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STRATEGIES AND PROSPECTS OF NASAL DRUG DELIVERY SYSTEMS

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ABSTRACT

The recent advancement of nasal drug delivery systems has increased enormously and is gaining significant importance. Intranasal therapy has been an accepted form of treatment in the Ayurvedic system of Indian Medicine. The non-invasive delivery of nasal drug delivery systems made to exploit for the development of successful treatment. The advantages, disadvantages, mechanism of action and application of nasal drug delivery system in local delivery, systematic delivery, nasal vaccines and CNS delivery are explained lucidly. The relevant aspects of biological, physicochemical and pharmaceutical factors of nasal cavity that must be considered during the process of discovery and development of new drugs for nasal delivery as well as in their incorporation into appropriate nasal pharmaceutical formulations are also discussed. Nasal route is more suitable for those drugs which cannot be administered orally due to gastric degradation or hepatic first pass metabolism of the drug. Intranasal drug delivery is found much promising route for administration of peptides and protein drugs. Much has been investigated and much more are to be investigated for the recent advancement of nasal drug delivery systems.

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 [1].

In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal therapy is the recognized form of treatment in the Ayurvedic systems of Indian medicine, and also called as NASAYA KARMA [2]. Nasal drug delivery which is practiced since 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 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. 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. It has been documented that nasal administration of certain hormones and steroids results in more complete absorption [3, 4]. This indicates the potential value of the nasal route for administration of systemic medications as well as utilization of 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, anticholinergic and vasoconstrictors. In recent years, increasing investigations of the nasal route have focused especially on nasal application for systemic drug delivery. Only a few nasal delivery systems used in experimental studies are currently in the market to deliver therapeutics into the nasal cavities, i.e., nasal drops as multiple or single dose formulation, aqueous nasal sprays, 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 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 & limitations of nasal drug delivery system, 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 [5]: The main advantages include are;

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.

Disadvantages [6]: Any delivery system poses certain disadvantages. The limitations of nasal delivery are;

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 the 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 of three main regions. Thay are nasal vestibule, olfactory region and respiratory region. The surface area in the nose is enlarged about 150cm^2 by the lateral walls of the nasal cavity which includes a folded structure. It has a very high surface area compared to its small volume. This folded structure consists of three turbinate's - the superior, the median and the inferior. The main nasal airway having the narrow passages usually 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 i.e.; non-olfactory and olfactory epithelium. In non-olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells where as in respiratory region, it has typical airways in the epithelium covered with numerous microvilli, resulting in a large surface area available for drug absorption and transport. 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 mucus as mucus granules which swell 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 proteins such as albumin, immunoglobulins, lysozyme and lactoferrin, and 1% lipids. The mucus secretion gives immune protection against inhaled bacteria and viruses. It also performs a number of physiological functions. It covers the mucosa, and physically and enzymatically protects it. The mucus has water-holding capacity. It exhibits surface electrical activity. It permits efficient heat transfer. It acts as adhesive and transports particulate matter towards the nasopharynx [7].

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 which 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. The two mechanisms that include there

- **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 show poor bioavailability [8].

- **Second mechanism:** It involves transport through a lipoidal route known as the transcellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs can also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. For example chitosan, a natural biopolymer from shell fish opens tight junctions between epithelial cells to facilitate drug transport [9].

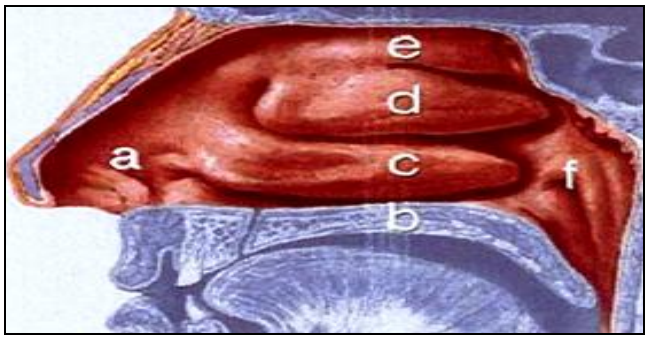

FIG. 1: PARTS OF NASAL CAVITY (a) NASAL VESTIBULE, (b) PALATE, (c) INFERIOR TURBINATE, (d) MIDDLE TURBINATE, (e) SUPERIOR TURBINATE (OLFACTORY MUCOSA), (f) NASOPHARYNX

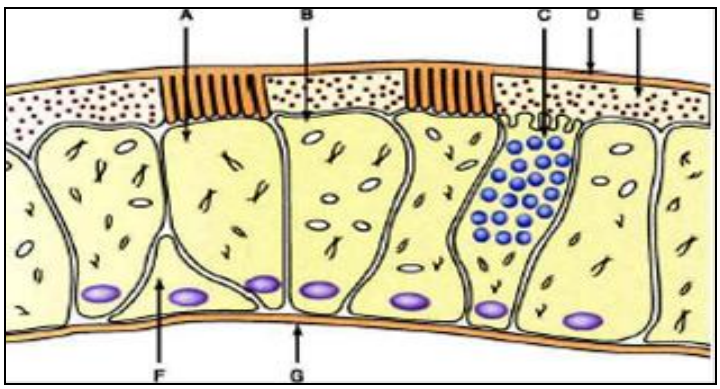

FIG. 2: CELL TYPES OF THE NASAL EPITHELIUM SHOWING CILIATED CELL (A), NON-CILIATED CELL(B), GOBLET CELLS(C), GEL MUCUS LAYER (D), SOL LAYER (E), BASAL CELL (F) AND BASEMENT MEMBRANE (G)

Barriers to Nasal Absorption: Nasal drug delivery systems are considered as a profitable route for the formulation scientist because it has easy and simple formulation strategies. The therapeutic efficacy and toxicities of intra-nasally administered drug products are influenced by number of factors. The following factors are the barriers to the absorption of drugs through nasal cavity.

- **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 example of this is the nasal administration of Fentanyl, where the T_{max} for both intravenous and nasal administration are shown to be very rapid (7 min or less) and the bioavailability was near 80%. The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability.

  Drugs can cross the epithelial cell membrane either by the transcellular route exploiting simple concentration gradients, by receptor mediated or vesicular transport mechanisms, or by the paracellular route through the tight junctions between the cells. Polar drugs with molecular weights below 1000 Da generally pass the membrane using the latter route. Larger peptides and proteins pass through the nasal membrane using an endocytotic transport process but only in low amounts.

- **Low Membrane Transport:** Another important factor is low membrane transport which 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 is shown that for both liquid and powder formulations that are not mucoadhesive, the half life of clearance ranges in the order of 15–20 min. It is further suggested that the deposition of a formulation in the anterior part of the nasal cavity can decrease clearance and promote absorption as compared to deposition further back in the nasal cavity. Most nasal sprays of various marketed preparations deliver the formulation to a limited area in the anterior part of the nasal cavity as opposed to nasal drops which deliver to a larger area further back in the nasal cavity [10]. The use of bioadhesive excipients in the formulations is an approach to overcome the rapid mucociliary clearance.

Factors influencing Nasal Drug Absorption: Several factors affect the systemic bioavailability of drugs which are administered through the nasal route. They include physiochemical properties of the drugs, 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.

Physiochemical properties of Drug:

- **Molecular Size:** The molecular size of the drug influence absorption through the nasal rout**e.** The lipophilic drugs have direct relationship between the molecular weight 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 [11].

- **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 is 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 [12, 13].

- **Enzymatic degradation in Nasal Cavity:** In case of peptides and proteins having low bioavailability across the nasal cavity, these may have possibility to undergo enzymatic degradation in the lumen of

the nasal cavity or during passage through the epithelial barrier. These both sites have exopeptidases (mono-aminopeptidases, di-aminopeptidases) which have the capability to cleave peptides at their N and C termini and endopeptidases (such as serine and cysteine) which can attack internal peptide bonds.

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 have low membrane permeability. So the compounds like peptides and proteins are mainly absorbed through the endocytotic transport process in low amounts. Water-soluble high molecular weight drugs cross the nasal mucosa mainly by passive diffusion through the aqueous pores (i.e. tight junctions).

- **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 occurrs 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 is found. This means that the nonionised lipophilic form diffuses through the nasal epithelial barrier via transcellular route, whereas the more lipophilic ionized form passes through the aqueous paracellular route [14].

- **Mucociliary Clearance (MCC):** Mucociliary clearance is one of the functions of the upper respiratory tract 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 [15]. Clearance of this mucus and the adsorbed/dissolved substances into the GIT is called the MCC. This clearance mechanism influence the absorption process, since the dissolved drugs in the nasal cavity are discharged by the both the mucus and the cilia which is the motor of the MCC. 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.

- **Rhinitis:** Rhinitis is a most frequently associated common disease. This condition impairs 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.

Delivery Effect Factors: The factors that affect the delivery of drug across nasal mucosa are surfactants, dose pH, osmolarity, viscosity, particle size and nasal clearance and drug structure. These can be used to enhance the absorption.

- **Formulation (concentration, pH, osmolarity):** The pH of the formulation and nasal surface can affect drug 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.

  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 which is shown to increase with drug concentration in nasal perfusion experiments. The absorption of salicylic acid is 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.

The sodium chloride concentration of the formulation affects the nasal absorption. The maximum absorption is 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.

- **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 effects 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 depend on the site of disposition. The anterior portion of the nose provides a prolonged nasal residential time for disposition of formulation and this enhances the absorption of the drug.

  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 [16]. The site of disposition and distribution of the dosage forms mainly depend 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 are to improve the nasal residence time, to enhance nasal absorption and to modify drug structure to change physicochemical properties. Any one or combinations of the approaches are used for enhancing the absorption and bioavailability of the formulations. Several methods that facilitate the nasal absorption of drugs are as follows;

- **Nasal Enzyme Inhibitors:** Nasal metabolism of drugs can be eliminated by using the enzyme inhibitors. For the formulations of proteins and peptide molecule development, enzyme inhibitors like peptidases and proteases are used. The absorption enhancers like salts and fusidic acid derivatives also show enzyme inhibition activity to increase the absorption and bioavailability of the drug [17]. The other enzyme inhibitors commonly used for the enzymatic activity are trypsin, aprotinin, borovaline, amastatin, bestatin and boroleucin inhibitors.

  Some of the chemical penetration enhancers are 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), Di-decanoyl – PC, Glycyrrhetinic acid derivates (Carbenozolone, Glycyr-rhizinate), Cyclodextrins (α, ß, and γ-cyclodextrins and their de-rivatives, Glycols (n-glycofurols and n- ethylene glycols) [18].

- **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 other functional groups. This prodrug approach is mainly to improve the nasal bioavailability especially for the proteins and peptides to enhance the membrane permeability along with increased enzymatic stability.

  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 preparing enamine derivatives. These agents show 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. Chemical modification of salmon calcitonin to ecatonin (C-N bond replaces the S-S bond) shows better bioavailability than salmon calcitonin.

- **Particulate Drug Delivery:** Design of a particulate drug delivery system plays an increasingly important role in absorption enhancement. Microspheres, nanoparticles and liposomes are all particulate 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 mainly increase the absorption and bioavailability by adhering to the nasal mucosa and increase the nasal residence time of drug [19].

  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 can be delivered through the nasal route.

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 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 [20]. The several types dosage forms available in liquid form are described below.

- **Instillation and Rhinyle Catheter:** Catheters are used to deliver the drops to a specified region of nasal cavity easily. The formulation is placed in the tube. One end is positioned in the nose, and the solution is delivered into the nasal cavity by blowing through the other end by mouth [21]. 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.

- **Compressed Air Nebulizers:** Nebulizer is a device used to administer medication in the form of a mist, inhaled into the lungs. The compressed air fills into the device, so it is called compressed air nebulizers. The common technical principle for all nebulizers is to 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. 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.

  These pharmaceuticals are inhaled instead of ingestion. It 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.

- **Squeezed bottle:** Squeezed nasal bottles are mainly used as delivery devices 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 applications 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.

- **Metered-dose Pump Sprays:** Most of the pharmaceutical nasal preparations in 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. Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by the 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 available in 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 prolonged contact with the nasal mucosa. The types of powder dosage forms are described below:

- **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.

- **Dry Powder Inhaler:** Dry powder inhalers (DPIs) are devices through which a dry powder formulation of an active drug is delivered for local or systemic effect via the pulmonary route. Dry powder inhalers are bolus drug delivery devices that contain solid drug, suspended or dissolved in a non polar volatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus.

  The medication is commonly held either in a capsule for manual loading or a proprietary form from inside the inhaler. Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a deep inhalation, holding their breath for 5-10 seconds. There are a variety of such devices. The dose that can be delivered is typically less than a few tens of milligrams in a single breath since larger powder doses may lead to provocation of cough [22].

- **Pressurized MDI's:** 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 dosage range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use. To use the inhaler, the patient presses down on the top of the canister, with their thumb supporting the lower portion of the actuator. The propellant provides the force to generate the aerosol cloud and is also the medium in which the active component must be suspended or dissolved.

Propellants in MDIs typically make up more than 99 % of the delivered dose. Actuation of the device releases a single metered dose of the formulation which contains the medication either dissolved or suspended in the propellant. Breakup of the volatile propellant into droplets, followed by rapid evaporation of these droplets, results in the generation of an aerosol consisting of micrometer-sized medication particles that are then inhaled.

Nasal Gels: Nasal gels are high-viscosity thickened solutions or suspensions. Until the recent development of precise dosing devices, there is not much interest in this system. The advantages of a nasal gel include 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. The deposition of the gel in the nasal cavity depends on the mode of administration. 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 [22].

Applications:

- **Delivery of Non-Peptide Pharmaceuticals:** Low molecular weight (below 1000 daltons) small non-peptide lipophilic drugs are well absorbed through the nasal mucosa even in the absence of permeation enhancer. Nasal membrane containing epithelium is highly vascularized and it contains large surface area and 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% [23].

  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 those 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 include Adrenal corticosteroids, Sex hormonses (17ß-estradiol, progesterone, norethindrone, and testosterone), Vitamins, Cardiovascular drugs (hydralazine, Angiotensin II antagonist, nitroglycerine, isosobide dinitrate, propanolol, and colifilium tosylate), Central nervous systems stimulants (cocaine, lidocaine).

- **Delivery of Peptide-Based Pharmaceuticals:** Peptides & proteins have generally a low oral bioavailability because of their physicochemical instability and susceptibility to hepato-gastrointestinal first pass elimination. Examples are insulin, calcitonin, pituitary hormones etc [24]. 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, with the use of absorption enhancers like surfactants, glycosides, cyclodextrin and glycols will increase the bioavailability. Nasal route is proving to be the best route for such biotechnological products.

- **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 reaches 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.

- **Delivery of Vaccines through Nasal Route:** Mucosal sites give first line of defense against the microorganisms entered into the body. Nasal mucosa acts 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 contain immunoglobulins (IgA, IgG, IgM, IgE) which protective proteins such as complement as well as neutrophils and lymphocytes in the mucosa [25-27].

  The main reasons for exploiting the nasal route for vaccine delivery are the nasal mucosa is the first site of contacts with inhaled pathogens, the nasal passages are rich in lymphoid tissue, creation of both mucosal and systemic immune responses and low cost, patient friendly, non-injectable, safe. Nasal delivery of vaccines is reported to not only produce systemic immune response, but also local immune response in the nasal lining, providing additional barrier of protection. 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.

  Recently, 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 [28]. The common diseases like measles, pertussis, meningitis and influenza are caused by the pathogens that mainly enter into the body through the nasal mucosal surfaces and hence are good candidates for nasal vaccines. Nasally administered vaccines, especially based on attenuated live cells or adjuvanted by means of an immuno-stimulator or a delivery system, can induce both mucosal and systemic (i.e. humoral and cell-mediated) immune responses.

- **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 is more suitable for systemic release of medicament into blood circulation, one 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 are diagnosed by using 'Secretin' and the secretory function of gastric acid are determined by Pentagastrin, a 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 the near future, let us 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.

REFERENCES

1. S.P. Vyas and R.K. Khar a text book of targeted and controlled drug delivery systems.
2. A J. Hickey, Pharmaceutical Inhalation Aerosol Technology, 2nd edition, Marcel Dekker, NY, 2004
3. Armengot M., Basterra J., Macro J., Rev.Larngol.Octol.Rhinol. 1990, 111,219- 226
4. Aulton M.E. "Pharmaceutics – The science of dosage form design" Churchill Livingston., 494, 2002
5. Aurora J. Development of Nasal Delivery Systems: A Review**.** Drug Deliv Technol 2002; 2, 7, 1-8.
6. Bawarshi RN, Hussain A, Crooks PA. Nasal absorption of 17a - ethinyloestradiol in the rat. J Pharm Pharmacol 1989; 41: 214-215.

7. Bernstein JM., Reddy MS., Scannapieco FA, Faden HS., Ballow M., The microbial ecology and immunology of the adenoid: implications for otitis media, Ann. N.Y. Acad. Sci.1997,830, 19 – 31.
8. Buri P. Hydrogels destines a la muqueuse nasale. Controle physiologique, Pharm. Acta Helv. 1966, 41, 88–101.
9. Chien YW., Su KSE., Chang SF., Nasal Systemic Drug Delivery, Marcel-Dekker, New York, 1-77, 1989
10. Chien YW, Chang SF. Intranasal drug delivery for systemic medications. Crit Rev Ther Drug Carr Syst 1987; 4:67-194
11. Corbo DC, Liu JC, Chien YW. Characterization of the barrier properties of mucosal membranes. J Pharm Sci, 1990; 79:202-206.
12. Dodane V, Khan MA, Merwin JR. Effect of chitosan on epithelial permeability and structure. Int J Pharm, 1999; 182: 21-32.
13. Donnelly A, Kellaway IW, Taylor G, Gibson M. Absorption enhancers as tools to determine the route of nasal absorption of peptides.J Drug Target 1998; 5:121-7
14. Durrani Z, McInterney TL, McLain L, Intranasal immunisation with a plant virus expressing a pep-tide from HIV-1 gp41 stimulates better mucosal and systemic HIV-1-specific IgA and IgG than oral immunization. J Immunol Methods, 1998; 220: 93-103.
15. Edman P, Bjork E, Ryden L. Microspheres as a nasal delivery system for peptide drugs, J of controlled release, 1992;21:165-72
16. Finlay, Warren H.The mechanics of inhaled pharmaceutical aerosols: an introduction. Boston: Academic Press. 2001.
17. Franz, M.R., Oth, M.P., U.S patent, 5232704, 1993.
18. Gizurarson S, Bechgaard E. Intranasal administration of insulin to humans. Diabetes Res Clin Prac, 1999; 12:71-84.
19. Hardy JC., Lee SW., Wilson CG., Intranasal drug delivery by spray and drops, J. Pharm. Pharmacol. 1985, 37, 294–297.
20. Harris AS., Nilsson IM,.Wagner ZG, Alkner U., Intra-nasal administration of peptides: Nasal deposition, biological response and absorption of desmopressin, J. Pharm. Sci. 1986,75, 1085–1088.
21. Harris AS., Nilsson IM., Wagener ZG., Alkner U., Intranasal administration of peptides: Nasal deposition, biological response and absorption of desmopressin, J. Pharm. Sci. 1986,75, 1085–1088.
22. Harris AS, Nilsson IM, Wagner ZG, Alkner U. Intranasal administration of peptides: nasal deposition, biological response, and absorption of desmopressin. J Pharm Sci 1986; 75(11):1085-1088.
23. Hirai S., Yashiki T., Mima, H., Effect of surfactants on nasal absorption of insulin in rats, Int. J. Pharm., 1981,9, 165-171.
24. Hofstee BH. Specificity of esterase. II. Behavior of pancreatic esterase I and II toward a homologous series of N-fatty acid esters. J Biol Chem 1952; 199:365-71
25. Hughes BL., Allen DL., Dorato MA., Wolff RK., Effect of devices on nasal deposition and mucociliary clear-ance in rhesus monkeys, Aerosol Sci. Technol. 1993,18, 241–249.
26. Hussain A, Hamadi S, Kagoshima M, Iseki K, Dittert L. Does increasing the lipophilicity of peptides enhance their nasal absorption. J Pharm Sci, 1991; 80:1180-1181.
27. Hussain AA., Hirai S., Bawarshi R., Nasal absorption of natural contraceptive steroids in rats-progesterone absorption, J. Pharm. Sci.1981, 70, 466–467.
28. Hussain A.A., Hirai S, Bawarshi R, Nasal absorption of propranolol in rats, J. PharmSci.1979,68,1196–119

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