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RECENT ADVANCEMENT IN NASAL DRUG DELIVERY SYSTEM: A CURRENT REVIEW

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ABSTRACT

Abstract:Intranasal medicine delivery – which has been rehearsed for thousands of times, has been given a new parcel of life. It's a useful delivery system for medicines that are active in low boluses and show no minimum oral bioavailability similar as proteins and peptides. Nasal delivery is the logical choice for topical treatment of original conditions in the nose and paranasal sinuses similar as antipathetic and non-allergic rhinitis and sinusitis. The nose is also considered an seductive route for needle-free vaccination and for systemic medicine delivery, especially when rapid-fire immersion and effect are asked. In addition, nasal delivery may help address issues related to poor bioavailability, slow immersion, medicine declination, and adverse events in the gastrointestinal tract and avoids the first-pass metabolism in the liver. The convenience of administration and bettered patient compliance are important in the design of nasal medicine delivery system which remains the favored route of medicine delivery in malignancy of colorful disadvantages. Remedy through intranasal administration has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. Nasal route is salutary for the medicines which are unstable on oral administration because they're significantly degraded in GIT or metabolized by first pass effect in liver. Nasal route is indispensable to parenteral remedy and also useful for long term remedy.

KEYWORDS:- Parcel,Medicines,Bioavailability,Vaccination,Convenience,Ayurvedic System, First Pass, GIT.

I. INTRODUCTION

We all know that Nose is an important part of our body. Now a day's researchers are giving more time to develop new things in Nasal Drug Delivery System. It has been practicing from thousand of years which are giving more advantages in life. It (nasal mucosa) has Faster and Higher rate of absorption because it can pass more compound than the GI Tract due to lack of pancreatic and gastric enzyme activity. In recent years many drugs are achieving best systemic bioavailability such as proteins and peptides by Nasal Route than by Oral Route. Intranasal Therapy, it is developed form of treatment in the Ayurvedic System also known as "NASYA KARMA" [1] . Researchers are also working on Administration of drugs to the CNS with the help of nasal Route by passing Blood Brain Barrier[2-5]. We can take this drug by self. In Emergency we can use nasal route in place of other routes. Through Nasal Passage we can administer Vaccines like (Influenza A and B, Proteosoma influenza, Adenovirus-vector influenza) [6] and some more drugs like Buserelin, Desmopressin, Calcitonin, Insulin, Growth Hormone, and Adreno-Corticotropic hormone are some peptides [7,8]. Antihypertensive(nifidipine, nitroglycerine, propranolol, hydralazine), Analgesic(buprenorphine) [9].

II. Anatomy and Physiology of Nose and Nasal Cavity

Position And Structure

Nasal cavity is the main route of air entry, consist of large irregular cavity, requirements divided into two equal parts by a septum.*The back portion* bony part of septum is formed by the Ethmoid bone and Vomer. *Frontaly*, it contains hyaline cartilage. *The upper part*consists the cribriform plate of the ethmoid bone and the sphenoid bone, frontal bone and nasal bones. *The lower part* is shaped by the roof of mouth and contains hard palate in front and soft palate behind. Hard palate has maxilla and palatine bones and soft palate has involuntary muscle. At *The middle* there is septum. *The side walls* consist of the maxilla, the ethmoid bone and the inferior conchae. *The back portion* is tamped by the posterior wall of the pharynx.

Lining of the nose :- The nose is stuffed with *ciliated columnar epithelium*(ciliated mucus membrane, respiratory mucosa) which have mucus secreting goblet cell. At front snout this brew with the skin and at back it broaden into the nasal part of pharynx.

Opening into the nasal cavity :- *The enterior nares, or nostril* , are the outlet from the exterior into the nasal cavity. Small hairs are present here, coated with viscous mucus. *The posterior nostrils* are the aperture from the nasal cavity into pharynx. *The paranasal sinus* are crater in bone of the face and the cranium, have complete air. They are coated with mucus membrane, linger with that of

nasal cavity. The main sinus are:- Maxilary sinus in the side walls, Frontal and sphenoidal sinus in shieling, Ethmoidal sinus in the upper part of the side walls.

Function of Sinus in speech, lighten the skull and also drains tears from the eyes.

Respiratory functions of nose

It is the respiratory passage by which the in-spired air passes. The function is to warm, moisten, and filter air processing.

The projecting *conchae* enhance the surface area and cause instability, growing, inspired air over the whole nasal surface. The large surface area escalate warming, humidification, and filtering.

Warming:- due to boundless vascularity of the mucosa. Have the large blood loss when a nose bleed occurs.

Filtering and Clearing:- Hairs engulf large particles. the mucus stick Smaller particle such as dust and bacteria. Mucus also defend epithelium from irritation and drying.

Humidification:- As air moves over the moist mucosa, it is found to be saturated with water vapour. Irritation cause *sneezing*, a reflex that forcibly evacuate an irritant.

The sense of smell

The nose is known as the organ of sense of smell(olfaction). Nerve ending that identify smell are found at the roof of the nose in the area of the cribriform plate of the ethmoid bones and the superior conchae. These nerve ending are excited by airborne odours. The resultant nerve signals are drifting by the *olfactory nerve* to the brain where the sensation of smell is recognised.

Some other points related to it

Some drugs which show adverse effect when it pass through nasal cavity are:- cocain, atropine, antihistamines, propranolol, etc.[11]

When we suffer from common cold then there is decrease in the therapeutic efficacy of many drugs due to dysfunction of mucociliary action which are important for clearing the nasal passage.[11]

Some elements are required to broadenwithinside the nasal drug shippingmachine like technique of approach of deposition, charge of clearance, minimization of pathological condition. Absorption promoters need to be used to get higher systemic bioavailability.[11]

Potential pathway for some substances for there absorption:-

FACTORS	POTENTIAL PATHWAY
EGG ALBUMIN	NASAL MUCOSA TO LYMPHATIC STREAM
SERUM ALBUMIN	NASAL MUCOSA TO LYMPHATIC STREAM
DOPAMINE	NASAL MUCUS MEMBRANE TO CSF AND SERUM
ESTRADIOL	NASAL MUCUS MEMBRANE TO CSF(WITHIN 1 MINUTE)
PROGESTERONE	nasal membrane to olfactory dendrites to nervous gadget to supporting cells withinside the olfactory
PENICILLINS	NASAL MEMBRANE TO BLOOD STREAM

III. ADVANTAGES [12-18]

- THERE WILL BE RAPID ABSORPTION, WILL BE HIGHER BIOAVAILABILITY, SO THAT LOWER DOSE IS POSSIBLE.
- THERAPEUTIC ACTION WILL BE HIGH.
- First byskip metabolism may be avoided
- NOT NECESSARY TO PASS GI TRACT.
- THERE WILL BE REDUCTION RISK OF OVERDOSE.
- NON-INVASIVE SO THAT THERE THE INFECTIOUS DISEASE TRANSMISSIOIN WILL NOT OCCUR.
- IT WILL IMPROVE PATIENT OBSERVANCE.
- THE DRUGS WHICH HAVE HIGHER MOLECULAR WEIGHT WILL NOT BE DELIVERED THROUGH THIS ROUTES.
- LARGE INTERSPECIES VARIABILITY IS OBSERVED.
- FOR PROTEINS AND PEPTIDES DRUGS NASAL ROUTE IS ACCEPTABLE.
- MINIMAL AFTER TASTE.
- SELF ADMINISTERABLE.
- Traditional nasal drug shippingapproachprovidehigherbenefits over injection or oral drug shipping, they may begoing throughchalanges that restriction efficacy.
- IT WILL PASS BLOOD BRAIN BARRIER EASILY.
- THE CANDIDATES WHO ARE NOT SUITABLE FOR ORAL ROUTE DRUGS ADMINISTRATION THEN CAN PASS THE DRUG BY NASAL ROUTE.
- CAN BE DELIVERED TO THE SYSTEMIC CIRCULATION AND CNS DIRECTLY.
- GOOD PENETRATION.

IV. LIMITATIONS [19,20]

- **RISK OF LOCAL SIDE EFFECTS AND IRREVERSIBLE DAMAGE OF CILIA OF NASAL MUCOSA.**
- **THE SURFACTANTS WHICH ARE USED AS ENHANCER MAY DISRUPT.**
- Mechanical lack of dosage shape into the alternativepart ofrespirationdevice like lungs may became aboutdue tounsuitablemethod of drug delivery.
- There might beopportunity of nasal infectionbecause ofexceedingly inconvenient to affected personwhilstas compared to oral drug transport system
- With admire to GI tract the nasal hollow space has smaller floor area

- **DELIVERY VOLUME IS RESTRICTED OVER 25-200 MICRO LITRE.**
- Drugs with a higher molecular weight that cannot enter the nasal passage.
- The drugs like Budesonide and azilactinemotiveinfection to the nose.
- **ENZYMETIC BARRIER TO PERMEABILITY OF DRUG.**
- When the drug administered via nasal direction it cannotbe excreted.
- Low bioavailability because of enzymatic degradation and metabolism at mucosal surface.

V. DISADVANTAGES [21-23]

- With respect to gastrointestinal tract the Nasal cavity has smaller absorption surface area.
- When we compare oral cavity with nasal cavity there is possibility of irritation in nasal passage.
- The constituents and substances which are mix with nasal drug dosage form they can cause irreversible damage of the cilia in nasal passage.
- Due to inappropriate technique of drug delivery can cause mechanical loss of dosage form in other parts of respiratory system like lungs.
- The surfactants which are used as enhancer in nasal cavity may be disturb and even dissolve the membrane at higher concentration.

VI. MECHANISM OF NASAL ABSORPTION [24,25]

At first the drug will soak upwithinside the mucus of the nasal cavity , massive particle can'tbyskipthru it. But small particle may beeffortlesslybyskip the mucus layer. It incorporates paracellular deliverythrumotionamongmobileular and transcytosis with the aid of using vesicle carriers, transcellular or easy diffusion throughoutmobileular membrane. The major protein of mucus is mucin, that havegreater inclination to paste solutes. Structure may bealternatebecause ofa few environmental modifications like temperature, pH, etc.

1.The first mechanism is switch of drug thruaquous route, which is likewisereferred to as paracellular route. It is a sluggish processing route, it has inverse log-log interplayamong intranasal absorption and molecular weight of water soluble compounds. The capsulesthat havebetter molecular weight than one hundreddaltonsthey'vebad bioavailability.

2.The 2nd mechanism is switch of drug via lipoidal route, additionallyreferred to as transcellular route. The tablets are lipophilic which indicatesfee of lipophilicity. Drugs byskip the membrane throughlivelyshipping route viaservice mediated means. For instance chitosan, a herbal biopolymers which opens tight junction among epithelial cells to enables drug delivery.

VII. FACTORS INFLUENCING NASAL DRUG ABSORPTION

Here on this article, in particular3elements which have an effect on nasal drug absorption are as follows:-

A. BIOLOGICAL FACTORS

- Structural features
- Biochemical changes
- Pathological condition

B. FACTORS RELATED TO DRUG

It is of two types:-

1. Physiological factors
   - Effect of deposition and absorption
   - Effect of mucocilliary clearance
   - Blood supply and neuronal regulation
   - Effect of enzymatic activity
   - Nasal secretion

2. Physiochemical factors
   - Molecular weight
   - Chemical form
   - Lipophilicity
   - Polymorphism
   - Partition coefficient and pKa

C. FACTORS ASSOCIATED WITH FORMULATION

- PH
- Osmolarity
- Drug concentration, dose, and dose volume
- Viscosity
- Buffer capacity

A. BIOLOGICAL FACTORS

- Structural features:- It has five section: nasal vestibule, atrium, respiratory area, olfactory region, and nasopharynx. These are the cells which influence the permeability. Enhancers also are used to growth the permeation of drug molecule. [26]
- Biochemical changes:- Nasal mucosa act as enzymatic barrier because large number of enzymes are present here includes oxidative and conjugative enzyme, and also peptidase and protease. These enzymes are used to degrade the drugs in nasal mucosa and develop pseudo first pass effect. Nasal decongestant, alcohols, nicotine, and cocain IS are metabolized due to p450 dependent monoxygenase system. Protease and peptidase are used for systemic degradation and subsequent lower

permeation of various peptide drugs like calcitonin, insulin, and desmopressin, some approaches are used here like bacitracin, amastatin, puromycin, etc.[27]

- Pathological condition:- hypo or hyper secretion, irritation of nasal mucosa due to some disease like common cold, rhinitis, nasal polyposis, and also drug permeation is affected.[28]

B. FACTORS RELATED TO DRUGS

1. Physiological factors

- Effect of deposition and absorption:- The formulation deposited in the anterior part of nasal cavity which have longer nasal residence time. The anterior part of the nose have low permeability but the posterior part have high permeability so that it have shorter residence time.[19]
- Effect of mucocilliary clearance:- The absorption of drug is affected by the retention(contact) time between drug and epithelial tissue. The mucocilliary clearance is reversed to the retention time and so it is inversely proportional to the absorption of drug.[19]
- Blood supply and neuronal regulation:- Nasal cavity is highly absorptive. Because of parasympathetic stimulation it has high blood supply gives contraction and because of sympathetic stimulation it has low blood supply which gives relaxation, which controls the up and down of the permeated drugs[29]. According to above lines we can say that when there will be parasympathetic stimulation then there will be high blood supply to the nasal cavity.
- Effect of enzymatic activity:- Many enzymes which are present in in nasal cavity which influence the stability of drug. Such as protein and peptides degrades by protease and amino peptidase at the mucus memberane. Peptide form a bond with immunoglobulins which is used to increase the molecular weight and also reduce permeability.
- Nasal secretion:- Nasal secretion are generated by anterior serous and seromucus glands. Daily about 200gm to 2litre mucus produced by respiratory mucosa. The permeability of drug by nasal mucosa is influenced by:-
  - I. Viscosity of nasal secretion:- If the sol layer is too thin then the viscous surface will inhibit the cilliary beating and if the sol layer is too thick then it will diminish the mucocilliary clearance, because of no contact with cilia. Permeation of drug is affected which is caused by damage of mucocilliary clearance by altering the time of contact of drug.
  - II. Solubility of drug in nasal secretion:- Solubility is necessary for drug permeation. A drug required to have suitable physiochemical property for dissolution in nasal secretion.
  - III. Diurnal variation:- nasal secretion are influenced by circadian rhythm. At night permeation of drug changes because secretion and clearance are decreased at night.
  - IV. PH of nasal cavity:- In adults pH is remarked between 5.5-6.5 and in infants pH is remarked as 5.0-7.0. If the pKa is greater than nasal pH then drug permeation will be more because under this condition the penetration molecule is survived as unionized species.

2. Physiochemical factor

- Molecular weight:- The drug which have permeation less than 300 dalton cannot be significantly affected by the physiochemical properties. The bioavailability of large molecule ranges from 0.5% to 5%. Mostly it permeate from aqueous channel of the membrane.[30]
- Chemical form:- Chemical form is defined by the absorption of drug which is present in nasal mucosa. The drug is chemically change by adding bio-cleavable lipophilic moiety which is used to improve drug absorption. The toxicity of prodrug itself needs to be fully evaluated.[31]
- Lipophilicity:- When there will be increase in lipophillicity then the permeability of drug will increases. Lipophilic drug easily cross biological membrane via transcellular routetill they are able to partition into the lipid(bilayer) of the cell membrane. Example:- testosterone.[19]
- Polymorphism:- It influence the dissolution rate and solubility of drug. Thus it is more important to study polymorphic stability and purity of drugs for nasal powder or suspension.[32]
- Partition coefficient and pKa:- PH partition theory states that ionized particle are low absorbable than unionized particle, this fact is also applied in the case of nasal absorption. There is relation between nasal absorption and pKa of drug. When the partition coefficient increases then the biological tissues concentration also increases. When the pH increases then the rate of absorption of aminopyrine also increases antd it was found to be fit well to theoretical profile.[33]

C. FACTORS RELATED TO FORMULATION [34]

- pH:- The nasal pH should be 4.5-6.5 to avoid nasal irritation. pH is determined as how much drug is ionized in nasal system. pH of nasal surface is 7.39 and pH of nasal secretion is 5.5-6.5 in adults and 5.0-6.7 in children.
- OSMOLARITY:- If there will be maximum osmolarity they can cause shrinkage of nasal mucosal cell. In this system generally isotonic formulation is preferred. Hence tonicity is also having impact on drug absorption.
- DRUG CONCENTRATION,DOSE,AND DOSE VOLUME:- These three are the variables which clash the performance of the nasal delivery performance. In nasal perfusion experiments, the drug L-Tyrosine play an important role which increases with drug concentration.
- VISCOSITY:- Viscosity increases contact time between drug and nasal mucosa thereby increasing the time for permeation.
- BUFFER CAPICITY:- Nasal drugs are transferred in small volume(20-25 micro litre) , buffer capacity can effect the unionized drug available for administration. Thus buffer capacity is used to maintain the Ph of the drug formulation.

VIII. STRATEGIES TO IMPROVE NASAL ABSORPTION[17,35,36,37,38]

There are three main strategies to improve nasal absorption as follows:-

1. Nasal Residence Time Improvement
2. To Enhance Nasal Absorption
3. Modification Of Drug Structure To Change Its Physicochemical Properties

1. NASAL RESIDENCE TIME IMPROVEMENT:-

Mucocilliary clearance acts to remove the foreign bodies and substances from nasal mucosa as quickly as possible. One way of delaying clearance is to apply the drug to the anterior part of the nasal cavity, an effect that is largely determined by the type of dosage form used. The preparation could also be formulated with polymers such as methylcellulose, hydroxy propyl methyl cellulose or polyacrylic acid, in which incorporation of polymer increases viscosity of the formulation and also acts as a bio adhesive with mucus. Increase in residence time does not necessarily lead to increase the absorption; this concept can be illustrated by considering insulin solution with similar viscosity containing carbopol and CMC. Here carbopol enhance the absorption whereas CMC solution doesn't enhance the absorption of insulin. If we increase the viscosity, slow diffusion of drug from matrix causes retention in absorption with CMC. Incase of carbopol causes enhancement of absorption due to opening the intracellular junctions. One more lucrative way to increase the nasal resistance time is using biodegradable microspheres as a carrier for drug delivery. Biodegradable microspheres swell in presence of water thereby increasing the viscosity. This phenomenon leads to increase the nasal residential time.

Various compounds used as an enhancer in nasal drug delivery system:-

Name of compounds	Examples
Surfactants	SDS, polyoxyethylene-9-laurylether, phosphatidylcholines.
Complexing and chelating agents	EDTA
Cyclodextrins and derivatives	α-, β-, γ-cyclodextrin, DMβ-, HPβ-cyclodextrin
Fusidic acid derivative STDHF Bile salts	Sodium taurocholate, sodium glycocholate
Dry microspheres	Degradable starch microsphere, dextran microspheres

SDS: Sodium dodecyl sulfate, EDTA: Ethylenediaminetetraacetic acid, STDHF: Sodium tauradihydrofusidate.

2. TO ENHANCE NASAL ABSORPTION:-

Nasal absorption enhancer is used to increase the rate at which drug passes through the nasal mucosa. Many enhancer change the structure of epithelial cells but they should complete without damaging or permanent change to nasal mucosa. Some requirements for penetration enhancer are as follows:-

- It have an effective role to increase drug absorption.
- It should not damage permanent epithelial cell of mucosa.
- It should not have irritant and toxic activity.
- It should not be effective in large quantity.
- When absorption is required then enhancing activity should occur.
- The effect should be for short term and it should be changeable.

Classification Of Penetration Enhancer:

- Solvent
- Alkyl methyl sulphoxides
- Pyrrolidones
- Dodecyl azacycloheptan-2-one
- Surfactants:- Polyozyethylene-9-lauryl ether (Laureth-9), Saponin.
- Phospholipids: Lysophosphatidylcholine (lyso-PC), Didecanoyl – PC
- Glycyrrhetinic acid derivates: Carbenozolone, Glycyrrhizinate

Mechanism of Penetration Enhancers:

- Increasing cell membrane permeability Opening tight junction and formation of intracellular aqueous channels.
- Increasing lipophilicity of the charged drug by forming ion pair.
- Inhibiting proteolytic activity.

3. MODIFICATIONS OF DRUG STRUCTURE TO CHANGE ITS PHYSICOCHEMICAL PROPERTIES:-

Modification of drug structure without altering pharmacological activity is one of the lucrative ways to improve the nasal absorption. The chemical modifica-tion of drug molecule has been commonly used to modify the physicochemical properties of a drug such as molecular size, molecular weight, pka and solubility are favorable to improve the nasal absorption of drug. Example, chemical modification of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) showed better bioavailability than salmon calcitonin (Hofstee BH 1952).

Absorption Enhancers in Nasal Drug Delivery[17,39] :

Unlike the most small drug molecules, some drugs and peptides do not cross the nasal membrane efficiently. As a result the nasal bioavailability in simple solution formulation is very low. The low nasal absorption can be attributed to poor membrane permeability due to molecular size, lack of lipophilicity or enzymatic degradation. Enzyme inhibitors can be added to nasal formulation to prevent enzymatic degradation. The nasal mucosa is almost impermeable to molecular size greater than 1000 Dalton. To overcome these problems of poor membrane permeability most frequent used approach is the use of absorption enhancers. They act by one or combination of the following mechanisms:

- Alteration of properties of mucosa layer.
- Opening tight junctions between epithelial cells.
- Reversed micelle formation between membranes.
- Increasing the membrane fluidity by,

A) Extraction or leaching of membrane components
B) Creating disorders in the phospholipids domain in the membrane.

Various types of penetration enhancers have been evaluated for organic drugs including surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetenic acid derivatives, cyclodextrins and glycols. Polyoxyethylene-9-lauryl ether (BL-9) in saline solution improves the nasal absorption of hydralazine in both in-situ and in vivo nasal absorption studies in rats. Polysorbate 80 (1 %) in saline solution was observed to promote the nasal absorption of atropine and hyoscine from nasal solution.

The absorption was rapid, complete and uniform with addition of sodium lauryl sulphate. A nasal formulation of meclizine (50 mg/ml) prepared in propylene glycol and 10 % glycerol results in 50 % of nasal drug absorption, which is equivalent to I.V.therapy. The nasal absorption of gentamycin (60 mg/ml in saline solution) in humans has observed to increase by incorporation of 1 % sodium glycocholate and peak serum levels were achieved in 30-60 min.

Breakthroughs of Nasal Drug Delivery System[39,40]:

1. Insulin administered through nasal route: Diabetes mellitus is a chronic disease that usually requires multiple insulin injections to achieve adequate glycaemic control. This represents a major cause of reduced compliance to treatment. Consequently, other routes for insulin administration have been explored. During recent years, much progress in the development of inhaled insulin has been made. Inhaled insulin has favorable properties, such as rapid onset of action, improved bioavailability and good tolerability, thereby providing satisfaction and ease of administration

2. Insulin gel administered through nasal route: The objective of the present study was to formulate insulin gel for intranasal administration and to evaluate with respect in-vitro release study and hypoglycaemic activity in animal model and healthy human volunteers. The insulin gel was formulated using the combination of carbopol and hydroxypropylmethylcellulose as gelling agent. The in-vivo efficacy of insulin gel administered intranasally was assessed by measuring the blood glucose levels at specified time intervals in rats and humans

3. Cancer pain management through nasal route: Cancer pain management necessitates the use of opioids when pain is moderate or severe. Opioids need to be versatile and effective. Newer formulations may improve patient compliance and may be more conductive to the management of transient flares of pain; they also may be tailored to treat certain special populations and may be particularly effective in certain clinical situations. For e.g. Newer opioids have been developed for transdermal, nasal and nebulized administration, providing a needle-less means of controlling pain in those unable to take oral medications. However, newer opioid formulations are not a substitute for good pain management strategies and will not control pain unless provided in adequate doses and schedules

4. Antibiotics and mucolytics are delivered to the nasal cavity: Decongestants, antibiotics and mucolytics are delivered to the nasal cavity, their intended site of action. Due to its accessibility, relatively large surface area 160 cm2 and rich vascular supply of the nasal mucosa, the nasal route of administration is attractive for many drugs for systemic absorption, including proteins and peptides

5. Microsphere as nasal drug delivery system: All types of microspheres that have been used as nasal drug delivery system are water insoluble but absorb water into the sphere matrix, resulting in swelling of the spheres and the formulation of a gel. The building materials in the microspheres have been starch, dextran, albumin and hyaluronic acid, and the bioavailability of several peptides and proteins has been improved in different animal models.

THERAPEUTIC CONSIDERATIONS:-

1. Local delivery

IN is a logical delivery choice for local (or topical) treatment. Prominent examples are decongestants for nasal cold symptoms, and antihistamines and corticosteroids for allergic rhinitis (Bloebaum, R.M 2002). Examples of nasal products with widespread use in this area include the histamine H1-antagonist levocabastine (Janssens and Vanden 1991), the anti-cholinergic agent ipratropium bromide (Milford et al., 1990) , and steroidal anti-inflammatory agents such as budesonide (Stanaland, B.E. 2004), mometasone furoate (Drunen et al., 2005).

2. Systemic delivery

Positive attributes of IN systemic delivery include a relatively large surface area for drug absorption, rapid drug onset, no first-pass metabolism, and non-invasiveness to maximize patient comfort and compliance. Specific pharmacokinetic attributes of IN delivery are reviewed elsewhere (Costantino et al., 2005). As discussed in the various case studies below, IN administration provides an alternative route for systemic delivery of drugs more conventionally delivered by oral or (for poorly orally absorbed compounds such as peptides and proteins) injection routes.

3. Chronic versus acute therapeutic use

When deciding on a delivery route, it is important to consider the dosing regimen for the drug. Is the intended use acute or chronic? For an acute indication, the advantage of patient comfort and compliance afforded by IN dosing (as compared with injections) may not be a major factor. Even so, there are advantages to IN dosing in certain acute situations. One example is the case of an emergency room setting, where the avoidance of accidental needle stick potential is desired (Wolfe and Barton 2003).

4. Vaccine delivery The nasal mucosa has received some attention as a vaccination route. Presentation of a suitable antigen with an appropriate adjuvant to the nasal-associated lymphoid tissue (NALT) has the potential to induce humoral and cellular immune responses (Zuercher et al., 2002). This approach may be a particularly effective approach to achieving rapid mass immunization, for instance in children and/or in developing countries and disaster areas (Roth et al., 2003). IN immunization may lead to development of local, as well as systemic, immunity. Furthermore, vaccination via the IN route does not require a sterile product or a sterile dosing technique (a distinct advantage in developing areas of the world). An example of an IN vaccine is FluMist®, a coldadapted live influenza virus (Kemble and Greenberg 2003). This product is given as one or two doses over the influenza season via a syringe sprayer.

Main reasons for exploiting the nasal route for vaccine delivery

- The nasal mucosa is the first site of contact with inhaled antigens .
- The nasal passages are rich in lymphoid tissue (Nasal) Associated Lymphoid Tissue-NALT.
- NALT is known as Waldeyer's ring in humans.
- Adenoid or nasopharyngeal tonsils.
- Bilateral lymphoid bands.
- Bilateral tubal and facial or palatine tonsils.
- Bilateral lingual tonsils.
- Creation of both mucosal (sIgA) and systemic (IgG) immune responses.
- Low cost, patient friendly, non-injectable, safe.

5. Nose to brain delivery IN delivery of drugs targeting the central nervous system (CNS) is currently an area of great interest, as reviewed elsewhere (Illum, L. 2004), (Vyas et al., 2005).

IX. BARRIERS TO NASAL ABSORPTION

Novel drug delivery system is very useful for scientist who is working on formulation process because it has simple formulation plan.

Following factors are the barriers to nasal absorption:-

1. Low Bioavailability.
2. Low membrane transport.
3. Enzymatic Degradation.

1. LOW BIOAVAILABILITY:-

As compared to polar drugs lipophilic drugs are more absorbable. Lipophilic drugs pharmacokinetics is same as obtained after an intravenous injection and bioavailability approaching 100%. A good example is the nasal administration of Fentanyl where the Tmax for both intravenous and nasal administration have been shown to be very rapid (7 min or less) and the bioavailability for nasal anterior part of the nasal cavity can decrease clear- administration was near 80%. The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability. Drugs can cross the epithelial cell membrane either by the transcellular route exploiting simple concentration gradients, by receptor mediated or vesicular transport mechanisms, or by the paracellular route through the tight junctions between the cells.

2. LOW MEMBRANE TRANSPORT:-

The general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism.This is specially for that drug which is not easily absorbed across the nasal cell membrane. For both powder and liquid formulation, are not mucoadhessive, 15-20 minutes are there half life. On the anterior part of the nasal cavity the clearance decreases.

3. ENZYMATIC DEGRADATION:-

It is less important factor in which peptides and proteins are low transferable across the nasal cell membrane is the possibility of an enzymatic degradation of the molecule either within the lumen of the nasal cavity or during passage across the epithelial barrier. And also contains both exopeptides (mono and di amino peptides) which joins the peptide bonds at their N and C terminal. And endopeptides(serine and cystein) which attack internal peptide bonds.

Table:- Barriers in nasal drug product development

Nasal barriers	Factors to be considered
1. Physiological barrier	
a. Nasal mucus	**Viscocity, pH of mucus and Drug/dosage form- mucus interaction.**
b. Nasal epithelial barrier	**Molecular weight, ionization constant, and mode of transport.**
c. Mucocilliary clearance	**Nasal residential time and nature of dosage form.**
d. Pathophysiology	**Volume of nasal secretion and Permiability of epithelium.**
e. Nasal Metabolism	**Nature of the molecules(protein and peptides).** **Nature of drug molecules and duration of therapy.**
f. Efflux transport system	
2. Physiochemical Barriers	
a. Drug solubility and dissolution	**Nature of dosage form, dose, pKa, and polymorphism.**
b. Molecular weight and size	**Less bioavailability with molecular weight more than 1000.**
c. Compound lipophillicity	**Effects the nose to blood and nose to brain absorption.** **Unionized pH flavors for absorption.**
d. pH and pKa	
3. Formulation Factors	
a. Drug concentration, dose, and volume	**High concentration for better bioavailability, maximum dose in minimum vehicle(less than 200 micro litre).**
b. Osmolarity	**Isotonic solution prevents epithelial damage and tonicity.**

c. Site of deposition	**Site of deposition bassed on viscosity, position of head, volume, delivery vehicle,deposition at anterior chamber prolong the nasal residential time.**

X.TYPES OF DRUG CANDIDATE WHO IS SUITABLE FOR NASAL DRUG DELIVERY:-[31]

- formulation administration per nostril should be 25-150 ml(appropriate aqueous solubility).
- Nasal absorption properties should be proper.
- Should not cause nasal irritation.
- Proper clinical grounds should be available for nasal doses forms e.g- rapid onset of action.
- Lowest dose should be less than 25 mg.
- Nasal metabolites should not be toxic.
- Bad smell should not be present in drug.
- Stability characteristics should be proper.

XI. NASAL DRUG DELIVERY TO TARGET CNS:-[41,42]

Only lipophilic drug can pass CNS. The delivery of drugs to CNS from the nasal route may occur through olfactory neuroepithelium. Drug delivery through nasal route into CNS has been reported for Alzheimer's disease, brain tumors, epilepsy, pain, and sleep disorder.

XII.RESEARCH AND DEVELOPMENT IN NASAL DRUG DELIVERY SYSTEM:-[43]

In India Nasal vaccines manufactured by Bharat Biotech their nasal vaccine are in the final stages of clinical trials and are soon going to launch vaccines in the global market. The nasal vaccines are most cost effective and efficient than that of intravenous injections. The nasal vaccines can also be easily administered to the children as the nasal spray stimulates a broad immune response and neutralizing IgG, mucosal IgA, and T cell responses.

Updates- McMaster researcher said that spider web immune response could occur from COVID nasal spray vaccine which can trap and kill pathogens like SARS-CoV-2 and influenza.

Most of the nasal preparation are in the form of solution which is used to treat nasal symptoms and also CNS problems. A simple drug is sufficient for this issue as it produces better dispersion over greater surface area. Nasal residence time is short(3-20 min) and exhibit high inter individual variability. As compared to intravenous injectable drug nasal drug has high peak level in circulation.

After animal experiment large no. of intranasal drugs are estimated for systemic bioavailability. Transnasal drugs in various doses forms are like sprays, powders, and microspheres has been undertaken to boost residence and bioavailability.

As compared to iv dose mucosal mucosal administration requires 1.1-1.5 times higher dose of fentanyl in nasal delivery. In terms of efficacy nasal vaccine delivery is a very attractive route.

XIII. BIO MEDICAL APPLICATIONS OF NASAL DRUG DELIVERY SYSTEM:-[44]

Nasal delivery of organic based pharmaceuticals:-

extensive metabolism such as progesterone, estradiol, testosterone, hydralazine, propronolol, coccain, nalaxone, etc. is highly absorbed through nasal mucosa and has 100% bioavailability.

Nasal delivery of peptide based pharmaceuticals:-

It has physiochemical instability and susceptibility to hepatogastro intestinal first pass elimination, so it has low bioavailability and are administered by parental route. It can be prepared as simple solution with preservatives.

Table:- Bio pharmaceutical data for some organic based pharmaceuticals:-

Sl No.	Pharmaceuticals	Animal Model	Tmax	Nasal Bioavailability(%)
1.	Buprenorphine	Rat Human	2-5 Min 5 Min	95 48
2.	Clofiliumtysolate	Rat	<10 Min	69.6
3.	Diazepam	Humans	60 Min	72-84
4.	Ergotamine tartrate	Rat	2 Min	62

Table:- Bio Pharmaceutical Data Analysis For Some Peptide Based Pharmaceuticals:-

Sl No.	Pharmaceuticals	Animal Model	Tmax	Bioavailability(%)
1.	Alsactide(ACTH-17)	Rat	1Hr	12%
2.	Glucagon(with Na Glycocholate)	Human	10 Min	50%
3.	Na Glycocholate	Rat	10-15 Min	7-8%
4.	Na Caprate	Rat	5 Min	98%

XIV.DOSAGE FORMS OF NASAL DRUG DELIVERY SYSTEM:-[43]

Different dosage forms are as follows:-

- Nasal drops
- Nasal sprays
- Nasal Gels
- Nasal Powders

Nasal Drops:- It is most simple and convenient part of nasal drug delivery system, disadvantages are lack of dose precision. So it is not suitable for prescription product. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

Types:-

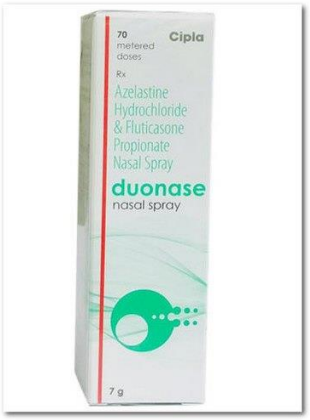
1. Instillation and rhinyle catheter :- Catheters are used to deliver the drops to a specified region of nasal cavity easily.

2. Compressed air nebulizers :- Nebulizer is a device used to administer medication in the form of a mist inhaled into the lungs. The compressed air is filling into the device, so it is called compressed air nebulizers.

3. Squeezed bottle :- Squeezed nasal bottles are mainly used as delivery de-vice for decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plas-tic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume.

Nasal Sprays :- Both solution and suspension formulations can be formulated into nasal sprays. Due to the availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 µm.

Types:- There are four types of nonprescription nasal sprays in common use—corticosteroids, nasal decongestants, sodium chloride, and cromolyn sodium.[44]



Nasal Gels :- Nasal gels are highly viscous solution or suspension. Here are some reduction of post nasal drip due to high viscosity. Reduction of taste impact due to reduced swallowing.

Nasal powders :- it is developed if solutin and suspension dosage forms cannot be developed, such as lack of drug stability. It is local application of drug, in this there is absence of preservatives.

XV. CONCLUSION :-

In summary I want to describe some points in brief :-

We all know that Nose is an important part of our body. It (nasal mucosa) has Faster and Higher rate of absorption because it can pass more compound than the GI Tract due to lack of pancreatic and gastric enzyme activity.

Hear I covered

- Respiratory functions of nose.
- Sence of smell(olfactory nerve).
- Advantages,limitations,disadvantages.
- Mechanism of nasal absorption.
- Factors influencing nasal absorption :- Biological factors, Factors related to drug, Factors related to formulations.
- Strategies to improve nasal absorption.
- Therapeutic considerations.
- Barriers to nasal absorption: Low Bioavailability, Low membrane transport, Enzymatic Degradation.
- Types of drug candidate who is suitable for nasal absorption :- Nasal absorption properties should be proper. Should not cause nasal irritation. Proper clinical grounds should be available for nasal doses forms e.g- rapid onset of action. Lowest dose should be less than 25 mg.
- Nasal drug delivery to target central nervous system:- Only lipophilic drug can pass CNS. Research and development in nasal drug delivery system :- In India Nasal vaccines manufactured by Bharat Biotech their nasal vaccine are in the final stages of clinical trials and are soon going to launch vaccines in the global market. **As compared to iv dose mucosalmucosal administration requires 1.1-1.5 times higher dose of fentanyl in nasal delivery. In terms of efficacy nasal vaccine delivery is a very attractive route.**
- Different dosage forms :- Nasal drops, Nasal sprays, Nasal Gels, Nasal Powders etc.

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