INTRANASAL ROUTE: A PROMISING TECHNIQUE FOR BRAIN TARGETING

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ABSTRACT

Targeted drug delivery seeks to concentrate the medication in the tissues of interest while reducing the relative concentration of medication in the remaining tissues. Thus improving efficacy of the drug and reducing side effects. Intranasal drug delivery – practiced for thousands of years, and given a new pact of life. It is a profitable delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides. The nasal route bypasses hepatic first pass elimination associated with the oral delivery: it is easily approachable and suitable for self-medication. The large surface area of the nasal mucosa affords a rapid onset of therapeutic effect, potential for direct-to-central nervous system delivery and non-invasiveness; all of which may maximize patient convenience, comfort, and compliance. Also it is fast in action and suitable for the drugs that degrade in gastrointestinal tract. Nose-to-brain delivery also avoids blood brain barrier which is important factor to be considered in formulation of CNS targeting drugs.

Keywords: *Intranasal drug delivery, Brain targeting, Protein & Peptides, Liposomes, Microspheres.*

❖ INTRODUCTION:

In ancient times the Indian Ayurveda system of medicines used nasal route for administration of drug and the process is called as **"Nasya"**. It has been used for local effects extensively in decongestant and local activity. But, in recent times intranasal drug delivery is being considered as a preferred route of drug delivery for systemic bioavailability. Various proteins & peptides have shown a good bioavailability. Nasal drug delivery system used conventionally for local delivery of drugs for treatment of nasal allergies and infections. In recent years research established that the nasal route is safe and acceptable alternate to oral and parentral administration of drugs. Nasal route is found to be valuable for targeting drugs to CNS via different mechanisms[1]. Many scientists have reported evidence of nose-to-brain transport. Many previously abandoned potent CNS drug candidates promise to become successful CNS therapeutic drugs vial intranasal delivery. Recently, several nasal formulations, such as ergotamine (Novartis), sumatriptan (GlaxoSmithKline), and zolmitriptan (AstraZeneca) have been marketed to treat migraine. Scientists have also focused their research toward intranasal administration for drug delivery to the brain especially for the treatment of diseases, such as epilepsy [2-4], migraine [5], emesis, depression [6] angina pectoris [7] and erectile dysfunction.

A. ADVANTAGES OF NASAL DRUG DELIVERY SYSTEM [8-9]:

1. Rapid absorption and onset of action of drugs.
2. Avoidance of hepatic first-pass metabolism
3. Avoids degradation of drug in gastrointestinal tract resulting
4. from acidic or enzymatic degradation
5. Rate of absorption comparable to IV medication

6. Non-invasive, Painless, needle-free administration mode
7. Easily accessible (even easier to access than IM or IV sites)
8. Elicitation of local immune response in respiratory infections such as influenza.
9. Ability to overcome first pass metabolism associated with oral medication of drugs.
10. Self-medication is possible.
11. The nasal bioavailability for smaller drug molecules is good.
12. Results in higher bioavailability thus uses lower dose & hence lower side effects.
13. Drugs that are orally not absorbed can be delivered to the systemic circulation by nasal drug delivery.
14. Useful for both local & systemic drug delivery
15. Studies so far carried out indicate that the nasal route is an alternate to parenteral route, especially, for protein and peptide drugs.
16. Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.
17. Drugs possessing poor stability in g.i.t. fluids are given by nasal route.
18. Polar compounds exhibiting poor oral absorption may be particularly suited for this route of delivery.
19. Easy accessibility and needle free drug application without the necessity of trained personnel facilitates self-medication, thus improving patient compliances compared to parenteral routes.
20. Good penetration of, especially lipophilic, low molecular weight drugs through the nasal mucosa. For instance the absolute nasal bioavailability of fentanyl is about 80%.
21. Direct transport into systemic circulation and CNS is possible.
22. Offers lower risk of overdose
23. Rapid absorption and fast onset of action due to relatively large absorption surface and high vascularization. Thus, the Tmax of fentanyl after nasal administration was less than or equal to 7 minute comparable to intravenous [i.v.]. Nasal administration of suitable drug would therefore be effective in emergency therapy as an alternative to parenteral administration routes.

B. DISADVANTAGES OF NASAL DRUG DELIVERY SYSTEM [10-11]:-

1. Concentration achievable in different regions of the brain and spinal cord varies with each agent
2. Delivery is expected to decrease with increasing molecular weight of drug.
3. Some therapeutic agents may be susceptible to partial degradation in the nasal mucosa or may cause irritation to the mucosa.

❖ NASAL ANATOMY AND PHYSIOLOGY:

The human nasal cavity has a total volume of about 16 to 19 ml, and a total surface area of about 150 cm2 [44] and is divided into two nasal cavities via the septum. The volume of each cavity is approximately 7.5 ml, having a surface area around 75 cm^2. Post drug administration into the nasal cavity, a solute can be deposited at one or more of here anatomically distinct regions, the vestibular, respiratory and olfactory region[12] that are distinguished according to anatomical and histological structure table-1 along with details given below;

a. The respiratory region:

The nasal respiratory region, also called conchae, is the largest part of the nasal cavity and it is divided in superior, middle and inferior turbinate's which are projected from the lateral wall. These specialized structures are responsible for humidification and temperature regulation of inhaled air. Between them there are spaces, called meatus, which are passageways where airflow is created to assure a close contact of the inhaled air with the respiratory mucosal surface.

The inferior and middle meatus receive nasolacrimal ducts and paranasal sinuses which are air-filled pockets located inside the bones of the face and around the nasal cavity[13]. The respiratory epithelium is composed of four types of cells, namely, non-ciliated and ciliated columnar cells, basal cells and goblet cells, These cells facilitate active transport processes such as the exchange of water and ions between cells and motility of cilia (where applicable). They may also serve to prevent drying of the mucosa by trapping moisture.

b. The olfactory region:

It is of about 10 cm^2 in surface area, and plays a vital role in transportation of drugs to the brain and the CSF. The olfactory region comprises of thick connective tissue, lamina propria, upon which rests the olfactory epithelium. Lamina propria has axons, bowman's bundle and blood vessels whereas the epithelium consists of three different cell types, basal cells, supporting cells, and olfactory receptor cells. Neurons are interspersed between supporting cells. The olfactory receptor cells are bipolar neurons with a single dendritic, extending from the cell body to the free apical surface where it ends in an olfactory knob carrying non-motile cilia, which extends above the epithelium. The epithelium of the nasal passage is covered by a mucus layer, which entraps particles. The mucus layer is cleared from the nasal cavity by cilia, and is renewed every 10 to 15 minutes.[14] The pH of the mucosal secretions ranges from 5.5 to 6.5 in adults and 5.0 to 6.7 in children. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 15 to 20 minutes. Numerous enzymes for instance, cytochrome P450 enzymes, carboxylesterases and glutathione S-transferases are found in nasal cavity.[15]

Table-1:- Showing Nasal Anatomy and Histology of Nasal Cavity

Nasal sections	Epithelial characteristics/cell function	Surface area	Vascularization	Permeability
Vestibule	Stratified squamous and keratinized epithelial cells with nasal hairs/support and protection	Approximately 0.6 cm^2	Low	Poor
Atrium	Stratified squamous cells/support Pseudostratified cells/support	NF	Low	Reduced
Respiratory region	Columnar non ciliated cells/support Ciliated cells/support and mucociliary clearance Goblet cells/mucus secretion Basal cells/progenitors of other cells	Approximately 130 cm^2	Very high	Good
Olfactory region	Sustentacular cells/support and olfactory receptor cells/olfaction perception	Approximately 15 cm^2	High	Direct access to CNS

NF- Not Found

c. The vestibular region:

This is located at the opening of nasal passages and is responsible for filtering out air borne particles. It is considered to be the least important of the three regions with regard to drug absorption. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water soluble compounds. Compounds, which are highly hydrophilic in nature and/or of low molecular weight, are most appropriate

for paracellular transport. A sharp reduction in absorption and poor bioavailability was observed for the drugs having molecular weight greater than 1000 Da. Moreover, drugs can also cross cell membranes by a carrier – mediated active transport route. For example, chitosan, a natural biopolymer from shellfish, stretches and opens up the tight junctions between epithelial cells to facilitate drug transport. The transcellular transport mechanisms / pathways mainly encompass transport via a lipoidal route [15].

❖ Drug selection properties to penetrate Blood- Brain/Blood-CSF Barriers: [11, 16]

1. Smaller molecular size of drug (>300 Da).
2. Moderately lipophilic drugs are good candidates for nose to brain targeting.
3. Volume of distribution near about 1 lit/kg.
4. Drug must be not strong ligand of an efflux pump at BBB/Blood CSF barrier.

❖ MECHANISM OF NOSE TO BRAIN DRUG TRANSPORT: [17]

It is important to examine the pathway/mechanisms involved prior to addressing the possibilities to improve transnasal uptake by the brain. The olfactory region is known to be the portal for a drug substance to enter from nose-to-brain following nasal absorption. Thus, transport across the olfactory epithelium is the predominant concern for brain targeted intranasal delivery.

Nasal mucosa and subarachnoid space; lymphatic plexus located in nasal mucosa and subarachnoid space along with perineural sheaths in olfactory nerve filaments and subarachnoid space appears to have communications between them. The nasal drug delivery to the CNS is thought to involve either an intraneuronal or extra neuronal pathway [14]. A drug can cross the olfactory path by one or more mechanism/pathways.

These include paracellular transport by movement of drug through interstitial space of cells transcellular or simple diffusion across the membrane or receptor / fluid phase mediated endocytosis and transcytosis by vesicle carrier [20] and neuronal transport. The paracellular transport mechanism/route is slow and passive. It mainly uses an aqueous mode of transport. Usually, the drug passes through the tight junctions and the open clefts of the epithelial cells present in the nasal mucosa.

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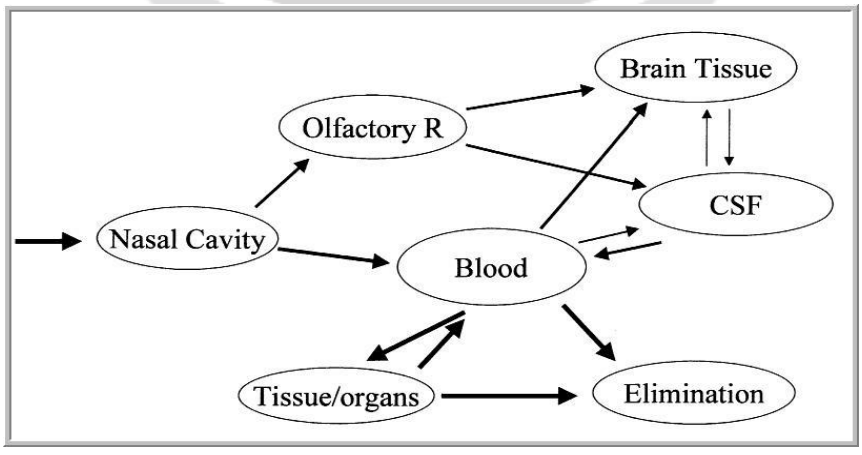


Fig-1: Nose to brain transport route

❖ FACTORS INFLUENCING NASAL ABSORPTION OF DRUGS:[17,19]

Some of the physicochemical, formulation and physiological factors are imperative and must be considered prior to designing intranasal delivery for brain targeting.

A) Physicochemical properties of drugs:

a. Chemical form:

The chemical form of a drug is important in determining absorption. For example, conversion of the drug into a salt or ester form can also alter its absorption. Huang *et al*., 1985 studied the effect of structural modification of drug on absorption. It was observed that in-situ nasal absorption of carboxylic acid esters of L-Tyrosine was significantly greater than that of L-Tyrosine.

b. Polymorphism:

Polymorphism is known to affect the dissolution rate and solubility of drugs and thus their absorption through biological membranes.

c. Molecular Weight:

A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Da.[20] Absorption decreases significantly if the molecular weight is greater than 1000 Da except with the use of absorption enhancers. The apparent cut-off point for molecular weight is approximately 1,000 with molecules less than 1,000 having better absorption. Shape is also important. Linear molecules have lower absorption than cyclic – shaped molecules.

d. Particle Size:

It has been reported that particle sizes greater than 10μm are deposited in the nasal cavity. Particles that are 2 to 10 μm can be retained in the lungs and particles of less than 1 μm are exhaled.

e. Solubility & dissolution Rate:

Drug solubility and dissolution rates are important factors in determining nasal absorption from powders and suspensions. The particles deposited in the nasal cavity need to be dissolved prior to absorption. If a drug remains as particles or is cleared away, no absorption occurs.

B) Formulation factors:

A. pH of the formulation:

Both the pH of the nasal cavity and pKa of a particular drug need to be considered to optimize systemic absorption. Nasal irritation is minimized when products are delivered with a pH range of 4.5 to 6.5.[22] Also, volume and concentration are important to consider. The delivery volume is limited by the size of the nasal cavity. An upper limit of 25 mg/dose and a volume of 25 to 200 μL/ nostril have been suggested.

- To avoid irritation of nasal mucosa;
- To allow the drug to be available in unionized form for absorption;
- To prevent growth of pathogenic bacteria in the nasal passage;
- To maintain functionality of excipients such as preservatives; and
- To sustain normal physiological ciliary movement.

Lysozyme is found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the nasal tissue is susceptible to microbial infection. It is therefore advisable to keep the formulation at a pH of 4.5 to 6.5 keeping in mind the physicochemical properties of the drug as drugs are absorbed in the unionized form.

B. Buffer Capacity:

Nasal formulations are generally administered in small volumes ranging from 25 to 200µL. Hence, nasal secretions may alter the pH of the administrated dose. This can affects the concentration of unionized drug available for absorption. Therefore, an adequate formulation buffer capacity may be required to maintain the pH in-situ.

C. Osmolarity:

Drug absorption can be affected by tonicity of formulation. Shrinkage of epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity. Low pH has a similar effect as that of a hypertonic solution. Suzuki *et al*., 1999 showed that a drug carrier such as hydroxypropyl cellulose was effective for improving the absorption of low molecular weight drugs but did not produce the same effect for high molecular weight peptides. Use of a combination of carriers is often recommended from a safety (nasal irritancy) point of view.

D. Solubilizers:

Aqueous solubility of drug is always a limitation for nasal drug delivery in solution. Conventional solvents or co-solvents such as glycols, small quantities of alcohol, Transcutol (diethylene glycol monoethyl ether), medium chain glycerides and Labrasol can be used to enhance the solubility of drugs. Other options include the use of surfactants or cyclodextrin such as HP-β-cyclodextrin that serve as a biocompatible Solubilizers and stabilizer in combination with lipophilic absorption enhancers.

E. Preservatives:

Most nasal formulations are aqueous based and need preservatives to prevent microbial growth. Parabens, benzalkonium chloride, phenyl ethyl alcohol, EDTA and benzoyl alcohol are some of the commonly used preservatives in nasal formulations. Van De Donk *et al*., 1980 have shown that mercury containing preservatives have a fast and irreversible effect on ciliary movement and should not be used in the nasal systems.

F. Antioxidants:

Usually, antioxidants do not affect drug absorption or cause nasal irritation. Chemical/physical interaction of antioxidants and preservatives with drugs, excipients, manufacturing equipment and packaging components should be considered as part of the formulation development program. Commonly used antioxidants are sodium metabisulfite, sodium bisulfite, butylated hydroxyl toluene and tocopherol.

G. Humectants:

Many allergic and chronic diseases are often connected with crusts and drying of mucous membrane. Adequate intranasal moisture is essential for preventing dehydration. Therefore humectants can be added especially in gel-based nasal products. Humectants avoid nasal irritation and are not likely to affect drug absorption. Common examples include glycerin, sorbitol and mannitol.

H. Drug Concentration, Dose & Dose Volume:

Drug concentration, dose and volume of administration are three interrelated parameters that impact the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments.

I. Role of Absorption Enhancers:

Absorption enhancers may be required when a drug exhibits poor membrane permeability, large molecular size, lack of lipophilicity and enzymatic degradation by amino peptidases. Osmolarity and pH may accelerate the enhancing effect. Examples of enhancing agents are surfactants, glycosides, cyclodextrins,

and glycols. Absorption enhancers improve absorption through many different mechanisms, such as increasing membrane fluidity, increasing nasal blood flow, decreasing mucus viscosity, and enzyme inhibition.

C) Physiological factors:

a. Effect of Deposition on Absorption:

Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. The anterior portion of the nose is an area of low permeability while posterior portion of the nose where the drug permeability is generally higher, provides shorter residence time.

b. Nasal blood flow:

Nasal mucosal membrane is very rich in vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air. The blood flow and therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels.

c. Effect of Mucociliary Clearance:

The absorption of drugs is influenced by the residence (contact) time between the drug and the epithelial tissue. The mucociliary clearance is inversely related to the residence time and therefore inversely proportional to the absorption of drugs administered[24]. A prolonged residence time in the nasal cavity may also be achieved by using bioadhesive polymers or by increasing the viscosity of the formulation.

d. Effect of Enzymatic Activity:

Several enzymes that are present in the nasal mucosa might affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and amino-peptidase at the mucosal membrane. The level of amino-peptidase present is much lower than that in the gastrointestinal tract. Peptides may also form complexes with immunoglobulin (Igs) in the nasal cavity leading to an increase in the molecular weight and a reduction of permeability.

e. Effect of Pathological Condition:

Intranasal pathologies such as allergic rhinitis, infections, or pervious nasal surgery may affect the nasal mucociliary transport process and/or capacity for nasal absorption. During the common cold, the efficiency of an intranasal medication is often compromised. Nasal clearance is reduced in insulin dependent diabetes. Nasal pathology can also alter mucosal pH and thus affect absorption.

❖ STRATEGIES TO INCREASE NASAL DRUG ABSORPTION:

1. Prodrug:

To improve the solubility of poorly soluble drugs. Ex: the L-dopa has a low water solubility of 1.65 mg/Ml[27], Testosterone, Estradiol Kao et al. produced various prodrug of L-Dopa and the solubility was increased to 660 mg/mL with butylester prodrug.

- To improve its lipophilic character, ultimately increasing its transport across a biological membrane.
- To improve enzymatic stability of drugs. For example, Yang et al. Stated that L-aspartate- β-ester prodrug of acyclovir was more permeable and less labile to enzymatic hydrolysis than its parent drug.
- It is a powerful strategy to increase the bioavailability of peptides.

2. Choice of salt form:

Cancer patients treated with nasally administered morphine gluconate experienced rapid onset of pain relief and good pain scores (Fitzgibbon et al., 2003; Pavis et al., 2002).

3. Co-solvents:

Diazepam and Clonazepam are administered to suppress epileptic convulsions requires rapid onset of action. However, these are poorly soluble and nasal formulations comprised of cosolvents demonstrated a *T*max of <5 min, and a pharmacodynamic response was seen in 1.5 min in a rabbit model (Li et al., 2000)

4. Enzymatic inhibitors:

- Proteases and Peptidases inhibitors - bestatine, amastatin, boroleucin, borovalin, and comostate amylase, puromycin, bacitracin (Ex: leucine encephalin and human growth hormone)
- Trypsin inhibitors – leupeptine and aprotinin (against degradation of calcitonin).
- Certain absorption enhancers - bile salts and fusidic acid.

5. Absorption enhancers:

They improve the absorption of poorly permeable molecules across nasal epithelium.

6. Physicochemical effects:

By altering the physicochemical properties of a drug in the formulation.

7. Membrane effects:

Induce reversible modifications of the structure of epithelial barrier.

- Modifying the phospholipid bilayer,
- Increasing membrane fluidity by
  a) Extraction or leaching of membrane components (proteins)
  b) Creating disorders in the phospholipids domain in the membrane.
- Reversed micelle formation between membranes.
- Opening tight junctions between epithelial cells.

❖ NASAL DOSAGE FORMS:

Due to typical anatomy and physiology of the nasal cavity, with non-ciliated part of nasal cavity and a ciliated region in the more posterior part of the nose, the site of deposition is extremely important for mucociliary clearance and in turn resident time of the formulation in nose; the most critical parameter for drug absorption. The deposition and deposition area are mainly a function of delivery system and delivery device[24]. It predominantly affects many factors such as mode of administration, particle size of formulation, velocity of the delivered particles, spray angle and cone. The selection of delivery system depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences[24]. Some of these delivery systems and their salient features are summarized below:

A) LIQUID DOSAGE FORMS:

1. Nasal Emulsions & Ointments:

Nasal emulsions and ointments have not been studied in detail as other nasal delivery systems. They offer advantages for local application mainly due to their viscosity. One of the major advantages is poor patient acceptability. The physical stability of emulsion formulations and precise delivery are some of the main formulation issues.

2. Nasal Drops:

Nasal drops one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable

for prescription products.[25] it has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

3. 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 µL. The particle size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

B) SEMI SOLID DOSAGE FORMS:

1. Nasal Gels:

Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing devices, there was not much interest in this system. The advantages of a nasal gel include the reduction of post – nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing / emollient excipients and target delivery to mucosa for better absorption. Vitamin B12 gel has been recently developed as a prescription product.

C) SOLID DOSAGE FORMS:

1. Nasal Powders:

This dosage form may be developed if solution and suspension dosage forms cannot be developed e.g. due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility particle size, aerodynamic properties and nasal irritancy of the active drug and/ or excipients. Local application of drug is another advantage of this system but nasal mucosa irritancy and metered dose delivery are some of the challenges for formulation scientists and device manufacturers.[26]

D) NOVEL NASAL DELIVERY SYSTEM:

1. Mucoadhesive drug delivery systems:

Mucoadhesion implies the attachment of the drug delivery system to the mucus, involving an interaction between mucin and a synthetic or natural polymer is called mucoadhesive. Mucoadhesives mostly used in IN delivery are chitosan, alginate and cellulose or its derivatives. Carbopol 934P and polycarbophil are mucoadhesive polymers that inhibit the trypsin proteolytic enzyme and therefore, increase the stability of peptide drugs.[27]

2. Liposomes:

They can effectively encapsulate small and large molecules with a wide range of hydrophilicity and pKa values. They enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration (attributed to the increasing nasal retention of peptides, protection of the entrapped peptides from enzymatic degradation).[28] Novel mucoadhesive multivesicular liposomes for transmucosal insulin delivery has been investigating. Liposomal drug delivery systems were also reported as useful for influenza vaccine and non-peptide drugs such as Nifedipine.

3. Microspheres:

Microsphere technology is one of the specialized systems becoming popular for designing nasal products. Microspheres may provide more prolonged contact with the nasal mucosa and thus enhance absorption. Microspheres for nasal applications have prepared using biocompatible materials, such as hyaluronic acid ester starch, albumin, dextran and gelatin. However, their toxicity / irritancy should be evaluated. It was hypothesized that in the presence of starch microspheres, the nasal mucosa is dehydrated due to moisture uptake by the micro spheres.[28] This results in reversible “shrinkage” of the cells, providing a temporary

physical separation of the tight (intercellular) junctions that increases the absorption of drugs. Microspheres based on mucoadhesive polymers (chitosan, alginate) present advantages for IN delivery. Microspheres may also protect the drug from enzymatic metabolism. Wang et al. were investigated gelatin microspheres as an IN delivery system for insulin. Positive results are found for nasal delivery of

- ✓ Metoclopramide microspheres of alginate/chitosan
- ✓ Carbamazepine chitosan microspheres
- ✓ Carvedilol alginate microspheres

4. Intranasal delivery of Peptide and Protein drugs:

Being hydrophilic polar molecules of relatively high molecular weight, are poorly absorbed across biological membranes with low bioavailabilities. This low uptake may adequate for some commercial products such as desmopressin and calcitonin (3432 Da, 3% (Novartis Pharmaceuticals, 2006).

- ✓ Novel formulation strategies
  - ➢ Absorption enhancers
  - ➢ Bioadhesive agents

5. Intranasal delivery of Vaccines:

Nasal mucosa houses lymphatic tissues involved in the first line defense against airborne microorganism. In humans the NALT is known as the Waldeyer´s Ring. Reasons for exploiting the nasal route for vaccine delivery.

- The nasal mucosa is the first site of contact with inhaled pathogens.
- The nasal passages are rich in lymphoid tissue.
- Creation of both mucosal and systemic immune responses.
- Low cost, patient friendly, non-injectable, safe.
- The majority of the invading pathogens enter the body *via* mucosal surfaces. Therefore, mucosal sites have a potential as first line of defense against entering pathogens.
- Nasal secretions are known to contain immunoglobulins (IgA, IgG, IgM, IgE), and neutrophils and lymphocytes in the mucosa.
- Nasal vaccine delivery stimulates the production of local secretory IgA and IgG
- Nasal vaccine systems based on live or attenuated whole cells, split cells, proteins or polysaccharides and with and without various adjuvants were investigating.

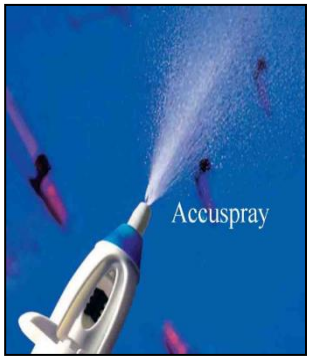
Fig-2: Nasal drug products for vaccination available in the market & H1N1 Nasal Spray Vaccine

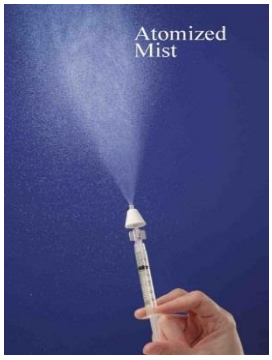
6. Breath Actuated Bidirectional Nasal drug delivery:

Developed by OptiNose. Based on two nasal anatomical features.

- ✓ First, during exhalation against a resistance the soft palate closes, separating the nasal and oral cavities. So small particles in nasal spray can be used and still avoid lung deposition by exhaling through the mouth during nasal administration.
- ✓ Second, during closure of the soft palate there is a communication pathway between the two nostrils, located behind the nasal septum. It is possible for air to enter via one nostril, turn through 180˚ passing through the communication pathway, and leave by the other nostril.

❖ NASAL DELIVERY DEVICES:





- ✓ Common devices are
  - ➢ Droppers
  - ➢ Squeeze bottles
  - ➢ Spray pumps/atomizers
    - (Accuspray Nasal Atomizer)
    - (MAD (Mucosal Atomization Device, nasal)
  - ➢ Gel applicators
  - ➢ Nasal Nebulizer's (Sinus Nebulizers Rhino Clear)
  - ➢ Pressurized Metered Dose Inhalers (pMDIs) Nasal (Ex: Landmark®)
  - ➢ Disposable Unit/Bi-dose dispensing devices
  - ➢ Powder Dispensing Systems
- ✓ **Novel Nasal spray pumps:**
  - ➢ Patient-independent Pumps
  - ➢ To minimise dose and spray variations related to the patient's hand actuation mode. (Equdel by Valois Pharma)
- ✓ **Preservative Free Systems (PFS) :**
  - ➢ To accommodate preservative-free drug formulations.
  - ➢ Preservatives may induce itching in chronic use
  - ➢ Can generate some formulation instabilities
  - ➢ Affect the smell and/or taste of the drug product. (Freepod by Valois Pharma)
- ✓ **Side-actuation Spray Pumps**
  - ➢ Eliminate any risk of the nasal nozzle entering the nostril too deeply.
  - ➢ Avoids contact between fingers and nostrils which improves hygiene during treatment.

Fig-3: Various Delivery devices

Fig-4: Various Delivery devices

❖ TECHNIQUES OF ADMINISTRATION[27, 28]:

A scale of factors play a role in the technique of administration of a nasal formulation as a spray or as drops. Head position, volume and frequency of administration, angle of spraying, inhaling or sniffing and compliance have all been investigated by many research groups. We have to emphasize that all studies were done with healthy volunteers and therefore the outcome might differ from the actual therapeutic outcome in patients.

a. Head position:

Nose sprays for nasal drugs are generally multidose container *sprays* and used in the upright position. The administration of nose *drops* is different. Four positions to instill nose drops have been described, all shown in figure.

The most simple (but unsuccessful) technique to use a nose drop is the Head Back (HB) position. This technique will give the drop the opportunity to go down the inferior meatus with a quick slide to the throat.

b. The Lying Head Back (LHB):

This position is "Lying down in supine position with the head just off the bed in hyperextension, so that the chin is the highest point of the head". It is recommended by some manufactures and it is actually the first position published (1926)144, 145 When republished in 1979 this position was the first of a sequence of steps and since then this position is often named after Mygind120. The sequence of 6 steps is probably too difficult for patients in their daily routine, but the initial position is comfortable and easy to use.

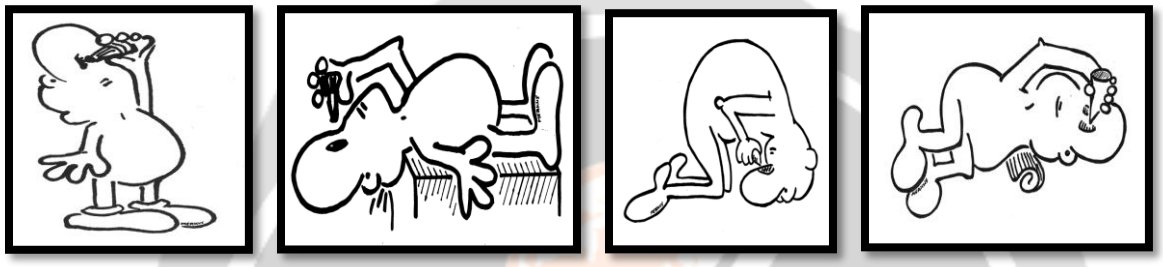
c. Head down and forward (HDF):

This is often referred as "Praying to Mecca"; "Kneeling down and with the top of the head on the ground. The face is upside down, the forehead close to the knees and the nostrils are facing upward".

d. Lateral head-low position (LHL):

The later described as the "new" Ragan position is the fourth known head position: "Lying on the side with the parietal eminence resting on the bed (pillow under the shoulders or no pillow). Nasal drops are instilled into the lower nostril".

These techniques of nasal drug administration to the middle meatus have been an ongoing topic for study and debate. Consensus about a superior administration method is lacking and remains a very interesting subject for further research.[29]



(A) **(B)** **(C)** **(D)**

Fig-5: Different techniques of nasal instillations.

❖ ANIMAL MODELS FOR NASAL ABSORPTION STUDIES:[7]

- *In Vivo* Nasal Absorption studies
- *Rat Model*
- *Rabbit Model*
- *Dog Model*
- *Sheep Model*
- *Monkey Model*
- *Ex Vivo* Nasal Perfusion Models

❖ CONCLUSION:

First-pass metabolism in the liver and pre-systemic elimination in the GI tract can be avoided. The area is well suited for a retentive device and has better patient compliance. The drug targeting to the brain should be evaluated for their safety and risk-benefit ratio for the patients. Currently the safety issue has been given great importance by the researchers during the research stage, and this issue will become critical when the drug is to be delivered is for a long term therapy. This route has shown great potential to directly target the brain with reduced systemic side effects. Few CNS drugs are already in market as their intranasal delivery system. However there are number of limitations which should be overcome to develop successful nose-to-brain drug delivery system. A number of novel formulations have been used to target brain via nasal administration. However more efforts are needed to make this route more efficient and popular for brain targeting.

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