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Intranasal drug delivery system- A glimpse to become maestro

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ABSTRACT

Intranasal drug delivery – which has been practiced for thousands of years, has been given a new lease of life. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides. One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the Mucociliary Clearance mechanism. The nasal route circumvents hepatic first pass elimination associated with the oral delivery: it is easily accessible 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, no first-pass metabolism, and non-invasiveness; all of which may maximize patient convenience, comfort, and compliance. IN delivery is non-invasive, essentially painless, does not require sterile preparation, and is easily and readily administered by the patient or a physician, e.g., in an emergency setting. Furthermore, the nasal route may offer improved delivery for “non-Lipinski” drugs.

Key words: Intranasal drug delivery, Mucociliary Clearance, Nasal cavity, first pass elimination, non-Lipinski.

INTRODUCTION

Nasal mucosa has been considered as a potential ad-ministration route to achieve faster and higher level of drug absorption because it is permeable to more com-pounds than the gastrointestinal tract due to lack of pancreatic and gastric enzymatic activity, neutral pH of the nasal mucus and less dilution by gastrointestinal contents(Krishnamoorthy and Mitra, 1998). In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called “NASAYA KARMA” (Chien and Chang, 1987). Intranasal drug delivery – which has been practiced for thousands of years, has been given a new lease of life. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides (Kisan R et al, 2007). One of the reasons for the low degree of absorption of peptides and proteins via the nasal route is rapid movement away from the absorption site in the nasal cavity due to the mucociliary clearance mechanism (Mahalaxmi et al, 2007). The nasal route circumvents hepatic first pass elimination associated with the oral delivery: it is easily accessible 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, no first-pass metabolism, and non-invasiveness; all of which may maximize patient convenience, comfort, and compliance (Costantino et al.,2007). IN delivery is

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non-invasive, essentially painless, does not require sterile preparation, and is easily and readily administered by the patient or a physician, e.g., in an emergency setting. Furthermore, the nasal route may offer improved delivery for “non-Lipinski” drugs (Johnson and Quay 2005). Drug candidates ranging from small metal ions to large macromolecular proteins have been tested in various animal models (Chien and Chang 1987). It has been documented that nasal administration of certain- hormones and steroids have resulted in a more complete absorption (Hussain et al, 1980, Hussain et al, 1990). Given these positive attributes, it is logical to consider IN administration when developing new therapeutics, or when extending the life or improving the profile of an existing drug. In order to assess the desirability and viability of such an approach, a series of questions regarding the drug and its use should be addressed.

ADVANTAGES (Aulton, 1998)

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

LIMITATIONS (Kadam et al.,1993, Hirai et al., 1981)

- 1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
- 2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
- 3) Nasal cavity provides smaller absorption surface area when compared to GIT.
- 4) There is a risk of local side effects and irreversible damage of the cilia on the nasal mucosa, both from the substance and from constituents added to the dosage form.
- 5) Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
- 6) There could be a mechanical loss of the dosage form into the other parts of the respiratory tract like lungs because of the improper technique of administration.

ANATOMY & PHYSIOLOGY OF NASAL CAVITY

The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril. The nasal cavity consists three main regions are nasal vestibule, olfactory region and respiratory region. The surface area in the nose can be enlarges about 150cm by the lateral walls of the nasal cavity includes a folded structure, it is a very high surface area compared to its small volume. This folded structure consists of three turbinates: the superior, the median and the inferior (Michael et al., 2005). The main nasal airway having the narrow passages, usually it has 1-3mm wide and these narrows structures are useful to nose to carry out its main functions. The nasal cavity is covered with a mucous membrane which can be divided into two areas; non olfactory and olfactory epithelium, in this non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, where as respiratory region, which has a typical airways epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport (Sarkar 1992).

In this way the mucus layer is propelled in a direction from the anterior to-wards the posterior part of the nasal cavity. The goblet cells are present in the mucus membrane which covers the nasal turbinate and the atrium; it secretes the mu-cus as mucus granules which are swelling in the nasal fluid to contribute to the mucus layer. The mucus secretion is composed of about 95% water, 2 % mucin, 1% salts, 1% of other proteins such as al-bumin, immunoglobulin s, lysozyme and lactoferrin, and b 1% lipids (Kaliner et al., 1984). The mucus secretion gives immune protection against inhaled bacteria and viruses. It also performs a number of physiological functions. (1) It covers the mucosa, and physically and enzymatically protects it. (2) The mucus has water-holding capacity. (3) It exhibits surface electrical activity. (4) It permits efficient heat transfer. (5) It acts as adhesive and transport s particulate matter towards the nasopharynx (Bernstein et al., 1997).

MECHANISM OF NASAL ABSORPTION

1. First mechanism

It involves an aqueous route of transport, which is also known as the paracellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble com-pounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability (Aurora 2002).

2. Second mechanism

It involves transport through a lipoidal route and it is also known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drug also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening

of tight junctions(Aurora 2002).

BARRIERS TO NASAL ABSORPTION (Alagusundara et al 2010)

Nasal drug delivery system is considered has a profitable route for the formulation scientist because it has easy and simple formulation strategies. Intra-nasally administered drug products therapeutic efficacy and toxicities are influenced by number of factors (Remeo VD et al., 1998). Following factors are the barriers to the absorption of drugs through nasal cavity.

Table 1: Barriers in nasal drug product development

Nasal barriers	Factors to be considered
I. Physiological barrier	
a. Nasal mucus	Viscosity, pH of mucus and drug/dosage form-mucus interaction
b. Nasal epithelial barrier	Molecular weight, ionization constant and mode of transport
c. Mucociliary clearance	Nasal residential time and nature of dosage form
d. Pathophysiology	Volume of nasal secretion and permeability of epithelium
e. Nasal metabolism	Nature of the molecules (e.g., protein and peptides)
f. Efflux transport system	Nature of drug molecule and duration of therapy
II. Physicochemical 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 lipophilicity	Affects the nose to blood and nose to brain absorption
d. pH and pKa	Unionized pH favors for absorption
III. Formulation factors	
a. Drug concentration, dose, and volume	High concentration for better bioavailability, maximum dose in Minimum vehicle (less than 200 μ l)
b. Osmolarity	Isotonic solution prevents epithelial damage and toxicity
c. Site of deposition	Site of deposition based on viscosity, position of head, volume, delivery device, deposition at anterior chamber prolong the nasal residential time

i) Low bioavailability

Lipophilic drugs are generally well absorbed from the nasal cavity compared to polar drugs. The pharmacokinetic profiles of lipophilic drugs are often identical to those obtained after an intravenous injection and bioavailability approaching 100%. A good examples of this is the nasal administration of Fentanyl where the t_{max} 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% (Striebel 1993).

Table 2: Strategies to improve nasal bioavailability

1. Nasal enzyme inhibitors e.g., bestatin, amastatin, boroleucine, fusidic acids, and bile salts
2. Nasal permeation enhancers e.g., cyclodextrins, surfactants, saponins, fusidic acids, and phospholipids
3. Prodrug approach e.g., cyclic prodrug, esters, and derivatization of C and N termini
4. Nasal mucoadhesives in nasal drug delivery e.g., carbopol, polycarbophil, cellulose derivatives, lecithin, and chitosan
5. Particulate drug delivery e.g., microspheres, nanoparticles, and liposome

ii) Low membrane transport

Another importance factor is low membrane transport is the general rapid clearance of the administered formulation from the nasal cavity due to the mucociliary clearance mechanism. This is especially the case for drugs that are not easily absorbed across the nasal membrane. It has been shown that for both liquid and powder formulations, that are not mucoadhesive, the half life of clearance is in the order of 15–20 min (Illum 1999, Soane et al., 2001).

iii) Enzymatic Degradation

Another contributing (but normally considered less important) factor to the low transport of especially peptides and proteins across the nasal membrane is the possibility of an enzymatic de-gradation of the molecule either within the lumen of the nasal cavity or during passage across the epithelial barrier. These sites both contain exopeptidases such as mono- and diaminopeptidases that can cleave peptides at their N and C termini and endopeptidases such as serine and cysteine, which can attack internal peptide bonds (Lee 1988).

FACTORS INFLUENCING NASAL DRUG ABSORPTION

Several factors affect the systemic bioavailability of drugs which are administered through the nasal route. The factors can be affecting to the physicochemical properties of the drugs, the anatomical and physiological properties of the nasal cavity and the type and characteristics of selected nasal drugs delivery system. These factors play key role for most of the drugs in order to reach therapeutically effective blood levels after nasal administration. 1) Physicochemical properties of drug.

- ❖ Molecular size.
- ❖ Lipophilic-hydrophilic balance.
- ❖ Enzymatic degradation in nasal cavity.

2) Nasal Effect

- ❖ Membrane permeability.
- ❖ Environmental pH
- ❖ Mucociliary clearance
- ❖ Cold, Rhinitis.

3) Delivery Effect

- ❖ Formulation (Concentration, pH, osmolarity)
- ❖ Delivery effects
- ❖ Drugs distribution and deposition.
- ❖ Viscosity

1) Physicochemical properties of drug

Molecular size

The molecular size of the drug influence absorption of the drug through the nasal route. The lipophilic drugs have direct relationship between the MW and drug permeation whereas water-soluble compounds depict an inverse relationship. The rate of permeation is highly sensitive to molecular size for compounds with $MW \geq 300$ Daltons (Corbo et al., 1990).

Lipophilic-hydrophilic balance

The hydrophilic and lipophilic nature of the drug also affects the process of absorption. By increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic character, it appears that these mucosae are primarily

lipophilic in nature and the lipid domain plays an important role in the barrier function of these membranes (Bawarshi et al., 1989, Hussain et al., 1991).

Enzymatic degradation in nasal cavity

In case of peptides and proteins are having low bio-availability across the nasal cavity, so these drugs may have possibility to undergo enzymatic degradation of the drug molecule in the lumen of the nasal cavity or during passage through the epithelial barrier (Lee 1988).

2) Nasal effect factors

Membrane permeability

Nasal membrane permeability is the most important factor, which affect the absorption of the drug through the nasal route. The water soluble drugs and particularly large molecular weight drugs like peptides and proteins are having the low membrane permeability. So the compounds like peptides and proteins are mainly absorbed through the endocytotic transport process in low amounts (Inagaki,1985).

Environmental pH

The environmental pH plays an important role in the efficiency of nasal drug absorption. Small water-soluble compounds such as benzoic acid, salicylic acid, and alkaloid acid show that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the nonionised form(Franz and Oth 1993).

Mucociliary clearance

Mucociliary clearance is a one of the functions of the upper respiratory tract is to prevent noxious substances (allergens, bacteria, viruses, toxins etc.) from reaching the lungs. When such materials adhere to, or dissolve in, the mucus lining of the nasal cavity, they are transported towards the nasopharynx for eventual discharge into the gastrointestinal tract (Armengot 1990).

Cold, Rhinitis

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

3) Delivery effect factors

Factors that affect the delivery of drug across nasal mucosa such as surfactants, dose pH, osmolarity, viscosity, particle size and nasal clearance, drug structure can be used to advantage to improve absorption.

Formulation (Concentration, pH, Osmolarity)

The pH of the formulation and nasal surface, can affect a drug's permeation. To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5 because lysozyme is

found in nasal secretions, which is responsible for destroying certain bacteria at acidic pH. Under alkaline conditions, lysozyme is inactivated and the tissue is susceptible to microbial infection. In addition to avoiding irritation, it results in obtaining efficient drug permeation and prevents the growth of bacteria (Arora et al., 2002). Concentration gradient plays very important role in the absorption / permeation process of drug through the nasal membrane due to nasal mucosal damage. Examples for this are nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments. Another is absorption of salicylic acid was found to decline with concentration. This decline is likely due to nasal mucosa damage by the permanent. The osmolarity of the dosage form affects the nasal absorption of the drug; it was studied in the rats by using model drug. The sodium chloride concentration of the formulation affects the nasal absorption. The maximum absorption was achieved by 0.462 M sodium chloride concentration; the higher concentration not only causes increased bioavailability but also leads to the toxicity to the nasal epithelium (Ohwaki 1985).

Drugs distribution and deposition

The drug distribution in the nasal cavity is one of the important factors, which affect the efficiency of nasal absorption. The mode of drug administration could effect the distribution of drug in nasal cavity, which in turn will determine the absorption efficiency of a drug. The absorption and bioavailability of the nasal dosage forms mainly depends on the site of disposition. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation, it enhances the absorption of the drug. And the posterior chamber of nasal cavity will use for the deposition of dosage form; it is eliminated by the mucociliary clearance process and hence shows low bioavailability (Gizurason and Bechgaard 1991).

Viscosity

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

STRATEGIES TO IMPROVE NASAL ABSORPTION

1. Nasal enzyme inhibitors

Nasal metabolism of drugs can be eliminated by using the enzyme inhibitors. Mainly for the formulation of proteins and peptide molecule development enzyme inhibitors like peptidases and proteases are used (Hussain et al., 1990). The absorption enhancers like salts and fusidic acid derivatives also shows enzyme inhibition activity to increase the absorption and bio-availability of the drug (Donnelly et al., 1998). The other enzyme inhibitors commonly used for the enzymatic activity are tripsin, aprotinin, borovaline, amas-tatin, bestatin and boroleucin inhibitors.

2. Permeation enhancers

The permeation enhancers are mainly used for the enhancement of absorption of the active medicament. Generally, the absorption enhancers act *via* one of the following mechanisms:

- ✓ Inhibit enzyme activity;
- ✓ Reduce mucus viscosity or elasticity;
- ✓ Decrease mucociliary clearance;
- ✓ Open tight junctions; and
- ✓ Solubilize or stabilize the drug.

The mechanism of action of absorption enhancer is increasing the rate at which drug passes through the nasal mucosa. Many enhancers act by altering the structure of epithelial cells in some way, but they should accomplish this while causing no damage or permanent change to nasal mucosa.

Qualities of Ideal penetration enhancer

- a. It should lead to an effective increase in the absorption of the drug.
- b. It should not cause permanent damage or alteration to the tissues
- c. It should be non irritant and nontoxic.
- d. It should be effective in small quantity
- e. The enhancing effect should occur when absorption is required
- f. The effect should be temporary and reversible
- g. It should be compatible with other excipients.

Various types of penetration enhancers have been evaluated for organic drugs including surfactants, bile salts, chelators, fatty acid salts, phospholipids, glycyrrhetic acid derivatives, cyclodextrins and glycols.

Classification of chemical penetration enhancer (Ramesh et al., 2009)

- ✓ Surfactants: Polyoxyethylene-9-lauryl ether (Laureth-9), Saponin
- ✓ Bile salts: Trihydroxy salts (glycol- and taurocholate), Fusidic acid derivatives (STDHF)
- ✓ Chelators: Salicylates, Ethylenediaminetetraacetic acid (EDTA)
- ✓ Fatty acid salts: Oleic acid, Caprylate (C8), Caprate (C10), Laurate (C12)
- ✓ Phospholipids: Lysophosphatidylcholine (lyso-PC), Didecanoyl – PC
- ✓ Glycyrrhetic acid derivatives: Carbenozolone, Glycyrrhizinate
- ✓ Cyclodextrins: α , β , and γ - cyclodextrins and their derivatives
- ✓ Glycols: n- glycofurols and n- ethylene glycols

3. Prodrug approach

Prodrug approach is mainly meant for optimizing favorable physicochemical properties such as solubility, taste, odor, stability, etc. Prodrug is usually referred as pro moiety, it is to cover the undesired functional groups with another functional groups. This prodrug approach is mainly for improving the nasal bioavailability especially for the proteins and peptides to enhance the membrane permeability along with increased enzymatic stability (Martin et al., 1997). The prodrug undergoes enzymatic transformation to release the active medicament, when it crosses the enzymatic and membrane barrier. The absorption of peptides like angiotensin II, bradykinin, caulein, carnosine, enkephalin, vasopressin and calcitonin are improved by pre-pared into enamine derivatives, these agents showed absorption enhancement with prodrug approach.

4. Structural modification

Modification of drug structure without altering pharmacological activity is one of the lucrative ways to improve the nasal absorption. The chemical modification 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).

5. Particulate drug delivery

Particle design is an increasingly important role in absorption enhancement. Microspheres, nanoparticles and liposomes are all systems which can be used as carriers to encapsulate an active drug. The properties of these can be varied to maximize therapeutic efficacy. Overall, this can result in increased absorption efficacy and stability and reduced toxicity of the active ingredient. Systems can be designed to be mucoadhesive to increase the retention time and facilitate sustained release. Microspheres are mainly increase the absorption and bioavailability by adhering to the nasal mucosa and increase the nasal residence time of drug (Edman et al 1992). The microspheres prepared by using polymers like dextran, chitosan, biodegradable starch microspheres successfully improved the bioavailability of various drugs. Liposomes are amphiphilic in nature are well characterized for favorable permeation of drugs through the biological membranes, so the water soluble drugs have been delivered to nasal drugs. Cationic liposomes are having good permeation capacity than negatively charged anionic liposomes (Chien et al., 1989).

6. Bioadhesive polymers as delivery systems for nose to brain delivery

Novel approaches that are able to combine active targeting of a formulation to the olfactory region with controlled release bioadhesive characteristics, for maintaining the drug on the absorption site are suggested. If necessary an absorption enhancer could be incorporated. Low methylated pectins have been shown to gel and be retained in the nasal cavity after deposition. Chitosan is known to be bioadhesive and also to work as an absorption

enhancer. Consequently, two types of pectins, LM-5 and LM-12, together with chitosan G210, can also be used. They can be characterized for molecular weight, gelling ability and viscosity. It has been suggested that an approach (Illum L. 2004), that combines a bioadhesive formulation with vectors that specifically target receptors on the olfactory region and possibly together with an absorption enhancer, may not only target and retain the formulation on the site of absorption for prolonged periods, but also enhance the transport through the membrane by transcytosis (e.g. receptor mediated) or paracellular mechanisms. We have evaluated the use of chitosan and pectins, which have previously been described in the literature as suitable excipients for nasal drug delivery formulations for the improvement of pharmacokinetic parameters (Illum L. 2003, Illum L. 2000). Pectin is a natural polysaccharide, consisting of methylated esters of polygalacturonic acid, linked by α -[1-4] glycosidic bonds and with carboxyl and methyl ester side chains. Pectin is commercially available in three different forms each varying in their substitution degree; high methoxyl (HM), low methoxyl (LM) and low methoxyl amidated (LMA) pectin. LMpectin is of most interest for nasal delivery of drugs because a LM pectin solution formulation is able to gel upon contact with the nasal mucosa without the addition of exogenous Ca^{2+} (L. Illum 2000). Chitosan is a natural polysaccharide present in fungi but is normally derived from chitin of crustacean origin by a process of deacetylation. Chitosan consists of copolymers of glucosamine and N-acetyl-glucosamine. The degree of deacetylation (DDA) of the chitosan is determined by the amount of the acetyl groups present. Chitosan has been shown to be mucoadhesive in the nasal cavity (Soane et al., 1999).

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 cold-adapted 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)

Possible routes of transport between the nasal cavity and the brain and CSF.

The blood-brain barrier (BBB), segregating the brain interstitial fluid from the circulating blood, and the blood-cerebrospinal fluid barrier (BCB), separating the blood from the cerebrospinal fluid (CSF) that encircles the brain, provide efficient barriers to the diffusion of drugs from the blood stream into the central nervous system (CNS) especially of polar drugs such as

peptides and proteins (Thorne et al., 2004). Hence, these barriers prevent the utilization of many novel therapeutic agents, for example neuropeptides, for treating CNS disorders such as Parkinson's and Alzheimer's diseases. It has been shown in animal and in human studies that after nasal administration drugs can be transported directly from the nasal cavity to the CNS via the olfactory epithelium and/or the trigeminal nerve system thereby bypassing the BBB and the BCB (L. Illum et al., 2004).

Studies indicative of nose to brain drug transport in man (Illum L 2003)

• *Functional evidence of facilitated transport to the brain was provided by changes in event related potential during performance of an oddball task*

- Arginin-vasopressin (n515)
- Cholecystokinin-8 (n520)
- Angiotensin II (n512)
- Insulin (n518)
- Adrenocorticotropin 4-10 (n554)
- Insulin (n512)
- *Direct evidence of nose to brain uptake*
- 99mTc-DTPA-hyaluronidase
- *Direct evidence of nose to CSF uptake*

- Insulin (n58)
- Apomorphine (n55)
- Melatonin/hydroxycobalamin (n52)

Intranasal delivery of IGF-I to the CNS was accompanied by activation of signaling pathways in several areas that express high levels of the IGF-I receptor, providing evidence that at least a portion of intranasally applied IGF-I reached CNS target sites intact (Thorne et al 2004). The results of the present study are further supported by the recent demonstration of a reduction in stroke volume and improved behavioral scores for rats receiving i.n. IGF-I following transient middle cerebral artery occlusion (Liu et al., 2001). The olfactory region in man is situated in the upper part of the nasal cavity, an area that is difficult to reach with presently available nasal spray or powder devices. Nasal spray or powder devices are now being developed (e.g. OptiNose and ViaNase) that claim to enable the targeting of formulations to specific sites within the nasal cavity in man or to provide a larger deposition area that includes the olfactory region.

6. Nasal delivery of peptides and proteins (Illum L 2003)

- ✓ Nasal salmon calcitonin Marketed by Novartis Novel nasal formulations under development by other pharmaceutical companies
- ✓ Nasal desmopressin Marketed by Ferring and partners
- ✓ Nasal buserelin Marketed by Aventis
- ✓ Nasal nafarelin Marketed by Searle
- ✓ Nasal PTH, nasal leuprolide, nasal insulin, nasal interferon, etc. In clinical trials.

NASAL DRUG DELIVERY SYSTEM DOSAGE FORMS

The selection of dosage form depends upon the drug being used, proposed indication, patient population and last but not least, marketing preferences.

A. Liquid Nasal Formulations

Liquid preparations are the most widely used dosage forms for nasal administration of drugs. They are mainly based on aqueous state formulations. Their humidifying effect is convenient and useful, since many allergic and chronic diseases are often connected with crusts and drying of mucous membranes. Microbiological stability, irritation and allergic rhinitis are the major drawbacks associated with the water-based dosage forms because the required preservatives impair mucociliary function (Zia 1993).

1. Instillation and rhinyle catheter

Catheters are used to deliver the drops to a specified region of nasal cavity easily. Place the formulation in the tube and kept tube one end was positioned in the nose, and the solution was delivered into the nasal cavity by blowing through the other end by mouth (Hughes 1993 Harris 1993).

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. The common technical principle for all nebulizers, is to either use oxygen, compressed air or ultrasonic power, as means to break up medical solutions/ suspensions into small aerosol droplets, for direct inhalation from the mouthpiece of the device (Knoch 2002).

3. Squeezed bottle

Squeezed nasal bottles are mainly used as delivery device for decongestants. They include a smooth plastic bottle with a simple jet outlet. While pressing the plastic bottle the air inside the container is pressed out of the small nozzle, thereby atomizing a certain volume. By releasing the pressure again air is drawn inside the bottle. This procedure often results in contamination of the liquid by microorganisms and nasal secretion sucked inside (Mygind and Vesterhauge 1978).

4. 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.

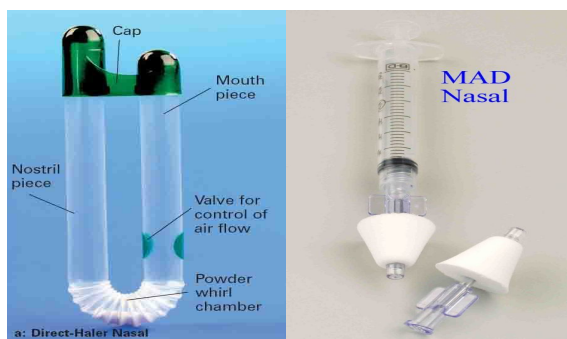


Fig 1 (Courtesy:DIRECT – HALER A/S) and (Courtesy: Wolfe Tory Medical, Inc)

B. Powder Dosage Forms

Dry powders are less frequently used in nasal drug delivery. Major advantages of this dosage form are the lack of preservatives and the improved stability of the formulation. Compared to solutions, the administration of powders could result in a pro- longed contact with the nasal mucosa.

1. Insufflators

Insufflators are the devices to deliver the drug substance 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 par-ticle 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 (Hughes et al., 1993).

2. 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 (Alagusundaram et al., 2010). 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 (Warren H. The).

Table 2 Formulation of intranasal dds (bhise et al., 2008)

Pharmaceutical excipients	Type of dosage form	Comments
Permeation enhancers e.g., 1. Cyclodextrins 2. Fusicidic acid derivatives 3. Phosphatidylcholines 4. Microspheres and liposomes 5. Bile salts and surfactants	Powders, gels, solutions	Improve the bioavailability of drugs particularly molecular weight above 1000 Da Causes nasal epithelial toxicity
Solvents e.g., ethanol, polyethylene, propylene glycols, etc.	Gels, solutions	To increase the concentration of drug in vehicle and reduce the dose volume. May act as a permeation enhancer
Viscosity modifiers e.g., cellulose derivatives	Gels, solutions	To improve nasal residential time
Mucoadhesive polymers e.g., carbopol, polycarbophil, cellulose derivatives, lecithin, and chitosan	Powders, gels, solutions	To improve the nasal residential time
Preservatives e.g., benzalkonium chloride	Gels, solutions	To maintain sterility of dosage form, may alter the nasal residential time
Enzyme inhibitors e.g., bestatin, amastatin, boroleucine, fusicidic acids, and bile salts	Powders, gels, solutions	To improve the bioavailability of protein and peptides
Tonicity modifiers/buffers e.g. sodium chloride, citrate buffer	Solutions	To avoid the nasal epithelial toxicity

C. Pressurized MDIs

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 accu-racy, protection of the contents and that they are quickly ready for use (Newhouse M.T. 1991).

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 micrometer-sized medication particles that are then inhaled (Warren H. 2001).

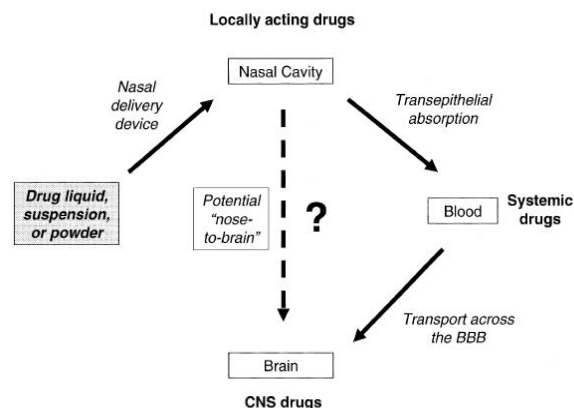


Fig 2 Effect of various locally acting drugs.

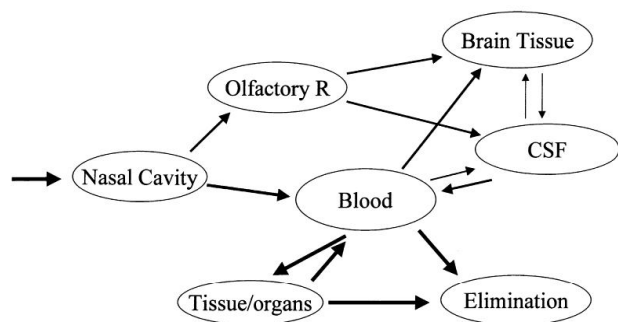


Fig 3 Connectivity of nasal cavity to other organs.

D. 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 (Junginger HE 1956).

The deposition of the gel in the nasal cavity depends on the mode of administration, because due to its viscosity the formulation has poor spreading abilities. Without special application techniques it only occupies a narrow distribution area in the nasal cavity, where it is placed directly. Recently, the first nasal gel containing Vitamin B12 for systemic medication has entered the market.

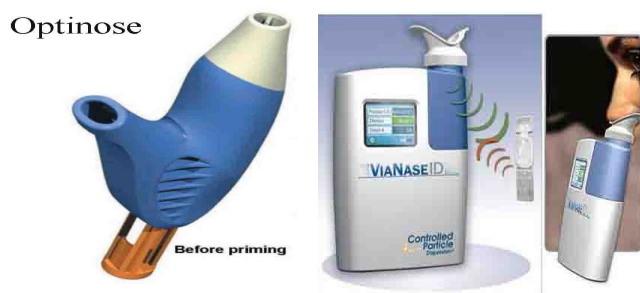


Fig 4 Devices used for Nasal delivery (Courtesy:Optinose US Inc. Courtesy and Kurve Technology, Inc).

CONCLUDING REMARKS

In order to ascertain whether IN delivery is appropriate for any given drug, various facets of the drug's characteristics and intended use need to be considered. IN delivery may be suitable for either topical or systemic delivery. In the latter case, rapid onset is a key feature of the typical IN PK profile and may provide a distinct advantage in certain circumstances, e.g., pain management. Another application for IN dosing is for vaccine therapeutics. IN delivery can be utilized for high molecular weight drugs such as peptides and proteins, however, systemic bioavailability is

dramatically dependent upon the presence of permeation enhancers.

IN administration may be particularly attractive for therapies requiring chronic dosing. For many drugs, IN administration provides a good alternative to the invasiveness of injections and to oral delivery, which may be associated with problems such as poor bioavailability and the potential for GI-related side-effects. These characteristics should be considered by the formulation scientist when considering IN dosing for new chemical entities and for product life extension. Intranasal drug delivery system is a promising alternative route of administration for the several systemically acting drugs with poor bioavailability and it has advantages in terms of improved patient acceptability and compliance compared to parenteral administration of drugs.

This delivery system is beneficial in conditions like Parkinson's disease, Alzheimer's disease or pain because it requires rapid and/or specific targeting of drugs to the brain and it is a suitable route to produce immune response against various diseases like anthrax, influenza etc., by delivering the vaccines through the nasal mucosa. In near future, we hope that intranasal products most probably comprise for crisis treatments, such as erectile dysfunction, sleep induction, acute pain (migraine), panic attacks, nausea, heart attacks and Parkinson's disease and novel nasal products for treatment of long-term illnesses, such as diabetes, growth deficiency, osteoporosis, fertility treatment and endometriosis, will also be marketed. The successful application of these attributes requires careful design of characteristics of both the drug formulation and delivery device, and a clear understanding of the ways in which they impact on each other.

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