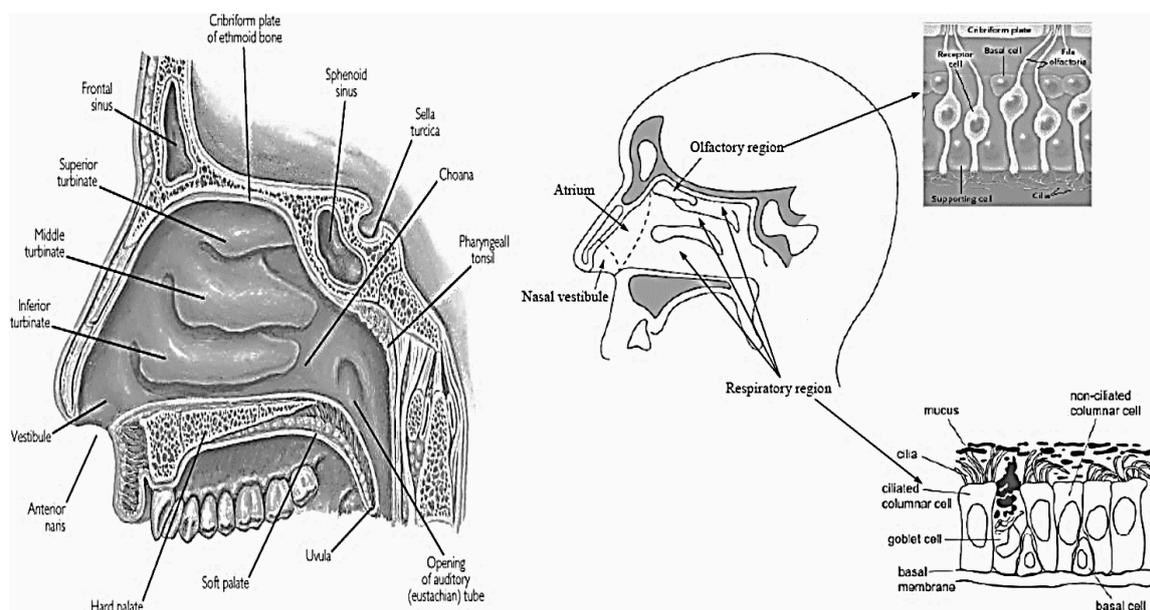


Figure: Anatomy of Nose and Distinct functional areas of nasal cavity.

BARRIERS TO NASAL ABSORPTION

1) Low bioavailability

Lipophilic drugs are generally well absorbed from the nasal cavity compared to polar drugs. The pharmacokinetic profiles of lipophilic drugs are often identical to those obtained after an intravenous injection and bioavailability approaching

2 Enzymatic Degradation

The presence of enzymes in the nasal cavity can form an enzyme barrier that is known to affect the stability of the drug in the nasal cavity. Proteins and peptides are prone to degradation by proteases and amino-peptidase within the nasal cavity. Although it is not exact as the first-pass effect that drugs undergo following oral administration, the enzymatic activity in the nasal cavity can result in

decreased therapeutic effects. The presence of P450 enzymes are much higher in the nasal mucosa when compared to the respiratory mucosa.

3) Low membrane transport

Another importance factor is low membrane transport is the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. This is especially the case for drugs that are not easily absorbed across the nasal membrane. It has been shown that for both liquid and powder formulations, that are not mucoadhesive, the half life of clearance is in the order of 15–20 min.

FACTORS INFLUENCING NASAL DRUG ABSORPTION

1) Physicochemical properties of drug

Molecular size.

Lipophilic-hydrophilic balance.

Enzymatic degradation in nasal cavity.

2) Nasal Effect

Membrane permeability.

Environmental pH

Mucociliary clearance

Cold, rhinitis.

3) Delivery Effect

Formulation (Concentration, pH, osmolarity)

Delivery effects

Drugs distribution and deposition.

Viscosity

1) Physicochemical properties of drug

Molecular size

The molecular size of the drug influence absorption of the drug through the nasal route. The lipophilic drugs have direct relationship between the MW and drug permeation.

Lipophilic-hydrophilic balance

By increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa.

Enzymatic degradation

In nasal cavity In case of peptides and proteins are having low bio-availability across the nasal cavity, so these drugs may have possibility to undergo enzymatic degradation of the drug molecule in the lumen of the nasal cavity or during passage through the epithelial barrier.

2) Nasal effect factors

Membrane permeability

Nasal membrane permeability is the most important factor, which affect 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.

Environmental pH

The environmental pH plays an important role in the efficiency of nasal drug absorption. Small water-soluble compounds such as benzoic acid, salicylic acid, and alkaloid acid show that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the nonionised form. However, at pH values where these compounds are partially ionized, substantial absorption was found. This means that the nonionised lipophilic form crosses the nasal epithelial barrier via transcellular route, whereas the more lipophilic ionized form passes through the aqueous paracellular route.

Mucociliary Clearance

Mucociliary clearance is one of the functions of the upper respiratory tract is to prevent noxious substances (allergens, bacteria, viruses, toxins etc.) from reaching the lungs. When such materials adhere to, or dissolve in, the mucus lining of the nasal cavity, they are transported towards the nasopharynx for eventual discharge into the gastrointestinal tract.

Cold, Rhinitis

Rhinitis is a most frequently associated common disease, it influence the bioavailability of the drug. It is mainly classified into allergic rhinitis and common, the symptoms are hyper secretion, itching and sneezing mainly caused by the viruses, bacteria or irritants

Drugs distribution and deposition

The drug distribution in the nasal cavity is one of the important factors, which affect the efficiency of nasal absorption. The mode of drug administration could effect the distribution of drug in nasal cavity, which in turn will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms mainly depends on the site of disposition. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation.

3) Delivery effect factors

Formulation (Concentration, pH, Osmolarity)

The pH of the formulation and nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection. In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria.

Concentration gradient plays very important role in the absorption / permeation process of drug through the nasal membrane due to nasal mucosal damage. Examples for this are nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. Another is absorption of salicylic acid was

found to decline with concentration. This decline is likely due to nasal mucosa damage by the permanent.

The osmolarity of the dosage form affects the nasal absorption of the drug; it was studied in the rats by using model drug. The sodium chloride concentration of the formulation affects the nasal absorption. The maximum absorption was achieved by 0.462 M sodium chloride concentration; the higher concentration not only causes increased bioavailability but also leads to the toxicity to the nasal epithelium.

Drugs distribution and deposition

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Viscosity

A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drug.

Recommendations To Overcome Barriers To Drug Transport From Nose To Brain

Mucoadhesive polymers, absorption enhancers, and drug delivery devices aimed for precise delivery of drug within the nasal cavity.

There have been a number of novel approaches evaluated in animal models to overcome the barriers to nose-to-brain delivery of drugs via the nasal route. The efforts have been concentrated toward increasing the residence time in the nasal mucosa and modifying the physicochemical properties of the drug using functional excipients and innovative drug delivery technologies. A few examples of these innovative technologies include a combination of.

Prodrug Approach

As previously discussed, the physicochemical properties of drugs, such as the molecular weight and lipophilicity, are critical parameters that have the most influence on drug delivery to the brain via the nasal epithelium. A

prodrug strategy can help in modifying these properties in such a manner that the rate and extent of drug absorption increases in the nasal cavity. Experimental studies both *in vivo* and *ex vivo* have shown that rapid and complete absorption of drug can be attributed to the degree of lipophilicity and smaller molecular weight of the test compound. Several water-soluble alkyl ester prodrugs of Ldopa were administered to rats via the nasal route, and it was observed that the concentration of butyl ester prodrug of Ldopa was significantly higher in the CNS of rats as compared to parent drug.^[14] While this approach has proven to work in many small molecules, this strategy presents some challenges for large molecules, such as proteins and other biologics. It has been difficult to increase the lipophilicity of proteins as there can be significant impact on the spatial structure of the protein, resulting in diminished biological activity.^[14]

Innovative Formulation Approach

Maintaining high drug concentration for passive diffusion on the nasal epithelium is important, and in order to achieve this, precise drug deposition and extended residence time must be optimized. There are several nasal formulations and devices that are designed to overcome these challenges. Experimental design in which N-cyclopentyladenosine (CPA) was formulated with mannitol-lecithin and chitosan hydrochloride microparticles were administered to rats via nasal administration showed higher amount of CPA present in the CNS of rats compared to the free CPA. The chitosan hydrochloride formation resulted in a 10-fold higher amount of CPA in the CSF compared to the mannitollecithin microparticles formulation.^[16]

Absorption Enhancers & Enzyme Inhibitors

Drugs that are highly lipophilic in nature and also have a very low molecular weight might not need a specialized formulation approach, including use of absorption enhancers. Absorption enhancers can be used in cases where the drug exhibits poor membrane permeability, has large molecular size, and is susceptible to enzymatic degradation by aminopeptidases.^[17,19,20] Drugs that are formulated using absorption enhancers may impart the following properties that will result in increased drug bioavailability following nasal administration:

- Improve the solubility of the drug
- Reduce the surface tension of the mucus
- Decrease the enzyme activity which may keep the drug in its stable form

Nasal Drug Delivery Devices

Drug delivery devices have been found to play an important role in ensuring that the entire drug is delivered to the target site in the nasal cavity. It is difficult to precisely deliver the drug to the olfactory region of the human nasal cavity as this region is found high up in the nasal cavity, above the superior conchae. This area is exposed to a very low volume of the air that penetrates the nasal cavity and can result in lower doses of the drug reaching the olfactory region. Some of the

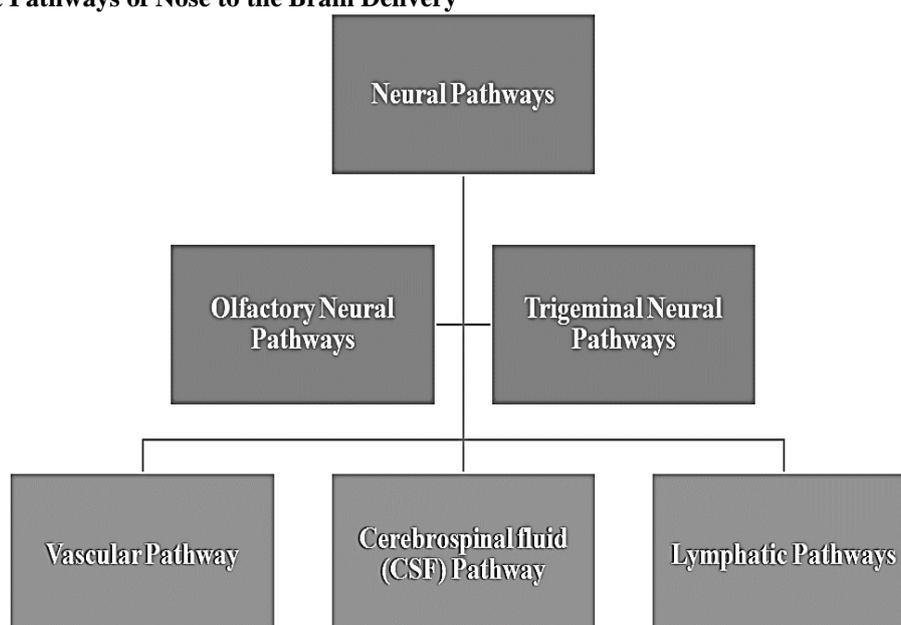
novel proprietary devices that have shown significant differences following administering the drug via the nasal route are shown in table.

Company	Device Name
Optinose	Bi-Directional Technology™
Impel NeuroPharma	POD Device
Kurve Technology	ViaNase Technology/Controlled Particle Dispersion (CPD) Technology Platform

Proprietary Nasal Drug Delivery Devices²²

Although the initial proof-of-concept studies using these novel nasal drug delivery devices does show promising results, they still need to be further tested using different types of molecules intended to be delivered to the CNS/brain via the nasal cavity/route of drug administration.

Drug Transport Pathways of Nose to the Brain Delivery



Olfactory pathway

Therapeutic modalities once administered via nose, it travels to the olfactory mucosa (also known as olfactory epithelium) represented in the. Olfactory mucosa contains olfactory receptor neurons that are responsible for the transduction. Transduction happens in olfactory receptors on the cilia which is the end of the olfactory receptor neurons. Molecules reach the olfactory receptor neurons by paracellular or transcellular mechanism. The integrity of nasal epithelium, along with the tight junctions, desmosomes, adherent junctions and space between the epithelial cells allows the entry of by paracellular transport [The neuronal pathway considered to be determining step of the nose to brain route. Drug moieties travels along axon and via nerve bundle cross the cribriform plate and reach the olfactory bulb which is actually appear on the surface of the brain. From the olfactory nerves, the therapeutic moiety can enter the cerebrospinalfluid (CSF) and olfactory bulb The drug

can be distributed from the CSF to brain by mixing with interstitial fluid in the brain. After a nasal administration of drug it takes only few minutes to reach brain via olfactory transport. Intra-neuronal pathway and extra-neuronal pathway are the two different pathways of the olfactory neuronal pathway into the brain. Intra-neuronal pathway involves axonal transport and it requires hours to days for active moiety to reach different regions of the brain. In case of extra-neuronal pathway which involves transport through perineural channels; it takes only few minutes to reach active moiety directly to brain. The olfactory neuronal pathway innervate to the deeper areas of brain such as cortex, cerebrum and cerebellum. Trigeminal.

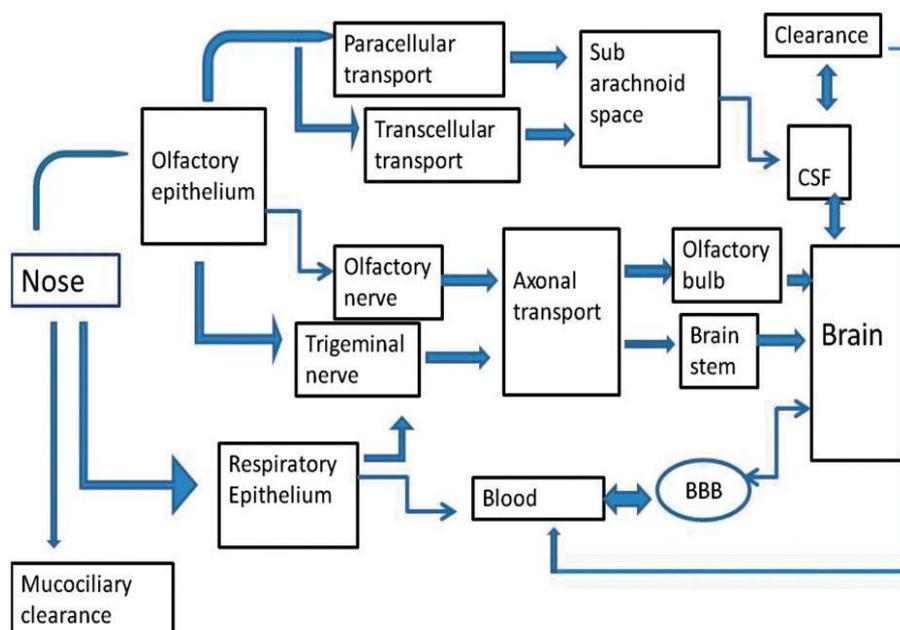


Fig. Overview of three different pathways after nasal administration.

Trigeminal Pathway

Trigeminal nerve pathway connecting to the tail part of the brain such as spinal cord, the medulla and the pons. Drug transported through nose via trigeminal nerve pathway by intracellular transport (axonal transport) or by endocytosis. The trigeminal nerve is the largest and fifth cranial nerve and it is composed of three branches such as ophthalmic, maxillary and mandibular. Out of these three mainly ophthalmic and maxillary branches play an important role in nose to brain drug delivery, the neurons from these branches pass directly through the nasal mucosa. Some segment of trigeminal nerve also ends in the olfactory bulbs. Branches from the ophthalmic part of the trigeminal nerve innervate to the dorsal part of the nasal mucosa and the anterior nose but considering maxillary branch innervate to the turbinates of the nasal mucosa. Once the compounds diffuse through the mucosa of the nasal cavity, it reaches the branches of trigeminal nerves in olfactory and respiratory regions, and via brain stem transported to the axonal route. A part of the trigeminal nerve that passes through the cribriform plate that may also be involved in the delivery of therapeutics from nasal cavity to the forebrain. Thorne *et al.*^[21] reported that after intranasal administration of insulin-like growth factor-I (IGF-I) rapidly reached brain via trigeminal neuronal pathway. Intranasally administered drug/nanoparticles absorbed from nasal cavity is passage through the mucus, this is the first step involved in absorption. After passing through the mucus, there are several mechanisms involved in the transportation through mucosa. There are paracellular, transcellular, carrier-mediated transport, receptor-mediated transport and transcytosis. Paracellular route is the transport of molecules between the cells. Transcellular route refers to the transport of drug across the cells; this may occur by carrier-mediated transport or by endocytosis. In transcellular route, adsorptive transcytosis mechanism involves transport of

macromolecules. This process involves interaction between the ligand in bloodstream and cell surface. This type of interaction may be due to electrostatic interaction between the positively charged ligand and such as protein or macromolecules and negatively charged membrane. Nanoparticles and some compounds undergo transcytosis for permeation.

Kimura *et al.* suggested that the mechanism of carrier-mediated absorption takes place by the organic cation transporters, P-glycoprotein, amino acid transporters, dopamine transporter acts as a carrier of molecules in nasal mucosa.

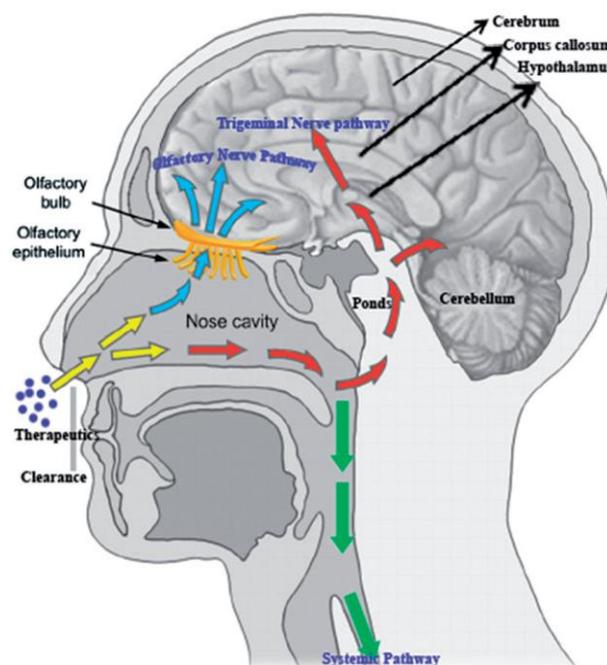
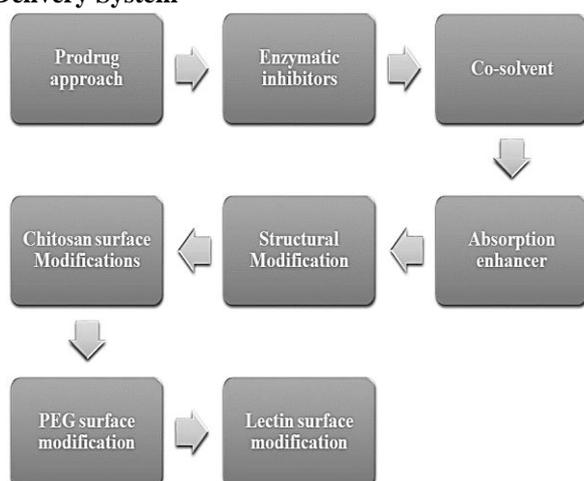


Figure: Transport mechanism of therapeutics from nose to brain.

4. Formulation Strategies for Nose to Brain Drug Delivery System



Prodrug approach

In Prodrug approach, the drugs that administered in the form of solution undergo dissolution prior to absorption. Lipophilic drugs get easily absorbed through nasal membrane, However they are poorly water soluble drugs. So the Prodrug approach may be utilized to get of higher hydrophilic character that can made as aqueous formulation of hydrophobic drugs. It should be also focused, when that formulation reaches to systemic circulation, Prodrug must be converted to the parent drug molecule.

Enzymatic inhibitors

Nasal mucus layer and nasal mucosa is act as enzymatic barriers for nasal drug delivery system (they have a wide variety of enzymes). Several approaches was used to avoid the enzymatic degradation, including the use of protease and peptidases inhibitors. Bestatin and comostate amylose were used as aminopeptidases inhibitor and leupeptine, Aprotinin as tyrosine inhibitors is probably involved in the degradation of calcitonin.

Co-solvent

This approach is used to increases the solubility of the drugs. Mostly used co-solvent includes glycerol, ethanol, propylene glycol and ethylene glycol, since these are nontoxic, non-irritant to nasal mucosa and pharmaceutical acceptable.

Absorption enhancer

Absorption enhancer, in which the poor permeability of hydrophilic drugs may be overcome by the used of absorption enhancers that induces reversible modification of epithelial barrier. The absorption enhancer is used in nasal delivery were surfactant (SLS, Poloxamer, tweens, spans), bile salts.

Colloidal Carriers in Nose to Brain Drug Delivery Systems

Colloidal drug carriers include microemulsion, nanoemulsion, nanoparticle, polymeric micelles,

liposomes, mucoadhesive solutions and microspheres. The intent behind use of colloidal drug carriers for nose to brain drug delivery was to increases the specifically towards cell or tissue to increases bioavailability of drugs by increasing their diffusion through the biological membranes and protect against enzymatic degradations.

Microemulsion

Microemulsion is a clear, stable, isotropic mixture of oil, water and surfactant are frequently in the combination with co-surfactants these approach is interested to the pharmaceutical scientist because of their considerable potential to act as drug delivery vehicle by incorporating of wide range drug molecules. They offer the advantages of spontaneous formation, easy manufacturing and scale up, thermodynamic stability and it's important to improve the solubilization and bioavailability. Preparing a pharmaceutically acceptable dosage from demands a clear understanding of the microemulsion structure, phase behaviour, factor leading to its thermodynamic stability, factors associated drug release from the formulation and potential uses and limitation of microemulsion system.

Nanoemulsion

Nanoemulsion is an isotropic mixture of oil, surfactant: cosurfactant (Smix) and drug is known as nanoemulsion. The colloidal size ranges from 50-100 nm are often referred to as Miniemulsion, nanoemulsion, ultrafine emulsion or the multiple emulsions. These nanoemulsion appear transparent and translucent to the necked eyes and the possess stability against sedimentation or creaming. These properties make nanoemulsion as carriers of vast interest for fundamental studies and practical applications in various fields like chemical, cosmetic and pharmaceutical and Biopharmaceutical fields.

Polymeric micelles

Polymeric micelles that may serve as nanoscopic drug carriers. Polymeric micelles are the self-assemblies of block of co-polymers and promising nanocarriers for drug and gene delivery, for drug delivery, polymeric micelles have been prepared from biodegradable and biocompatible blocks of copolymers. Polymeric micelles are characterized by core shell structure have reported that mixed micelles of bile salts and fatty acid have a synergistic effect on the nasal absorption of peptides.

Nanoparticles

Nanoparticle is a nanosized particle range size range of 1-1000 nm. It is applicable to improve the solubility of poorly soluble drugs and permeability of drug molecules This nanoparticulate system is based on biodegradable polymers, have been extensive exploited in targeting drug delivery as they offer excellent improvement in nose to brain delivery by protecting the encapsulated drug from biological and chemical degradation, the extracellular transport by P-gp efflux system is increases the CNS availability of drugs. The poly-lactic acid (PLA), poly-glycolic acid (PGA), poly-lactide-co-

glycolic acid (PLGA), poly-g-caprolactone (PCL), poly-methyl methacrylate, are the polymers known to be biodegradable, biocompatible and non-toxic. Illum *et al.* demonstrated that chitosan based nanoparticles can enhance nose-to-brain delivery of drugs compared to equivalent drug solutions formulations due to the protection of the drug from degradation and/or efflux back into the nasal cavity. Have reported olanzapine-loaded PLGA nanoparticles for the treatment of psychotic illness, schizophrenia, *via* nose to brain drug delivery platform.

Nasal Delivery Devices

Nasal drug delivery devices is versatile tool for direct drug delivery in nasal cavity by using various nasal device devices do exist, and more are in development.

Powder formulation devices

The powder nasal devices are more convenient and it is having a maximum stability than liquid nasal devices. In powder nasal devices preservatives are not required for preparation. It is having a larger dose of drug and they improve stability of formulation. They can be free from microbial growth. The nasal powder administration is increases the patient compliances and patient acceptance.

Insufflators

In this nasal devices, to deliver the pharmaceutical molecule for inhalation. This devices is mainly constructed in the straw or tubes which contains the pharmaceutical molecules. It is a pre-dose powder capsules.

Dry powder inhaler

Dry powder inhalers (DPIs)) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non-polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may lead to provocation of cough **Pressurized Metered-Dose Inhale (PMDI).**

The pressurized metered dose inhaler is a nasal device (Fig.7) to deliver optimum amount of drug to the lungs, this is a short burst aerosolized drug that inhaled the patient. A PMDI devices are important to deliver the optimum amount of medication to the lungs.

LIQUID FORMULATION DEVICES

Sprays and Solution

The solutions of drug molecule are administered in nasal cavity is act as a nasal sprays (Fig.7) and nasal solutions. The optimum dose of API is based on the amount of drug molecule or volume of drug in pharmaceutical formulations. It is most convenient approach for delivering the drug formulation for nose to brain delivery bypassing the BBB.

Instillation and rhinyle catheter

Rhinyle catheter is a 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 administration. This system is applicable for the experimental studies only.

Compressed air nebulizers

Nebulizers 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 delivering the drug formulation to nasal cavity. This devices is more applicable for targeting the drug formulation to respiratory tract to give rapid on-set of action and reduces the toxic effects. This devices is not applicable for drug delivering into systemic pathways.

Squeezed bottle

In this devices are 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 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.

Metered-dose pump sprays

Marketed nasal formulation such as suspension, emulsion, solution are directly delivered to intranasal pathway by using metered dose pump sprays. It is applicable for treatment of nasal hypersensitivity and other nasal disorders. It is based on hand operated pump mechanism. It is important to give local effect such as topical decongestants, antihistamines. This containers can be contain the pump, valve and the actuator. Dose of metered dose pump sprays depends upon the viscosity and surface tension of that formulations).

Single and duo dose spray devices

Single dose devices are administered single dose of drug formulation to the intranasal pathway and duo dose device administered more than one dose of different or same drug formulation intranasal 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.

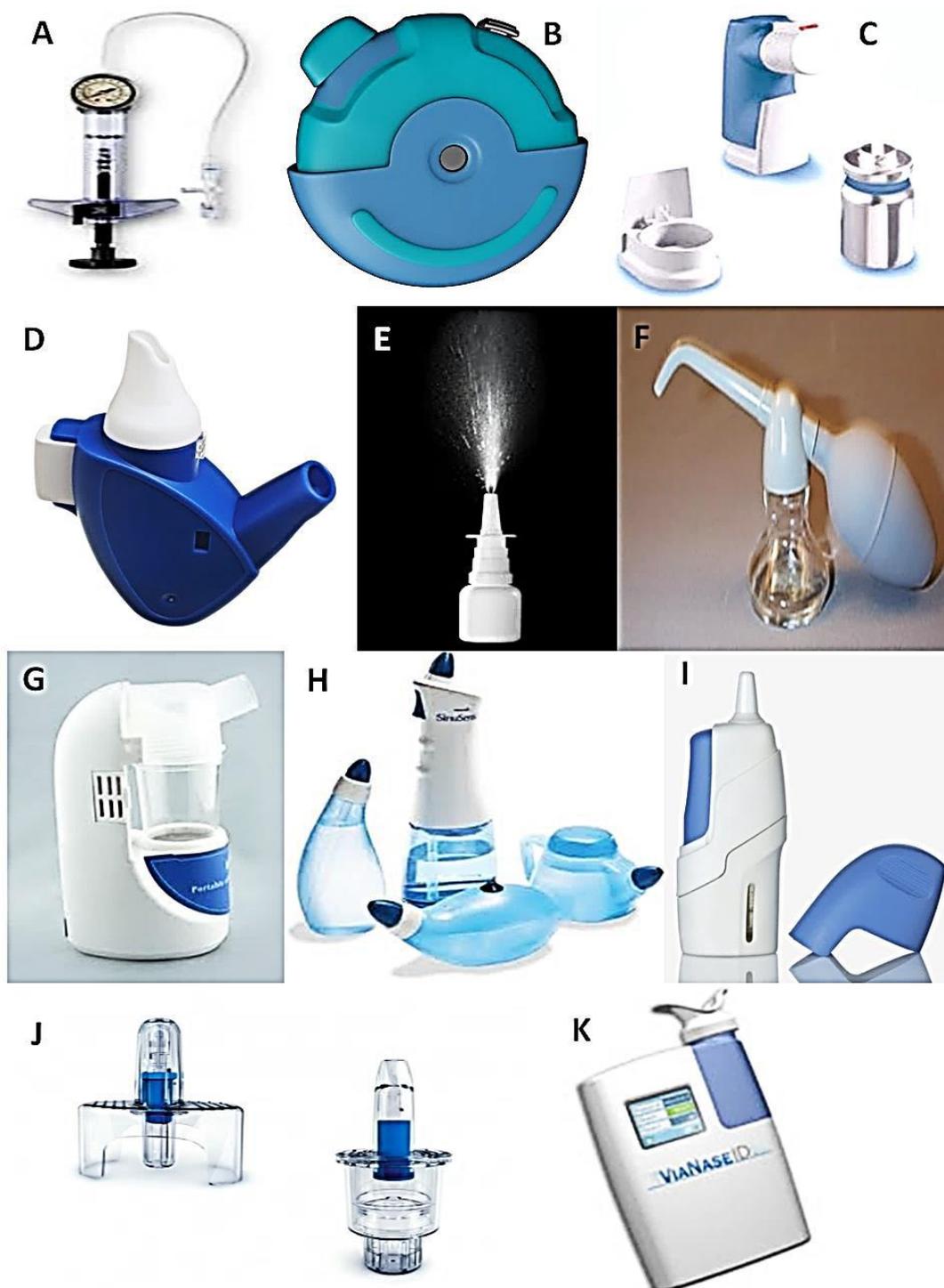


Figure: Nasal delivery devices: Insufflators (A), Dry powder inhaler (B), Pressurized Metered-Dose Inhale (C), Breath-powered Bi-Directional technology (D), Sprays and Solution (E), Instillation and rhinyle catheter (F), Compressed air nebulizers (G), Squeezed bottle (H), Metered-dose pump sprays (I), Single and duo dose spray devices (J), ViaNase atomizer (K).

CONCLUSION

The nose-to-brain delivery is often an alternative to oral therapies for the CNS that can present problems, usually related to the characteristics of the drug. There are many reasons a CNS drug can be a good candidate for intranasal nanoemulsion, as an alternative to the oral administration (Table 1).

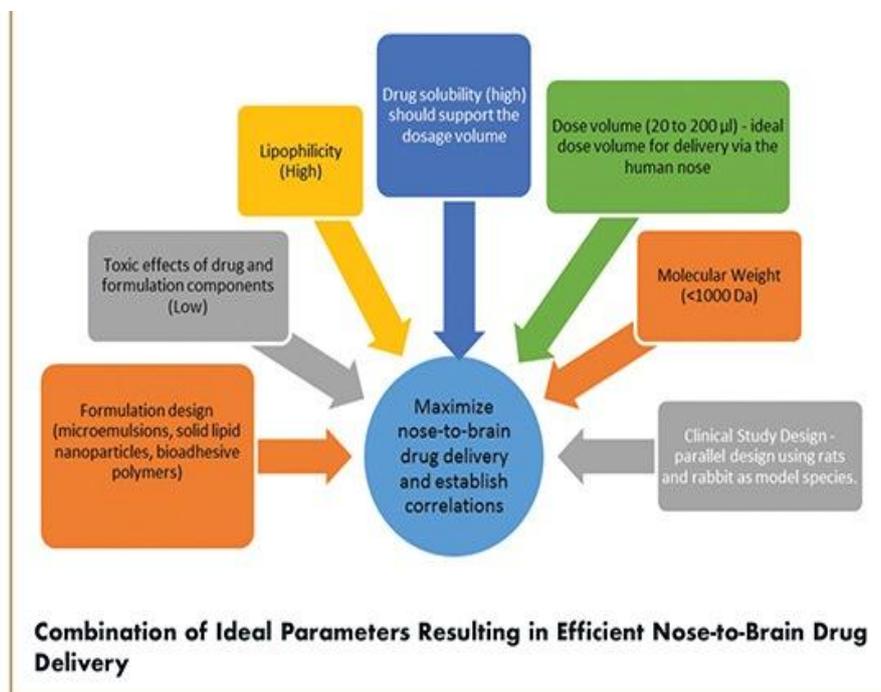
However, as demonstrated by the reported literature, intranasal administrations of NEs often lead to better results, also with respect to intravenous administrations. These good results can be explained by mechanisms of transcytosis/endocytosis of the nanodroplets by the brain endothelial cells. Moreover, the surfactant(s) present in the nanoemulsions could have a fluidizing effect on

endothelial cell membranes, determining an enhanced drug permeability and favoring by this mechanism the olfactory and trigeminal pathways.

Nanoemulsions for nasal administration represent a promising strategy for nose-to-brain drug delivery and to achieve CNS targeting for the treatment of neurodiseases. However, clinical studies of these

formulations are still needed to demonstrate their appropriateness in clinical practice.

Addition of absorption enhancers and mucoadhesive polymers did result in higher bioavailability of drugs in animal models via the nasal route when compared to parenteral administration of the same drug. Figure 1 shows a combination of ideal parameters that will maximize nose-to-brain drug.



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