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ADVANCED DRUG DELIVERY FROM NOSE TO BRAIN: AN OVERVIEW

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ABSTRACT

In recent years the nasal route has received a great deal of attention as a convenient and reliable method for the systemic administration of drugs. Present review highlights the potential of nasal mucosa as an administration route for targeting the central nervous system (CNS), in particular, the brain. Delivery of drugs to the brain is a most formidable challenge in current scenario due to presence of physiological barriers that restricts the delivery of drugs to CNS. Thus, since last few decades, nasal route has attracted a wide attention of researchers as a convenient, non-invasive, reliable, and safe route to achieve faster and higher levels of drug in the brain. It is thought to do so through olfactory route of drug transport which bypass the blood-brain barrier (BBB) and allow the direct transport of drug from the nose to the brain. Nose to brain drug delivery techniques and devices of brain drug transport that have been feasible in treating various brain disorders. This review sets out to discuss some Drug Transport Pathways, Factors Influencing Nasal Drug Absorption, Formulation Strategies Nose to Brain, Colloidal Carriers in Nose to Brain Drug Delivery Systems, Nasal Delivery Devices and patents on Nose to Brain drug delivery systems and Marketed product under nasal drug delivery system.

KEYWORDS: Nose to Brain, Blood-Brain barrier, brain targeting, Nasal drug delivery, delivery pathways and devices.

INTRODUCTION

Nose to brain drug delivery System is a targeted approach in which drug is targeted in nasal route for systemic effect. Nasal drug delivery system is recognized as an excellent route of therapeutic compounds including in Pharmaceuticals and Biopharmaceuticals. Nasal Mucosa

is considered as potential administration route to achieve rapid and higher level of drug absorption. Nasal cavity having a Larger surface area, porous endothelial membrane, high total blood flow and avoidance of problem of first pass metabolism are this few reasons Researchers are interested in nasal route for the systemic delivery of medications due to their high degree of permeability of nasal mucosa. Delivery of drug to the brain is Major challenge due to Presence of two Physiological barriers that restricts the delivery of drug to the Central Nervous System (CNS), The Blood Brain Barrier (BBB) and Blood Cerebrospinal Fluid Barrier (BCSFB). Nasal drug delivery system is explored for the conventional and local delivery of drugs for the treatment of local disorders like nasal allergy, nasal infections and nasal congestion. But, since that few decades Nasal route is attracted a wide attention of researchers as a Convenient, reliable, non-invasive and safe to achieve faster and maximum level of drug absorption. 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 is shown in Figure 1.

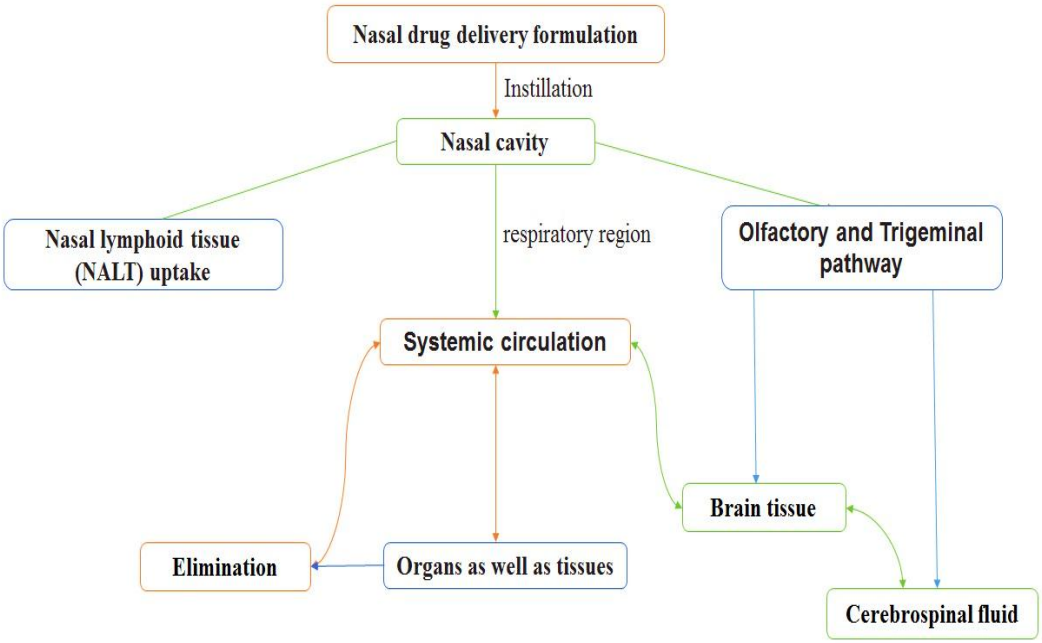

Figure 1: Drug instillation to the nasal cavity.

Advantages of nasal drug delivery system

1. Hepatic first pass metabolism is avoided.
2. Rapid drug absorption and quick onset of action is achieved.
3. Drug degradation in GI tract is avoided.
4. Some drugs is not absorbed orally can be delivered to systemic circulation by nasal route.
5. Transport for the Protein and Peptide drugs.
6. It can shows excellent bioavailability for low molecular weight drugs.
7. Bioavailability of larger molecules is improved by using Absorption Enhancers.
8. Better patient compliance.

Limitations of nasal drug delivery system

1. Rapid elimination of drug substance from nasal cavity due to Mucocilliary Clearance.
2. Nasal cavity provides a smaller absorption surface area as compared to gastrointestinal tract.

3. Absorption enhancer may create mucosal toxicity used in formulation.
4. Low bioavailability may results from enzymatic degradation and metabolism at mucosal surface.
5. Mechanical loss of the dosage form could occur due to improper technique of administration.

Reasons for Optimizations and Development of nose to brain targeted drug delivery system

Nose to brain targeted approach is used to treatment of various CNS disorders. Hydrophilic and large molecular weight drugs is usually phase the problem for Transportation in brain. Presence of endothelial membrane which separates systemic circulation and central intestinal fluid, the blood brain barrier (BBB). Hence, many pharmaceutical agents have been abandoned because of their inability to attain sufficient levels in the brain systemic circulation. Protein and Peptides, macromolecular biologics are too large to hydrophilic molecules are penetrate BBB from the systemic circulation and it is rapidly degraded by gastrointestinal enzyme or the liver cytochrome, it they are administered orally. A Non-invasive therapy is desirable for patients particularly those suffering from disease that requires chronic dosing. Animal and human investigation is proved that transport of exogenous materials directly from nose to brain targeted drug delivery system is a potential route for bypassing the blood brain barrier (BBB).

Nasal drug delivery system comparison between oral, Parenteral and Transdermal drug delivery system (DDS)

Nasal drug delivery system is a novel approach of drug delivery system in which, drug is targeted in Nose to brain. It is a unique approach to target the drug direct from nose to brain bypassing the BBB. The Nasal drug delivery system Comparison with oral, Parenteral and transdermal drug delivery system is reported in Table 1.

Table 1: Nasal DDS Comparison between Oral, Parenteral and Transdermal DDS.

Parameters	Nasal	Oral	Parenteral	Transdermal
Higher drug levels	Yes	No	Yes	Yes
BBB and CSF bypass	Yes	No	No	No
Rapid onset	Yes	No	Yes	Yes
Pain at the site of administration	No	No	Yes	No
Mucosal irritation	No	Yes	No	Yes
Systemic activity	Yes	No	Yes	Yes

Self-administration	Yes	Yes	No	Yes
Patient compliance	High	High	Low	Low
Drug degradation	No	High	No	Low
Hepatic first pass metabolism	No	Yes	No	No
Targeted delivery	Yes	No	Yes	Yes

Anatomy and Physiology of nasal cavity

In nasal cavity nose as an important organ. Nose is complex multifunctional organ. The major function of nasal cavity comprise cleansing the inhaled air and olfaction. Moreover, it is exerts protective and supportive activity. It filters, heats and humidifies the inhaled air before it reaches the lower parts of the airways. Nasal hairs and mainly nasal mucosa with its sticky mucus blanket help to prevent xenobiotics (allergens, pathogens or foreign particles) from reaching the lungs. It represents a most efficient first line of defense for the body's airway as it copes with more than 500 liters of air that are filtered hourly into the lungs and anatomy of nose is shown in Figure 2.

Mucocilliary activity is removing mucus towards the nasopharynx, immunological activities is involving a variety of immune competent cells and metabolism of endogenous substances are further essential functions of nasal cavity. The nasal cavity was connected to other cavities such as the frontal, maxillary sinus and the ear also serve as resonant body. There were three distinct functional areas in the nasal cavity, vestibules to olfactory and respiratory zones and the distinct functional areas of nasal cavity is shown in Figure 3.

The vestibular area approx. 0.6 cm^2 serve as a first barrier against airborne particles with low vascularization comprised of stratified squamous and keratinized epithelial cells with nasal hairs. Olfactory area is approx. 15 cm^2 enables olfactory perception is highly vascularized. The respiratory area approx. 130 cm^2 serves with its mucus layer produced by highly specialized cells as an efficient air cleansing system. The surface of this zone is enlarged by division of the cavity by lateral walls into three nasal conchae and the magnification of mucosa by microvilli and cilia. This zone is highly vascularized. The posterior region of the nasal cavity is the nasopharynx, its upper region consists of ciliated cells and lower part consists of squamous epithelium. This area is also part of mucosal immune system, due to rich vascularization, the olfactory and respiratory zones may serve as an efficient absorption surface for topically applied drugs. The olfactory region with its vicinity to the cerebrospinal fluid (CSF) and direct nervous interface to the brain is attracted approach in researcher's interest for possible nose to brain delivery. The respiratory epithelium or other parts of nasal

cavity and airway were lined by superficial epithelium consisting primarily of two types of cells, the globet cells (20%) and ciliated cells (80%). The various cell types of the epithelium were joined together tight junctions and cell types of nasal epithelium is shown in Figure 4.

Mucus is continuously produced by globet cells traps inhaled particulates and infectious debris while the propulsive force bout 1,000 strokes/min) generated by ciliated cells transports the mucus towards the nasopharynx and gastrointestinal tract for elimination. This effective cleansing mechanism is Mucocilliary clearance. The Mucocilliary clearance is approximately 20 min. but, it subject to great inter subject variability. The Mucocilliary clearance is dependent on the function of the cilia and the characteristics of the covering mucus which can be influenced by acute and chronic illness (common cold, allergic rhinitis).

Many substances is influences the Mucocilliary clearance of the airways, either by stimulation or inhibition. A stimulatory effect of drugs on the Mucocilliary clearance is a clinical importance, because these substances can possible used to improve pathological conditions of Mucocilliary clearance. Components (Drug and other ingredients) of nasally administered formulation with a too be pronounced Mucocilliary clearance impairing activity may limit their use.

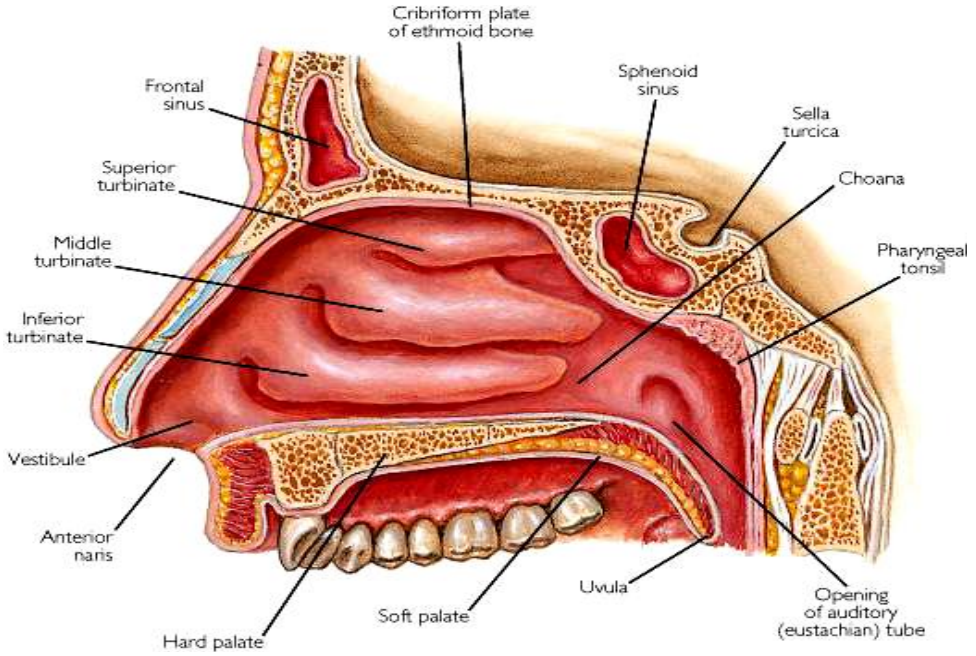

Figure 2: Anatomy of nose.

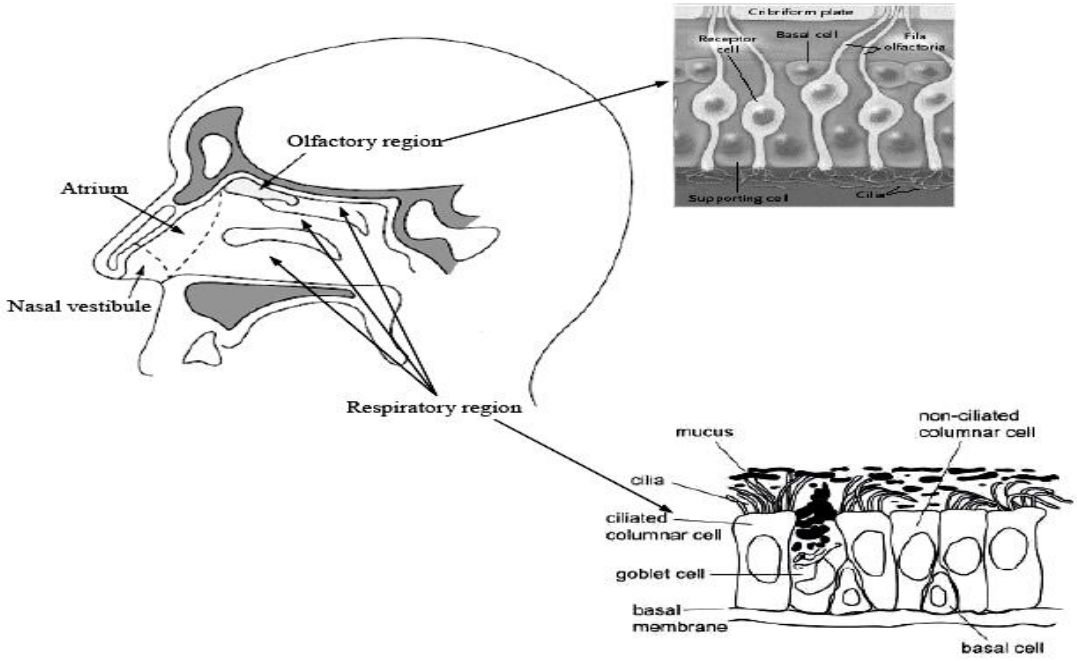

Figure 3: Distinct functional areas of nasal cavity.

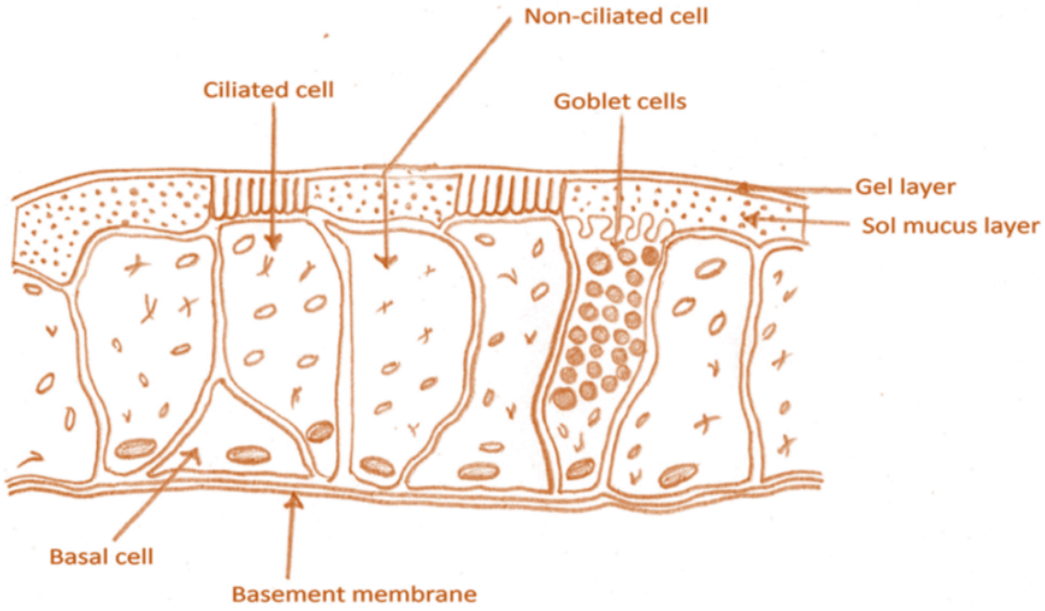

Figure 4: Cell types of the nasal epithelium.

Mechanism of drug absorption across nasal mucosa

Drug across nasal mucosa under two mechanisms, the paracellular and the transcellular mechanisms. The First paracellular (extracellular) mechanism is passive and slow aqueous route of transport through intracellular tight junctions or the open clefts of the epithelial cells of the nasal mucosa. In nose to brain transport of drug, the paracellular transport involves two extracellular routes, first across the olfactory neurons and the second across the trigeminal

nerve. After reaching the olfactory bulb or trigeminal region the Pharmaceutical agent is enter other brain regions by simple diffusion, facillated diffusion by arterial pulsation driven perivascular pump. Paracellular mechanism is demonstrated inverse log-log correlation between intranasal absorption and molecular weight of hydrophilic compounds. Poor bioavailability is observed for drugs having molecular weight greater than 1000 Daltons irrespective of their lipophilicity. Molecules like chitosan is tried to manipulate the junctions between the nasal epithelium cells to facilitate transnasal absorption.

The second transcellular (intracellular) mechanism entails transport through a lipoidal route by either by receptor mediated endocytosis (passive diffusion, fluid phase endocytosis). This Mechanism for the transnasal absorption of both small and large lipophilic molecules. Transcellular drug uptake is mainly a function of lipophilic nature of drug molecules with highly lipophilic drugs being expected to have rapid transnasal uptake. However, the transcellular mechanism is a slow process for taking hours for nasally administered drugs to reach the olfactory bulb via intracellular axonal transport by processes like endocytosis within the olfactory neurons.

Drug transport pathways of nose to the brain delivery

Neural pathways

The neural pathways is include olfactory and trigeminal neural Pathways which provide connection between the nasal mucosa and the brain, it is a unique pathway for the nose to brain delivery of pharmaceuticals and therapeutics.

1. Olfactory neural pathways

Olfactory neural pathways**,** drug material is travelled from the olfactory region in the nasal cavity to CSF or brain parenchyma, It is also transverse to the nasal olfactory epithelium. In this pathway, the arachnoid membrane surrounding the subarachnoid space having a three different pathways across the olfactory epithelium, first is transcellular pathways especially across the Sustentacular cells were receptor mediated endocytosis, fluid phase endocytosis or the passive diffusion for the lipophilic drugs is mediated rapidly and at a high rates. This route is mainly responsible for the transport of lipophilic drug molecules and the transport rate is depended in their lipophilicity.

Second is paracellular pathways in which, the tight junctions between Sustentacular cells having the clefts between Sustentacular cells and olfactory neurons. Nasal absorption of hydrophilic drugs under diffusion mechanism through aqueous channels or pores. This

pathway is slow and it is responsible for the transport of hydrophilic drugs under rate dependency on the molecular mass of the drug material. Drugs with a molecular weight in the range between 300 to 1000 Dalton without absorption enhancer shows good bioavailability and the molecular weight of drugs up to 6000 Dalton with absorption enhancers.

Third is olfactory nerve pathway in which, the drug is taken up to the neuronal cells by endocytosis or pinocytosis mechanism and transported by the intracellular axonal transport to the olfactory bulb. Thus, the different modes of drug transport across the nasal olfactory epithelium are the transcellular passive diffusion, Paracellular passive diffusion, efflux transport, transcytosis transports and the olfactory region of brain is shown in Figure 5.

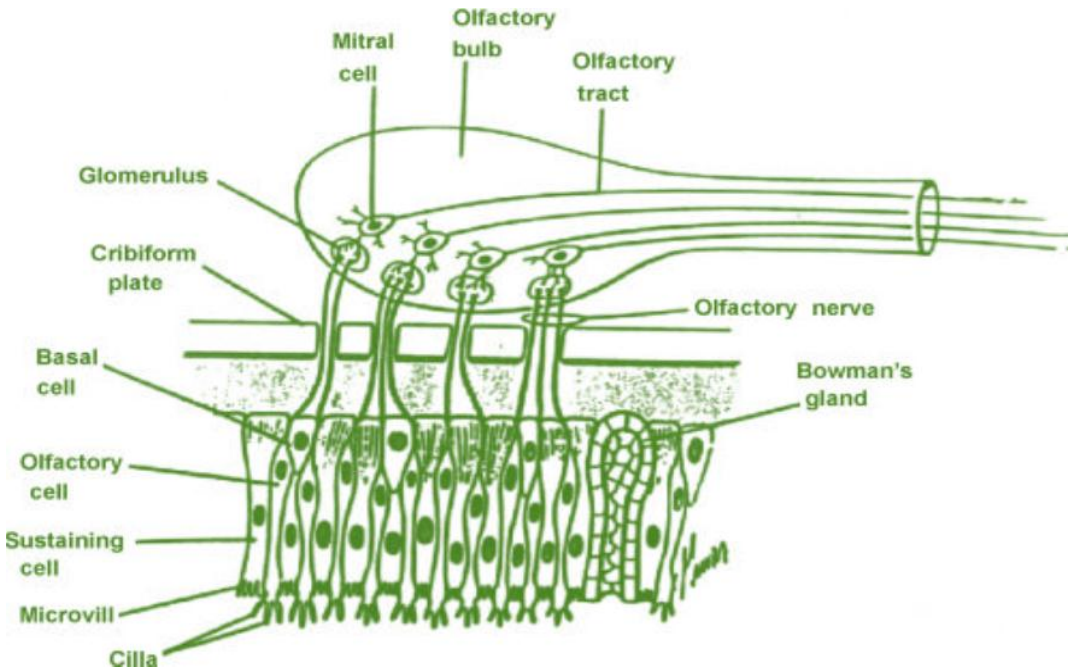

Figure 5: Olfactory region of brain.

2. Trigeminal neural pathways

Trigeminal nerve pathways is the largest nerve pathway among all cranial nerve pathways in which, innervates the respiratory and olfactory epithelium of the nasal passages and enters the central nervous system (CNS). The small portion of the trigeminal nerve pathways is terminates the olfactory bulbs. The trigeminal nerve is communicates in sensory information from the nasal cavity, oral cavity, eyelids and the cornea to CNS via ocular, maxillary and the mandibular divisions of trigeminal nerves. The former two is sensory functions while later the both sensory and motor functions.

The ocular and maxillary nerve is important for nose to brain delivery as neurons from these branches passed directly through the nasal mucosa. The unique feature of the trigeminal nerve is that enters the brain from the respiratory epithelium of the nasal passages at the two sites first through anterior lacerated foramen near the pons and second through cribriform plate near olfactory bulb is creating the entry points into the both caudal and rostral brain areas following the nose to brain administrations. Since the portion of the trigeminal nerve pathway enters the brain through the cribriform plate along the olfactory pathway, It is difficult to differentiate the nose to brain administered drugs reach the olfactory bulbs and other rostral brain areas (anterior olfactory nucleus and frontal cortex) via olfactory pathway, brainstem, spinal cord via trigeminal pathway and the both extracellular, intracellular pathways is involved for bypassing the BBB.

Vascular pathway

Pharmaceutical or Therapeutic agents is transported in nose to brain through the blood vessels supplying the nasal cavity to systemic circulation following the nasal administration. Nose to brain route is utilize to deliver drug to the systemic circulation through absorption into the capillary blood vessels underlying the nasal mucosa. The nasal mucosa is highly vascularised for receiving blood supply from branches of both the internal and external carotid artery, including the branches of the facial artery and maxillary artery. The olfactory mucosa was received blood from the anterior and posterior ethmoidal artery (smallest artery of ocular cavity), where the respiratory mucosa is received the blood from the sphenopalatine artery (they are branches of the maxillary artery). The relative density of the blood vessels is greater in the respiratory mucosa than the olfactory mucosa, making the former an ideal region for adsorption of drug into the systemic circulation. The respiratory region is the combination of the continuous and fenestrated endothelium that allowing the egress of both small and large molecules into the blood subsequent transport cross the BBB to the brain. This is especially true for small lipophilic drugs which more easily enter to the blood stream and it can cross the BBB compared to large hydrophilic molecules such as proteins and peptides or high molecular weight compounds. The therapeutics is distributed throughout the systemic circulation and it enter in the blood supply to the nasal passages to be rapidly transferred to that carotid arterial blood supply to the brain and spinal cord, this process known as counter-current transfer. The drug material is enter to the brain through the perivascular spaces in the nasal passages or after reaching the brain parenchyma to be distributed throughout the brain. The perivascular spaces is act as a lymphatic system for the

brain, where the neuron derived substance is cleared from brain interstitial fluid by entering perivascular channels associated with cerebral blood vessel. This pathway is involving perivascular channels associated with blood vessel as a potential for nose to brain drug transport mechanism. Perivascular transport is a bulk flow mechanism rather than the diffusing alone the arterial pulsations were driving forces for the perivascular transports. The high level of drug in the walls of cerebral blood vessels and carotid arteries, even after removal of blood by saline perfusion, that suggested to nose to brain delivery of the drugs gain access to the perivascular spaces.

Cerebrospinal fluid (CSF) pathway

This pathway is connected to the subarachnoid space containing CSF, perineural spaces encompassing olfactory nerves and the nasal lymphatics. The CSF circulation and drainage provide access for nose to brain administered therapeutics to the CSF and other areas of the brain. The CSF was produced by secretion at the four choroid plexi, especially at the fourth and lateral ventricles. CSF is a secretory fluid produced by the choroid plexi to cushion the brain. The tracers is injected into the CSF in the cerebral ventricles or subarachnoid space drain to the underside of the olfactory bulbs into channels associated with olfactory nerves traversing the cribriform plate that reach the nasal lymphatic system and cervical lymph nodes. Hence CSF flows along the olfactory sub mucosa in the roof of the nasal cavity. Nose to brain administration of drugs is a same pathways from the nasal cavity to CSF into the brain interstitial spaces and perivascular spaces for distribution throughout the brain. In nose to brain administration is demonstrated by the drugs gains direct access to the CSF form the nasal cavity followed by subsequent distribution to the brain and spinal cord. This transport being dependant on the lipophilicity, molecular weight and degree of ionization of drug molecules.

Lymphatic pathways

The CSF production via choroid plexus and its absorption via arachnoid villi to the cerebral venous sinuses had remained widely accepted. The functional and anatomical connection between the extracranial lymphatics (nasal submucosa and cervical lymphatics) and subarachnoid spaces via the perineural spaces to the cribriform plate. Nasal submucosa is consist of dense vascular network that leads to systemic circulation and dense network of lymphatics that communicates directly with the subarachnoid spaces. The nasal submucosal lymphatics leads directly to the subarachnoid space via a perineural route to the cribriform

plate. Nasal lymphatics is offers a direct transport through the subarachnoid space and have been proposed as a potential pathways for the invasion of the pathogens such as S. pneumoniae, N. meningitis or H. influenza responsible for bacterial meningitis.

Factors influencing nasal drug absorption

There were several factor that affect the permeation of drugs is administered through nasal route. The factor affecting nasal absorption of drugs, The Biological, Physicochemical and formulation factor.

Biological factors which affect nasal drug absorption

1. Nasal blood flow

Nasal mucosa is supplied by rich vasculature and presents a large surface area making an optimal drug absorption. The blood flow is influences significantly the systemic nasal absorption of drugs that enhanced the drug is passing through the membrane reaching to the general circulation. Drug absorption is take placed by the diffusion, the optimal blood flow is essential to maintain the concentration gradient from the site of absorption to blood. The vasodilation and vasoconstriction may determine the blood flow and the rate extent of drug to be absorbed. The blood vessels in the nasal mucosa is surrounded by adrenergic nerves which act as an alpha adrenoreceptor stimulation of these receptors is shows to decreases blood flow and blood content in the nose of the humans and animals. The nasal blood flow is affected by the external and physiological factors such as ambient temperature, humidity, vasoactive drugs, trauma and inflammation. The psychological factors such as emotion, fear, anxiety and frustration. The Nasal flow was sensitive to different locally or systemically acting drugs, such as oxymetazoline and clonidine decreases the blood flow of histamines, albuterol, isoproterenol, Phenylephrine and fenoterolare is shown to increases the blood flow, this effect is important in determining the nasal drug absorption due to their effect on blood flow.

2. Enzymatic activity

Nasal administration of drugs in circumvent gastrointestinal and hepatic first pass effect. The drug is significantly metabolized in lumen of nasal cavity and the passage across the nasal epithelial barrier due to the presence of cytochrome P450 dependant Monooxygenase, lactose dehydrogenase, oxidoreductase, hydrolase, acid phosphatase and esterase. The cytochrome P450 isoenzyme metabolized the drug such as cocaine, nicotine, alcohols, progesterone and decongestants. The proteolytic enzymes (aminopeptidases and protease) were found they are belived to be the major barrier against the absorption of protein and peptide drugs such as,

calcitonin, insulin and Desmopressin. This enzymes is exist in the nasal mucosa may affect the pharmacokinetic and pharmacodynamics profile of nasally administered drugs.

3. Mucocilliary clearance

Mucocilliary clearance is important function to removal of foreign substances and particles from the nasal cavity consequently preventing them from reaching the lower airways. Nasal administration of formulation is cleared from the nasal cavity with a half-life of clearance about 15 min. with the result of limiting time available for absorption.

The normal Mucocilliary transit time of humans 12-15 min. having a rapid mucociliary clearance of drug formulations that are deposited in the nasal cavity. It is an important factor underlying the low bioavailability of nose to brain administration of drugs. Most of drug having hormonal changes in the body, pathological conditions and formulation factors especially rheology to affect Mucocilliary clearance and turn to exert significant influence on drug permeability.

4. Physical condition of the nasal mucosa

The physical condition of nasal mucosa is important effect on the drug absorption. There were times when the mucosa is crushing, blending or dry. The infection may be suffering from rhinorrhoea, sinitis and nasal infection. In any person suffering from several nasal allergies as an excessive nasal secretions away the formulation before the drug is chance to getting absorbed through the mucosa before acting locally.

Physiochemical factors influencing nasal drug absorption

1. Molecular weight

The compound having a molecular weight less < 300 Dalton in solution are quickly and efficiently absorbed across the nasal membrane in aqueous channels having a 100% bioavailability. Molecular weight of lipophilic drugs is more than 1000 Dalton, the nasal absorption is reduced. The therapeutic agent molecular weight 1000-6000 Dalton achieve good bioavailability with the help of absorption enhancers.

2. Lipophilicity

Lipophilicity is a major physicochemical factor that limits the transport of therapeutics on nasal administration. On increasing lipophilicity of the compounds, the permeation of the

compounds normally increases through nasal mucosa. The lipid domain plays an important role in the barrier function of these membranes.

3. Dissociation constant

The Nasal absorption is depends on the dissociation constant (pKa) of the drug and on the pH of the nasal absorption site (5.0-6.5). pKa is depends in degree of ionization and degree of non-ionization. The nasal absorption of weak electrolytes depends on their degree of ionization and the highest absorption occurs for the nonionized species.

4. Partition coefficient

The nasal membrane is predominantly lipophilic, hence the drug absorption is diminish with decreases in lipophilicity. Thus the polar drug is not easily transported across nasal mucosa. The lipophilicity is too high, the drug does not dissolved in the aqueous environment of nasal cavity. In general, the passage across bimembranes is affected not only by lipophilicity/ hydrophilicity but also by the amount of drug existing as uncharged species, it was observed that absorption rate increases linearly with increase in partition coefficient.

5. Solubility

Drug Solubility is a major factor for determining the rate and extent in absorption of drug in nasal physiological pH. The relationship between the drug solubility and its absorption via the nasal route. As nasal secretion are more watery in nature, a drug having an appropriate water solubility for increased dissolution rate. The several approaches that may increase solubility of poorly soluble drugs for nasal administration, the Prodrug, salt forms, co-solvency and Complexation (cyclodextrines Complexation).

6. Polymorphism

Polymorphism is affect the dissolution rate and solubility of drug molecule and thus their absorption through biological membranes. It is important to study polymorphic stability and purity of drugs for nasal powders and suspensions.

Formulation factors for Nasal Drug Absorption

1. pH and Mucosal irritancy

The pH of the formulation and nasal surface is affect the drug permeation, to avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5-6.5. In addition to

avoiding irritation, it result in obtaining efficient drug permeation and prevents the growth of bacteria.

2. Osmolarity

The osmolarity of formulations, between 285 and 310 mOsmol/l for nasal drug delivery to avoid the nasal mucosal irritations, precisely the tonic effects. The isotonic solutions with osmolarity of 308 mOsmol/l were preferred for safe and effective drug administration.

3. Viscosity

The viscosity of the formulation intended for nasal drug delivery ensured the proper contact time between the drug formulation and nasal mucosa. The viscosity is increases, increases the contact time and increases the time of permeation. The viscosity of formulation not too high its optimum because it can interfere the normal functions such as ciliary beating or mucociliary clearance and it alter the permeability of drug. Hence viscosity of formulation is optimum, higher the residence time that will affect the total absorption of drug and improve bioavailability.

Formulation strategies for nose to brain drug delivery system

The Nasal route is efficient for CNS and systemic delivery of wide range of drugs, most of the drugs exhibit low bioavailability even when administered by this route. The low bioavailability may be due to the low solubility of drugs, rapid enzymatic degradation in nasal cavity, poor membrane permeability and rapid mucociliary clearance. Several strategies is employed to overcome these limitations include, Prodrug approach, enzymatic inhibitor, structural modifications, absorption enhancers and mucoadhesive drug delivery system.

1. Prodrug approach

Prodrug approach, in which 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 compounds 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. L-dopa is a poorly water soluble drug, but when administered as Prodrug its solubility is increases significantly in Comparision with parent drug molecules. Similar results were obtained with testosterone, which is a poor water-soluble drug but in the Prodrug form with higher lipophilic nature, Permeation increases through the membrane. Prodrug approach also applicable to inhibit the

enzymatic degradation of drugs in nasal mucosa and to render the formulation for maintaining the enzymatic stability (Kushwaha et al., 2011). L-aspartate--b-ester Prodrug of acyclovir is more permeable and more stable toward enzymatic degradation (it is an example of Prodrug approach). Prodrug approach is a powerful approach for enhancement of bioavailability of large molecular weight compounds such as protein and peptides drugs by this drug delivery.

2. 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. The bacitracin, amastatin, boroleucin and puromycin is used to avoid the enzymatic degradations of drugs such as leucine, encephalin and human growth harmone. Finally enzymatic inhibition can be achieved by using certain absorption enhancers such as bile salts and fusidic acid. Disodium ethylene-diamine-tetra acetic acid, an absorption enhancer that reduces enzymatic degradation of beta sheet peptide, used for the treatment of Alzheimer's disease.

3. 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.

4. 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 (sodium glycodeoxycholate, sodium taurodeoxycholate), fatty acids (taurodihydrofusidate, oleic acid, ethyl oleate), Chelators (EDTA, citric acid), peppermint oil and polymers. Some examples of polymers such as cyclodextrines and methylated cyclodextrines, chitosan and trimethyl chitosan, carbopol, starch and animated gelatine. This is responsible to changes the permeability of epithelial layers of nasal mucosa by modifying phospholipids bilayer and also changes fluidity or reversible openings of tight junctions between epithelial cells and increases paracellular transport of drug molecule.

The high molecule weight polymeric absorption enhancers was not absorbed and reduced the systemic toxicity in comparison with low molecular weight. Chitosan can interact with protein kinase C and its open tight junctions between epithelial cells to increases the paracellular transport of polar drugs, its strongly interact with the nasal mucous layer and increases the contact time to overcome mucociliary clearance, thus it can widely use in intranasal dosage forms. Cyclodextrines complexes interact with the lipophilic components of natural biological membrane and increases the permeability of drugs to increase the absorption. Although cyclodextrines are widely used for nasal drug delivery, some local and systemic toxicity was reported. The Novel formulations such as mucoadhesive, micro and nanoemulsion, microspheres and nanoparticles containing absorption enhancers are demonstrated to better for bypassing the BBB.

5. Structural modification

Modification of structure of drug without altering pharmacological activity. It is one of the important factor to improve the Nasal drug absorption. On structural modification of drug molecule, the physicochemical characteristics that are commonly modified, the molecular weight, molecular size, partition coefficient and solubility, all favourable for nasal drug absorption. Examples of structural modification in which, the chemical modification of salmon calcitonin into ecatonin (C-N bond replaced by an S-S bond) was help to improved bioavailability when compared with parent drug molecule.

6. Chitosan surface modifications

Chitosan an alkaline hydrolytic derivative of chitin has better solubility profile, its having a less Crystallinity and it is delightful to chemical modifications due to presence various reactive functional group such as hydroxyl, acetamide and amines. Chemical modification of chitosan would not change the fundamental skeleton of the chitosan, would not change the fundamental skeleton of chitosan, would keep the basic physicochemical and biochemical characteristics of the chitosan and finally would yield a novel derivatives with improved properties. This was the prime reason behind extensive interest of researchers around the all over world for utilization of chitosan in pharmaceutical and biochemical applications. The various chemical modifications have been carried out on chitosan which includes oligomerization, carboxylation, thiolation, sulfation, phosphorylation, enzymatic modifications and graft copolymerization. The chemical modification affords a wide range of

derivatives with modified properties for specific applications in diversified areas mainly of pharmaceutical, biomedical and biotechnological fields.

7. PEG surface modification

The surface modification with polyethylene glycol (PEG) add new physicochemical properties to existing polymers, to overcome this limitations associated with them, especially regarding their solubility. The conjugates of a kDa homopolymer PEG to the surface of 100-200 nm PS nanoparticles, diffusion coefficient of nanoparticles through by 20 and 381 times respectively. This is potentially relevant because a low PEG molecular weight and high PEG surface coverage were required for rapid penetration of the mucus. PEG is adsorbed onto the PS surface rather than covalently attached and consequently may have been desorbed or displaced from the nanoparticles surface in biological environment. Other variables may also affect the ability of PEG modified nanoparticles to penetrate mucus and therefore reach epithelial cells, these include PEG molecular weight (longer PEG chains may increasingly interact with mucus fibers to reduced trans mucosal movement of nanoparticles) and composition of core of nanoparticle which affect that surface charge of particle, the effect of protein adsorbed an nanoparticle surface from biological milieu.

8. Lectin surface modification

Lectin modification in which, it is a class of proteins and glycoproteins, purified from many plant sources such as tomatoes, jack bean and wheat germ. Lectins occurs abundantly in nature and can recognise sugar residues on biological surfaces. Their selective affinity for biological surfaces may be useful for the direct nose to brain drug delivery. Recently wheat germ agglutinin (WGA), lectin is conjugated to coumarin loaded PEG poly lactic acid (PEG-PLA) nanoparticles having a 85-90 nm diameter and it's administered by intranasally in rat models. WGA binds to N-acetyl-d-glucosamine and sialic acid residues both of which abundant on the nasal epithelial membrane. A 2-fold increases in coumarin is observed in the olfactory bulb, olfactory tract, cerebrum and cerebellum within 15 h of single dose of lectin modified nanoparticles, without any evidence of ciliotoxicity.

Colloidal carriers in nose to brain drug delivery systems

Colloidal drug carriers includes, 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.

1. 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.

2. Nanoemulsion

Nanoemulsion is an isotropic mixture of oil, surfactant: cosurfactant (S_{mix}) 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 emulsion. 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 field like chemical, cosmetic and pharmaceutical fields.

Kumar et al. (2008) proposed the intranasal nanoemulsions loaded with risperidone, as drug carriers for brain targeted drug delivery system. Their study demonstrated rapid and larger extent of transport of risperidone into the rat brain.

3. 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. Seju et al., (2011) have reported olanzapine-loaded PLGA nanoparticles for the treatment of psychotic illness, schizophrenia, *via* nose to brain drug delivery platform.

4. 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 nd biocompatible blocks of copolymers. Polymeric micelles are characterized by core shell structure. Mitra et al. have reported that mixed micelles of bile salts and fatty acid have a synergistic effect on the nasal absorption of peptides. Jain et al., (2010) have reported the formulation and evaluation of micellar nanocarriers for nose to brain delivery of zolmitriptan to treat migraine headache. Their results suggested the potential of micellar carrier as safe, stable and effective new generation vehicle for brain targeting.

5. Liposomes and Proliposomes

Liposomes and Proliposomes is a novel approach of drug delivery system is important to deliver the various routes. Liposomes can be used for targeting and introduction of therapeutic agents to specific site by conjugation or cross linking of targeting moiety to the native liposome or by surface modification of the fabricated liposomal formulation. Positively charged liposomes possessed maximum bioadhesion prolonging the residence time within the nasal cavity there by improving the bioavailability. Free flowing Proliposomes containing propranolol hydrochloride were prepared by Shim *et al.* and evaluated their potential for transnasal delivery of propranolol to sustain its plasma concentration. In a study on rats by Wattanathorn *et al.* intranasal liposomes containing quercetin decreased anxiety like behavior and increased spatial memory. US Patent 6342478 describes a nasal micellar or liposomal preparation for the delivery of fibroblast growth factor to the brain. Vyas *et al.* have reported multilamellar liposomes for intranasal delivery of nifedipine.

6. Mucoadhesive solutions

The mucoadhesive solutions comparison with mucoadhesive polymers like chitosan, cellulose polymers, polycarbophils, Poloxamers have been reported to enhance drug permeation Trans nasally. These system being viscous and mucoadhesive provide a longer residence time for better drug absorptions. Illum *et al.* have reported an enhancement in the absorption of insulin across the nasal mucosa of rat and sheep using cationic chitosan based nasal solution. Numerous studies have demonstrated that chitosan and their derivatives are effective and safe absorption enhancers to improve mucosa delivery of hydrophilic macromolecules such as peptides and protein drugs. However, these systems suffer from post-nasal dripping and anterior leakage when compared to gels or powder formulations

7. Microspheres

Microspheres including, mucoadhesive microspheres are the novel systems that are becoming increasingly popular with nasal drug delivery system. Microspheres may provide prolonged Contact with the nasal mucosa enhancing the rate and extent of drug absorption. Microspheres or for nasal applications are usually prepared using biocompatible materials, such as starch, albumin, dextran, hyaluronic acid, chitosan and gelatine, hydroxypropyl methylcellulose, carbopol 934P and various combinations of these polymers. These polymers on absorbing nasal secretions form a gel-like layer which is slowly cleared from the nasal cavity. However, the toxicity of the polymer on the nasal mucosa cells should be critically evaluated. Starch microspheres are most frequently used nasal delivery systems and have been successfully tried for insulin, gentamicin, human growth hormone, metoclopramide and Desmopressin. Starch microspheres cause drying of the nasal mucosal surface due to uptake of moisture by the microspheres. This results in reversible “shrinkage” of the cells, providing a temporary physical separation of the tight (intercellular) junctions that increases the absorption of drugs. Illum *et al.* studied the absorption of insulin from bioadhesive DEAE dextran microspheres Shaji *et al.* studied the brain delivery of clonazepam from gelatin-chitosan based nasal mucoadhesive microspheres in rats. Rassu *et al.* have reported nasal chitosan microspheres for improved and prolong delivery of rokitamycin to the brain for treating granulomatous amoebic encephalitis.

Nasal delivery devices

Nasal drug delivery devices is versatile tool for direct drug delivery in nasal cavity by using various nasal device. The nasal devices include Powder formulation devices and liquid

formulation devices. Liquid formulations currently completely dominate the nasal drug market, but nasal powder formulations and devices do exist, and more are in development.

1. Powder formulation devices

Powder medication formulations can offer advantages, including greater stability than liquid formulations and potential that preservatives may not be required. Powders tend to stick to the moist surface of the nasal mucosa before being dissolved and cleared. The use of bioadhesive excipients or agents that slow ciliary action may decrease clearance rates and improve absorption. A number of factors like moisture sensitivity, solubility, particle size, particle shape, and flow characteristics will impact deposition and absorption.

The function of nasal powder devices is usually based on following principles

Powder sprayers with a compressible compartment to provide a pressure that when released creates a plume of powder particles fairly similar to that of a liquid spray. Breath-actuated inhalers where the subject uses his own breath to inhale the powder into the nostril from a blister or capsule and Nasal insufflators describe devices consisting of a mouthpiece and a nosepiece that are fluidly connected. Delivery occurs when the subject exhales into the mouthpiece to close the velum, and the airflow carries the powder particles into the nose through the device nosepiece similar to the rhinyle catheter described Drug Delivery and Transl. Res. above. The principle can be applied to different dispersion technologies and has been further developed and extended into the breath-powered Bi-Directional™ delivery technology.

A) Insufflators

Insufflators are the devices to deliver the drug sub-stance for inhalation; it can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also. The achieved particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient deaggregation of the particles and results in a high coefficient of variation for initial deposition areas. Many insufflator systems work with pre-dosed powder doses in capsules.

B) 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 medication is commonly held either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are a variety of such devices. 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.

C) Pressurized Metered-Dose inhale (PMDI)

A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine that is inhaled by the patient. It is the most commonly used delivery system for treating asthma, chronic obstructive pulmonary disease (COPD) and other respiratory diseases. The medication in a metered dose inhaler is most commonly a bronchodilator, corticosteroid or a combination of both for the treatment of asthma and COPD. Other medications less commonly used but also administered by MDI are mast cell stabilizers, such as (cromoglicate or nedocromil). The advantages of MDIs are their portability and small size, availability over a wide do-sage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use. To use the inhaler the patient presses down on the top of the canister, with their thumb supporting the lower portion of the actuator. The propellant provides the force to generate the aerosol cloud and is also the medium in which the active component must be suspended or dissolved. Propellants in MDIs typically make up more than 99 % of the delivered dose. Actuation of the device releases a single metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometre-sized medication particles that are then inhaled.

D) Breath-powered Bi-Directional™ technology - A new nasal drug delivery concept

This novel concept exploits natural functional aspects of the upper airways to offer a delivery method that may overcome many of the inherent limitations of traditional nasal devices. Importantly, the breath-powered Bi-Directional™ technology can be adapted to any type of dispersion technology for both liquids and powder.

This “breath-powered” mechanism enables release of liquid or powder particles into an air stream that enters one nostril, passes entirely around the nasal septum, and exits through the

opposite nostril, following a "Bi-Directional™" flow path. Actuation of drug release in devices employing this approach has been described using manual triggering as well as mechanisms automatically triggered by flow and/or pressure. By optimizing design parameters, such as the nosepiece shape, the flow rate, the particle size profile, and release angle, it is possible to optimize delivery to target sites beyond the nasal valve, avoid lung deposition, and to assure that particles are deeply deposited without exiting the contralateral nostril. The Bi-Directional™ devices currently in phase three clinical trials are a multi-dose liquid device incorporating a standard spray pump and a capsule-based powder multi-use device with disposable drug chamber and nosepiece, but other configurations are possible. Importantly, the Bi-Directional™ delivery concept can be adapted to a variety of dispersion technologies for both liquids and powders.

2. Liquid formulation devices

The liquid nasal formulations are mainly aqueous solutions, but suspensions and emulsions can also be delivered. Liquid formulations are considered convenient particularly for topical Indications where humidification counteracts the dryness and crusting often accompanying chronic nasal diseases.

A) Drops delivered with pipette

Drops and vapour delivery are probably the oldest forms of nasal delivery. Dripping breast milk has been used to treat nasal congestion in infants, vapours of menthol or similar substances were used to wake people that have fainted, and both drops and vapours still exist on the market. Drops were originally administered by sucking liquid into a glass dropper, inserting the dropper into the nostril with an extended neck before squeezing the rubber top to emit the drops. For multi-use purposes, drops have to a large extent been replaced by metered-dose spray pumps, but inexpensive single-dose pipettes produced by "blow-fill-seal" technique are still common for OTC products like decongestants and saline. An advantage is that preservatives are not required. In addition, due to inadequate clinical efficacy of spray pumps in patients with nasal polyps, a nasal drop formulation of fluticasone in single-dose pipettes was introduced in the EU for the treatment of nasal polyps. The rationale for this form of delivery is to improve drug deposition to the middle meatus where the polyps emerge. However, although drops work well for some, their popularity is limited by the need for head-down body positions and/or extreme neck extension required for the desired gravity-driven deposition of drops. Compliance is often poor as patients with rhinosinusitis often experience increased headache and discomfort in head-down positions.

B) Instillation and Rhinyle catheter

Catheters are used to deliver the drops to a specified region of nasal cavity conveniently. Put the formulation in the tube and kept tube one end was positioned in the nose, and the solution was approached into the nasal cavity by blowing through the other end by mouth. Dosing of catheters is determined by the filling prior to administration and accuracy of the system and this is mainly used for experimental studies only.

C) Squeeze bottles

Squeeze bottles are mainly used to deliver some over the counter (OTC) products like topical decongestants. By squeezing a partly air-filled plastic bottle, the drug is atomized when delivered from a jet outlet. The dose and particle size vary with the force applied, and when the pressure is released, nasal secretion and microorganisms may be sucked into the bottle. Squeeze bottles are not recommended for children.

D) Metered-dose pump sprays

Most of the pharmaceutical nasal preparations on the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays. Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to generally alleviate cold or allergy symptoms such as nasal congestion or systemically, see nasal administration. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by action of a hand-operated pump mechanism. The three main types available for local effect are: antihistamines, corticosteroids, and topical decongestants Metered- dose pump sprays include the container, the pump with the valve and the actuator. The dose accuracy of metered-dose pump sprays is dependent on the surface tension and viscosity of the formulation. For solutions with higher viscosity, special pump and valve combinations are on the market.

E) Single and Duo dose spray devices

Metered-dose spray pumps require priming and some degree of overfill to maintain dose conformity for the labelled number of doses. They are well suited for drugs to be administered daily over a prolonged duration, but due to the priming procedure and limited control of dosing, they are less suited for drugs with a narrow therapeutic window. For expensive drugs and vaccines intended for single administration or sporadic use and where tight control of the dose and formulation is of particular importance, single-dose or duo-dose spray devices are preferred. A simple variant of a single-dose spray device (MAD) is offered

by LMA (LMA, Salt Lake City, UT, USA). A nosepiece with a spray tip is fitted to a standard syringe. The liquid drug to be delivered is first drawn into the syringe and then the spray tip is fitted onto the syringe. This Drug Delivery and Transl. Res. device has been used in academic studies to deliver, for example, a topical steroid in patients with chronic rhinosinusitis and in a vaccine study. A pre-filled device based on the same principle for one or two doses (Accuspray™, Becton Dickinson Technologies, and Research Triangle Park, NC, USA) is used to deliver the influenza vaccine FluMist, approved for both adults and children in the US market. A similar device for two doses was marketed by a Swiss company for delivery of another influenza vaccine a decade ago. This vaccine was withdrawn due to occurrence of adverse events (Bell's palsy) potentially related to the cholera toxin adjuvant used. The device technology is now owned by a Dutch vaccine company (Crucell N.V. Leiden, the Netherlands), but to our knowledge is not currently used in any marketed products. The single- and duo-dose devices mentioned above consist of a vial, a piston, and a swirl chamber. The spray is formed when the liquid is forced out through the swirl chamber. These devices are held between the second and the third fingers with the thumb on the actuator. A pressure point mechanism incorporated in some devices secures reproducibility of the actuation force and emitted plume characteristics. Currently, marketed nasal migraine drugs like Imitrex and Zomig, Pfeiffer/Aptar single-dose device) and the marketed influenza vaccine Flu- Mist (Becton Dickinson single-dose spray device) are delivered with this type of device. With sterile filling, the use of preservatives is not required, but overfill is required resulting in a waste fraction similar to the metered-dose, multi-dose sprays. To emit 100 µl, a volume of 125 µl is filled in the device (Pfeiffer/Aptar single-dose device) used for the intranasal migraine medications Imitrex (sumatriptan) and Zomig (zolmitriptan) and about half of that for a duo-dose designings.

F) Nasal pressurized metered dose inhalers

Most drugs intended for local nasal action are delivered by spray pumps, but some have also been delivered as nasal aerosols produced by pMDIs. Following the ban on ozonedepleting chlorofluorocarbon (CFC) propellants, the number of pMDI products for both pulmonary and nasal delivery diminished rapidly, and they were removed from the US market in 2003. The use of the old CFC pMDIs for nasal products was limited due to complaints of nasal irritation and dryness. The particles from a pMDI are released at a high speed and the expansion of a compressed gas, which causes an uncomfortable "cold Freon effect". The particles emitted from the traditional pMDIs had a particle velocity much higher than a spray pump (5,200 vs.

1,500 cm/s at a distance 1–2 cm from the actuator tip). The issues related to the high particle speed and "cold Freon effect" have been reduced with the recently introduced hydrofluoroalkane (HFA)-based pMDI for nasal use offering lower particle speeds. Recently, the first nasal pMDI using HFA as propellant to deliver the first generation topical steroid beclomethasone dipropionate (BDP) was approved for allergic rhinitis in the USA. Like spray pumps, nasal pMDIs produce a localized deposition on the anterior non-ciliated epithelium of the nasal vestibule and in the anterior parts of the narrow nasal valve, but due to quick evaporation of the spray delivered with a pMDI, noticeable "drip-out" may be less of an issue.

G) Aeroneb Solo vibrating mesh nebulizer

Distinct anterior deposition in the valve area with nebulizers is confirmed in another very recent publication comparing nasal inhalation from a nasal sonic/pulsating jet nebulizer (Atomisor NL11S® sonic, DTF-Medical, France) and a new nasal mesh nebulizer system designed to minimize lung inhalation (Aeroneb Solo®, Aerogen, Galway, Ireland;) with the equal mean particle size (5.6 ± 0.5 μm). The new system consists of two integrated components: the nebulizer compressor administering a constant airflow rate transporting the aerosol into one nostril via a nozzle and a pump simultaneously aspirating from a second nozzle in the other nostril at the same airflow rate while the subject is instructed to avoid nasal breathing. The new nasal mesh nebulizer produced more deposition in terms of volume of liquid (27 % vs. 9 %, i.e., 0.81 vs. 0.27 ml) in the nasal cavity. The much higher concentration found in the nasal cavity in this present study is probably a result of the shorter nebulizing time and smaller delivered volume in the study testing the PARI pulsating nebulizer (20 s at a rate of 3 mcg/ml/min to each nostril versus delivery of 3 ml for up to 10 min) before assessment of deposition was performed. With much longer delivery time, the gastrointestinal (GI) tract will be cleared by the fraction dose beyond the nasal valve. Aerosol distribution deposition showed a distinct maximum value at 2 cm from the nostril for both nebulizers corresponding to deposition in the nasal valve region. Furthermore, aerosol distribution deposition in the vertical plane showed a similar profile for both nebulizers with a distinct maximum close to the floor of the nose. Importantly, the delivery strength for nebulizers and delivery techniques appear very low with only 27 % vs. 9 %, i.e., 0.81 vs. 0.27 ml, possibly due to the long delivery time and resulting differences in mucociliary and other mechanisms of clearance. In other words, a study assessing deposition after several minutes of delivery is likely to underestimate the actual exposure to the posterior ciliated part of the

nose compared to the study assessing deposition after a short period of delivery of less than 1 min (20 s × 2).

H) Impel nitrogen driven atomizer

A nasal atomizer driven by highly pressurized nitrogen gas is under development by Impel Inc. The device is intended to enable drug delivery to the upper parts of the nose in order to achieve N2B delivery. To date, only animal data has been presented, making it difficult to evaluate its potential in human use, as nasal deposition and the assessment of nasal deposition in animal models vary significantly from humans. As previously noted, however, pMDIs are associated with a number of limitations. It therefore remains to be seen if a pressurized "open-palate" nebulizer will be capable of creating the desired delivery pattern.

I) ViaNase atomizer

A handheld battery-driven atomizer intended for nasal drug delivery has been introduced (Via Nase by Kurve Technology Inc., Lynnwood, WA, USA). This device atomizes liquids by producing a vortical flow on the droplets as they exit the device. The induced vortical flow characteristics can be altered in circular velocity and direction to achieve different droplet trajectories. As discussed above, it is not clear that vortex flow is desirable for penetration past the nasal valve; however, it has been suggested that this technology is capable of targeting the sinuses, and some gamma-deposition images suggesting delivery to the sinuses have been published. However, no information related to impact of prior surgery or numerical quantification of nasal or sinus deposition verifying the claimed improved deposition to the upper parts of the nose has been published. The ViaNase device has been used to deliver nasal insulin in patients with early Alzheimer's disease (AD), and clinical benefit has been demonstrated. In these studies, delivery of insulin was performed over a 2-min period by nasal inhalation. However, when insulin is delivered with this device, lung deposition is likely to occur, and some concerns related to airway irritation and reduction in pulmonary function have been raised in relation to long-term exposure to inhaled insulin when Exubera was marketed for a short period as a treatment for diabetes. This example highlights the issue of unintended lung delivery, one important potential clinical problem associated with using nebulizers and atomizers producing respirable particles for nasal drug delivery.

Patents on nose to brain drug delivery systems

Despite the fact that many of them have not reached the market so far, a good number of patents have been received on various drug molecules loaded in a variety of carriers for direct nose to brain drug delivery. Due to the challenges of large scale commercial production, only few patents have been transferred into commercial marketed products. Some patents related to direct nose to brain drug delivery systems are illustrated in Table 2.

Marketed product under nasal drug delivery system

The marketed product under nasal drug delivery system for treatment of various disorders is reported in Table 3.

Future perspectives

In the last few decades, the attention of various research groups has shifted to the development of novel drug delivery systems to circumvent the BBB. This is due to the significant challenges faced by researchers, academicians and industrialists looking at effective treatment strategies for increasing incidence of brain disorders in the elderly population Present review embodies the fact that many of the drug delivery systems like polymeric micro- and nanoparticles, nanoemulsions, polymeric micelles, liposomes, etc. are potential carriers for delivery of drugs across the BBB for treatment of CNS disorders. However, there are still a stack of challenges, as most of the potent CNS acting drugs are hydrophilic in nature which makes it difficult for them to cross the BBB. Surface modification of drug delivery carriers serves as one of the promising approaches to circumvent this budding problem. Considering the potential benefits of nasal drug delivery systems (patient compliance and risk benefit ratio), utilization of this non-invasive method of drug delivery offers a potential alternative to invasive methods and could be exploited, in the near future, for development of novel drug delivery systems. No doubt, this direct nose to brain drug delivery system would have a bright future in the pharmaceutical industry and would definitely bring a large number of commercial products to the pharmaceutical market in near future.

Table 2: Patents on nose to brain drug delivery systems.

Drug	Applicability	Drug delivery	Patent
Proteasomes glatiramer	Neurodegenerative disorders	Nanoemulsion	Frenkel et al. US20060229233A1 (2006)
Diazepam	Epilepsy	Microemulsion	Choi and Kim US20050002987A1 (2005)

			Choi and Kim WO04110403A1 (2004)
Benzodiazepines, valproic acid,	Epilepsy	Nasoadhesive microemulsion	Misra and Vyas 1061/MUM (2005)
Carbamazepines Sedatives	Insomnia	Nasoadhesive microemulsion	Misra and Vyas 1124/MUM/(2005)
Triptans, caffeine	Migraine	Nasoadhesive microemulsion	Misra and Vyas 1125/MUM/(2005)
Lorazepam	Epilepsy	Nasal spray	Wermeling US20016610271B2 (2003) Wermeling US20010055571A1 (2001)
Zolpidem	Insomnia	Cyclodextrin/chitosan sols	Castile et al. US20070140981A1 (2007)
NMDA receptor antagonist	PD and AD	Extended-release dosage form	Meyerson et al. US20050245617A1 (2005)
Insulin	Brain disorders	Solution	Frey US20016313093B1 (2001)
Neurological agents	Brain disorders	-	Frey US20016180603B1 (2001)
Neurotropic agents	Brain disorders	-	Frey US19975624898A (1997) Frey US20030072793A1 (2003) Frey US20030215398A1 (2003)
Therapeutic cells	Neurodegenerative disorders	-	Frey et al. US20128283160B2 (2012)

Table 3: Marketed product for nasal drug delivery system.

Brain disorders	Product name	Drug name	Nasal delivery	Manufacturer
Migraine	Migranal	Dihydroergotamine	Nasal spray	Novartis Pharma
Migraine	AscoTop/ Zomig	Zolmitriptan	Nasal spray	AstraZeneca
Migraine and pain	Stadol NS	Butorphanol tartarate	Nasal spray	Bristol-Myers Squibb
Cranial diabetes insipidus	DDAVP	Desmopressin	Nasal spray	Ferring Pharmaceuticals Ltd
Lactation induction	Syntocinon	Oxytocin	Nasal spray	Novartis Pharma

CONCLUSION

Nose to brain drug delivery bypasses the BBB to target CNS, reducing systemic exposure of drug, thereby reducing the systemic side effects. It is an attractive option of drug delivery due to its non-invasiveness. These reported findings may be crucial in developing therapeutically efficacious product in the management of chronic brain diseases otherwise difficult to treat brain tumors, epilepsy, migraine and neurodegenerative diseases. Despite the enormous progress, still there is a need for a device for selective delivery of the product at the olfactory region in the nasal cavity. The drug delivery targeting the brain should be evaluated for their safety and risk-benefit ratio for the patients. It is an important point that needs to be noticed that any delivery systems developed should have no significant impact, short or long term, on the functions of the brain. Colloidal carriers offer endless opportunities in the field of drug

delivery. It should be looked into detail so that it would provide useful information and progress in this line of research.

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