www.ijrps.pharmascope.org

ISSN: 0975-7538
Review Article

Nasal drug delivery system - an overview

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ABSTRACT

The use of the nasal route for the delivery of challenging drugs such as small polar molecules, vaccines, hormones, peptides and proteins has created much interest in nowadays. Due to the high permeability, high vasculature, low enzymatic environment of nasal cavity and avoidance of hepatic first pass metabolism are well suitable for systemic delivery of drug molecule via nose. Many drug delivery devices for nasal application of liquid, semisolid and solid formulation are investigated to deliver the drugs to the treat most crisis CNS diseases (i.e., Parkinson's disease, Alzheimer's disease) because it requires rapid and/or specific targeting of drugs to the brain. It is well suitable for the delivery of biotechnological products like proteins, peptides, hormones, DNA plasmids for DNA vaccines to give enhanced bioavailability. This review sets out to discuss some factors affecting nasal absorption, bioavailability barriers, strategies to improve nasal absorption, new developments in nasal dosage form design and applications of nasal drug delivery system.

Keywords: Nose; peptides and proteins; vaccines; bioavailability; nasal drug delivery.

INTRODUCTION

Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds 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 R *et al.*, 1998; Kisan R *et al.*, 2007). 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 YW *et al*., 1989).

Nasal 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 (Mahalaxmi R *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. During the past several decades, the feasibility of drug delivery via the nasal route has received increasing attention from pharmaceutical scientists and clinicians. Drug candidates ranging from small metal ions to large macromolecular proteins have been tested in various animal models (Chien YW *et al*., 1989). It has been documented that nasal administration of certain- hormones and steroids have resulted in a more complete absorption (Hussain AA. *et al*., 1979; Hussain AA *et al*., 1981). This indicates the potential value of the nasal route for administration of systemic medications as well as utilizing this route for local effects.

For many years drugs have been administered nasally for both topical and systemic action. Topical administration includes the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions, and has resulted in a variety of different medications including corticoids, antihistamines, anti-cholinergic and vasoconstrictors. In recent years, increasing investigations of the nasal route have focused especially on nasal application for systemic drug delivery (Kublik H *et al*., 1998). Only a few nasal delivery systems used in experimental studies are currently on the market to deliver therapeutics into the nasal cavities, i.e. nasal drops as multiple or single-dose formulation, aqueous nasal sprays, a nasal gel pump, pressurized MDIs and dry powder inhalers. Intranasal delivery is currently being employed in treatments for migraine, smoking cessation, acute pain relief, osteoporosis, nocturnal

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Received on: 21-07-2010
Revised on: 13-09-2010
Accepted on: 15-09-2010

enuresis and vitamin-B_{12} deficiency. Other examples of therapeutic areas under development or with potential for nasal delivery include cancer therapy, epilepsy, anti-emetics, rheumatoid arthritis and insulin-dependent diabetes.

This review article provides a brief overview of the advantages and limitations of nasal drug delivery system and anatomy of nasal cavity, mechanism of nasal absorption, barriers to nasal absorption, strategies to improve nasal absorption, nasal drug delivery formulation issues and applications of nasal drug delivery systems.

ADVANTAGES (Aulton M.E *et al.,* 2002, Krishnamoorthy R *et al*., 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 (Hirai S *et al*., 1993; Kadam SS *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^2 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 carryout its main functions.

The nasal cavity is covered with a mucous membrane which can be divided into two areas; nonolfactory 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 MA, 1992). In this way the mucus layer is propelled in a direction from the anterior towards 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 mucus 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 albumin, immunoglobulin s, lysozyme and lactoferrin, and b 1% lipids (Kaliner M *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 JM *et al*., 1997).

MECHANISM OF NASAL ABSORPTION

The absorbed drugs from the nasal cavity must pass through the mucus layer; it is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin, it has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. pH, temperature, etc.) (Illum L *et al*., 1999). So many absorption mechanisms were established earlier but only

two mechanisms have been predominantly used, such as:

a) **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 compounds. The molecular weight greater than 1000 Daltons having drugs shows poor bioavailability (Aurora J *et al*., 2002).

b) **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 J et al., 2002).

For examples: chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport (Dodane V *et al*., 1999).

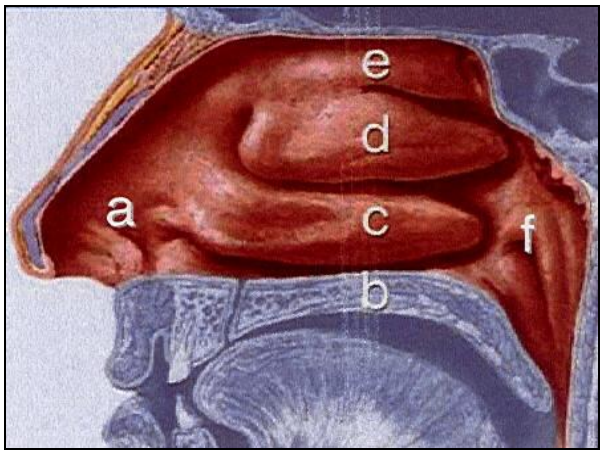

Figure 1: Parts of nasal cavity consists of a – nasal vestibule, b – palate, c–inferior turbinate, d-middle turbinate, e – superior turbinate (olfactory mucosa),f – nasopharynx

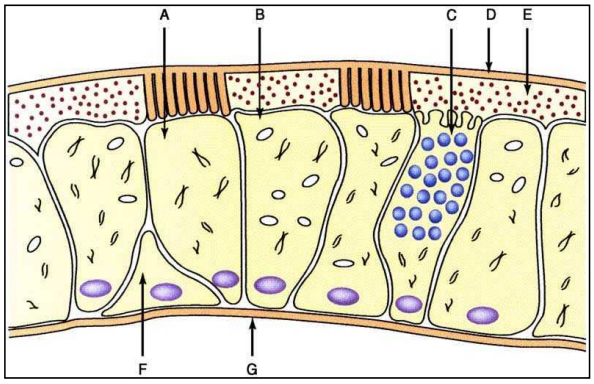

Figure 2: Cell types of the nasal epithelium showing ciliated cell (A), non-ciliated cell(B), goblet cells(C), gel mucus layer (D), sol layer (E), basal cell (F) and basement membrane (G)

BARRIERS TO NASAL ABSORPTION

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.

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 HW *et al*., 1993). 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. Polar drugs with molecular weights below 1000 Da will generally pass the membrane using the latter route (McMartin C *et al*., 1987). Larger peptides and proteins have been shown to be able to pass the nasal membrane using an endocytotic transport process but only in low amounts (Inagaki M *et al.,* 1985).

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 L *et al.,* 1987; Soane RJ, 1999). It has further been suggested that the deposition of a formulation in the anterior part of the nasal cavity can decrease clear- ance and promote absorption as compared to deposition further back in the nasal cavity (Harris AS *et al* 1986). Most nasal sprays of various makes have been shown to deliver the formulation to a limited area in the anterior part of the nasal cavity as opposed to nasal drops which will be delivered to a larger area further back in the nasal cavity. The use of bioadhesive excipients in the formulations is an approach to overcome the rapid mucociliary clearance. The clearance may also be reduced by depositing the formulation in the anterior, less ciliated part of the nasal cavity thus leading to improved absorption (Kublik H et al., 1998 ; Harris AS et al., 1986).

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 degradation of the molecule either within the lumen of the nasal cavity or during passage across the epithelial barrier. These sites both contain exo-peptidases such as mono- and di-aminopeptidases that can cleave peptides at their N and C termini and endopeptidases such as serine and cysteine, which can attack internal peptide bonds (Lee VHL, 1988). The use of enzyme inhibitors and/or saturation of enzymes may be approaches to overcome this barrier (Morimoto K *et al.,* 1995).

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 physiochemical 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. The factors influencing nasal drug absorption are described as follows.

1) Physiochemical properties of drug.

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

2) Nasal Effect

- Membrane permeability.
- Environmental p^H
- Mucociliary clearance
- Cold, rhinitis.

3) Delivery Effect

- Formulation (Concentration, p^H, osmolarity)
- Delivery effects
- Drugs distribution and deposition.
- Viscosity

1) Physiochemical 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 ≥ 300 Daltons (Corbo DC *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. Lipophilic drugs like naloxone, buprenorphine, testosterone and 17a-ethinyl- oestradiol are almost completely absorbed when administered intranasal route (Bawarshi RN *et al*., 1989; Hussain A *et al.*, 1991).

Enzymatic degradation in nasal cavity

In case of peptides and proteins are having low bioavailability 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. These both sites are having exo-peptidases and endopeptidases, exo-peptidases are mono-aminopeptidases and di-aminopeptidases. These are having capability to cleave peptides at their N and C termini and endopeptidases such as serine and cysteine, which can attack internal peptide bonds (Lee V.H.L, 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 M *et al.,* 1985). Water-soluble high molecular weight drugs cross the nasal mucosa mainly by passive diffusion through the aqueous pores (i.e. tight junctions).

Environmental p^H

The environmental pH plays an important role in the efficiency of nasal drug absorption. Small water-soluble compounds such as benzoic acid, salicylic acid, and alkaloid acid show that their nasal absorption in rat occurred to the greatest extent at those pH values where these compounds are in the nonionised form. However, at pH values where these compounds are partially ionized, substantial absorption was found. This means that the nonionised lipophilic form crosses the nasal epithelial barrier via transcellular route, whereas the more lipophilic ionized form passes through the aqueous paracellular route (Franz MR *et al.,*1993.).

Mucociliary clearance

Mucociliary clearance is a one of the functions of the upper respiratory tract is to prevent noxious sub-

stances (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 M *et al.,* 1990). Clearance of this mucus and the adsorbed/dissolved substances into the GIT is called the MCC. This clearance mechanism influence the absorption process due to the dissolved drugs in the nasal cavity are discharge by the both the mucus and the cilia, which is the motor of the MCC and the mucus transport rate is 6 mm/min. It is of utmost importance that the MCC is not impaired in order to prevent lower respiratory tract infections (Jorissen M *et al*., 1995).

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. Allergic rhinitis is the allergic airway disease, which affects 10% of population. It is caused by chronic or acute inflammation of the mucous membrane of the nose. These conditions affect the absorption of drug through the mucus membrane due the inflammation.

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 P *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 (Satish BB *et al*., 2008).

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 K *et al.,* 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 (Gizurarson S *et al*., 1991). The site of disposition and distribution of the dosage forms are mainly depends on delivery device, mode of administration, physicochemical properties of drug molecule.

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

Various strategies used to improve the bioavailability of the drug in the nasal mucosa which includes

1. To improve the nasal residence time
2. To enhance nasal absorption
3. To modify drug structure to change physicochemical properties.

Any one or combination of above approaches are used for the enhancing the absorption and bioavailability of the formulations. Several methods have been used to facilitate the nasal absorption of drugs includes:

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 MA *et al.,* 1990). The absorption enhancers like salts and fusidic acid derivatives also shows enzyme inhibition activity to increase the absorption and bioavailability of the drug (Donnelly A *et al.,* 1998). The other enzyme inhibitors commonly used for the enzymatic activity are tripsin, aprotinin, borovaline, amastatin, bestatin and boroleucin inhibitors.

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. General requirement of an ideal penetration enhancer are as follows.

1. It should lead to an effective increase in the absorption of the drug.
2. It should not cause permanent damage or alteration to the tissues
3. It should be non irritant and nontoxic.
4. It should be effective in small quantity
5. The enhancing effect should occur when absorption is required
6. The effect should be temporary and reversible
7. 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, glycyrrhetenic acid derivatives, cyclodextrins and glycols.

Classification of chemical penetration enhancer includes (Ramesh RP *et al.,* 2009):

Surfactants**:** Polyozyethylene-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

Glycyrrhetinic acid derivates**:** Carbenozolone**,** Glycyrrhizinate

Cyclodextrins**:** α, ß, and γ- cyclodextrins and their derivatives

Glycols**:** n- glycofurols and n- ethylene glycols

Prodrug approach

Prodrug approach is mainly meant for optimizing favorable physicochemical properties such as solubility, taste, odor, stability, etc. Prodrug is usually referred as promoiety, 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 E *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 prepared into enamine derivatives, these agents showed absorption enhancement with prodrug approach.

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).

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 P *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 YW *et al.,* 1987).

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. Four basic formulations must be considered, i.e. solution, suspension, emulsion and dry powder systems.

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 H *et al*., 1993) and the reduced chemical stability of the dissolved drug substance and the short residence time of the formulation in the nasal cavity are major disadvantages of liquid formulations (Illum L *et al.,* 1987; Hardy JC *et al.,* 1985). The several types dosage forms available in liquid form are described below.

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 BL *et al.,* 1993; Harris AS *et al.,* 1986). Dosing of catheters is determined by the filling prior to administration and accuracy of the system and this is mainly used for experimental studies only.

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 principal 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 M *et al*., 2002). Nebulizers accept their medicine in the form of a liquid solution, which is often loaded into the device upon use. Corticosteroids and Bronchodilators such as salbutamol (*Albuterol* USAN) are often used, and sometimes in combination with ipratropium (Hickey AJ, 2004). The reason these pharmaceuticals are inhaled instead of ingested is in order to target their effect to the respiratory tract, which speeds onset of action of the medicine and reduces side effects, compared to other alternative intake routes This device is not suitable for the systemic delivery of drug by patient himself.

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. Dose accuracy and deposition of liquids delivered via squeezed nasal bottles are strongly dependent on the mode of administration. The differences between vigorously and smoothly pressed application influence the dose as well as the droplet size of the formulation. Thus the dose is hard to control. Therefore squeezed bottles with vasoconstrictors are not recommended to be used by children (Mygind N *et al*., 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. The dose accuracy of metered-dose pump sprays is dependent on the surface tension and viscosity of the formulation. For solutions with higher viscosity, special pump and valve combinations are on the market.

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. The types of powder dosage forms are described below:

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 particle size of these systems is often increased compared to the particle size of the powder particles due to insufficient deaggregation of the particles and results

in a high coefficient of variation for initial deposition areas. Many insufflator systems work with pre-dosed powder doses in capsules (Hughes BL *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 M *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 (Finlay, 2001).

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) (Hickey AJ., 2004).The advantages of MDIs are their portability and small size, availability over a wide dosage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use(Newhouse MT., 1991).

To use the inhaler the patient presses down on the top of the canister, with their thumb supporting the lower portion of the actuator. The propellant provides the force to generate the aerosol cloud and is also the medium in which the active component must be suspended or dissolved. Propellants in MDIs typically make up more than 99 % of the delivered dose. Actuation of the device releases a single metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometer-sized medication particles that are then inhaled (Finlay, 2001).

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 ad- vantages 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.

APPLICATIONS

1. Delivery of non-peptide pharmaceuticals

Low molecular weight (below 1000 daltons) small non-peptide lipophilic drugs are well absorbed through the nasal mucosa even though absence of permeation enhancer. Nasal membrane containing epithelium is highly vascularized and it contains large surface area it is readily accessible for drug absorption because presence of nasal turbinates.

Drugs with extensive pre-systemic metabolism, such as progesterone, estradiol, propranolol, nitroglycerin, sodium chromoglyate can be rapidly absorbed through the nasal mucosa with a systemic bioavailability of approximately 100% (Ramaprasad YV *et al*., 1996; Hussain AA *et al*., 1980). These drugs can reach widespread circulation within few minutes after dosing, as the venous blood passes from the nose directly into the systemic circulation. In fact, many drugs that are administered intranasally are often absorbed faster and more efficiently than hose from oral administration translating into a quick uptake

Some of non-peptide drugs being studied for nasal delivery and have shown good bioavailability by this route includes:

1) Adrenal corticosteroids
2) Sex hormonses: 17ß-estradiol, progesterone, norethindrone, and testosterone.
3) Vitamins: vitamin B
4) Cardiovascular drugs: hydralazine, Angiotensin II antagonist, nitroglycerine, isosobide dinitrate, propanolol, and colifilium tosylate.
5) Autonomic nervous system:
   a. Sympathomimetics: Ephedrine, epinephrine, phenylephrine,
   b. Xylometazoline, dopamine and dobutamine.
   c. Parasympathomimetics: nicotine, metacholine

d. Parasympatholytics: scopolamine, atropine, ipatropium
e. Prostaglandins

6) Central nervous systems stimulants: cocaine, lidocaine
7) Narcotics and antagonists: bupemorphine, naloxane
8) Histamine and antihistamines: disodium cromoglycate, meclizine
9) Antimigrane drugs: dierogotamine, ergotamine, tartarate
10) Phenicillin, cephalosporins, gentamycin
11) Antivirals : Phenyl-p-guanidine benzoate, enviroxime.
12) Inorganic compounds: Inorganis salts, colloidal gold, colloidal carbon, colloidal silver.

2. Delivery of peptide-based pharmaceuticals

Peptides & proteins have a generally low oral bioavailability because of their physico-chemical instability and susceptibility to hepato-gastrointestinal first-pass elimination. Examples are insulin, calcitonin, pituitary hormones etc (O'Hagan DT *et al.,* 1990).These peptides and proteins are hydrophilic polar molecules of relatively high molecular weight, are poorly absorbed across biological membranes with bioavailabilities obtained in the region of 1–2% concentrations when administered as simple solutions. To overcome this problem mainly we are using the absorption enhancers like sufactants, glycosides, cyclodextrin and glycols to increase the bioavailability. Nasal route is proving to be the best route for such biotechnological products.

3. Delivery of Drugs to Brain through Nasal Cavity:

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. The development of nasal delivery system to brain will increase the fraction of drug that reach the CNS after nasal delivery. The olfactory region located at the upper remote parts of the nasal passages offers the potential for certain compounds to circumvent the blood-brain barrier and enter into the brain. The recent studies express neurotrophic factors such as NGF, IGF-I, FGF and ADNF have been intranasally delivered to the CNS shows good results to increase the bioavailability of drug in the brain. Studies in humans, with proteins such as AVP, CCK analog, MSH/ACTH and insulin have revealed that they are delivered directly to the brain from the nasal cavity.

4. Delivery of Vaccines through Nasal Route:

Mucosal sites gives first line of defense against the microorganisms entered into the body, nasal mucosa act by filtering the pathogens from the inspired air by compaction and mucociliary clearance. Nose with nose- associated lymphoid tissue (NALT) acts as an effective site of immune system, it is called Waldeyer´s Ring in human beings and nasal secretions mainly contains immunoglobulins (IgA, IgG, IgM, IgE), protective proteins such as complement as well as neutrophils and lymphocytes in the mucosa (Mestecky J *et al.*, 1997; Kuper CF *et al*., 1992; Durrani Z *et al* 1998). Main reasons for exploiting the nasal route for vaccine delivery are 1) the nasal mucosa is the first site of contacts with inhaled pathogens, 2) The nasal passages are rich in lymphoid tissue, 3) Creation of both mucosal and systemic immune responses, 4) Low cost, patient friendly, non-injectable, safe.

Nasal delivery of vaccines has been reported to not only produce systemic immune response, but also local immune response in the nasal lining, providing additional barrier of protection (Mestecky J *et al.,* 1997). Delivering the vaccine to the nasal cavity itself stimulates the production of local secretory IgA antibodies as well as IgG, providing an additional first line of defense, which helps to eliminate the pathogen before it becomes established (Durrani Z *et al* 1998).

Recently, for the diseases like anthrax and influenza are treated by using the nasal vaccines prepared by using the recombinant Bacillus anthracis protective antigen (rPA) and chitosan respectively(Read RC *et al*., 2005; Soane RJ *et al*., 2001). The common diseases like measles, pertussis, meningitis and influenza causing pathogens are mainly enter into the body through the nasal mucosal surfaces and hence good candidates for nasal vaccines. Nasally administered vaccines, especially if based on attenuated live cells or adjuvanted by means of an immunostimulator or a delivery system, can induce both mucosal and systemic (i.e. humoral and cell-mediated) immune responses.

5. Delivery of diagnostic drugs:

Nasal drug delivery system also play very important role in the delivery of diagnostic agents for the diagnosis of various diseases and disorders in the body. Because the intranasal route better for systemic release of medicament into blood circulation, so can get quick results with less toxicity. Phenolsulfonphthalein is a diagnostic agent used to diagnose the kidney function of the patients. Pancreatic disorders of the diabetic patients were diagnosed by using the 'Secretin'. And the secretory function of gastric acid was determined by Pentagastrin, diagnostic agent.

CONCLUSION

Nasal 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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