

A REVIEW ON NASO-PULMONARY DRUG DELIVERY SYSTEM

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ABSTRACT

Nasal drug delivery has received a great deal of attention as a convenient, reliable and promising method for the systemic administration of drugs. It is especially for those molecules which are ineffective orally and only effective if administered by injection. This is due to high vascularity, large surface area, the avoidance of hepatic first pass metabolism, gut wall metabolism and/or destruction in gastrointestinal tract. Since nasal mucosa offer several benefits for target delivery, a wide variety of therapeutic compounds may be administered intranasally for topical, systemic and central nervous system action.

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. Pulmonary drug delivery has attracted tremendous scientific and biomedical interest in recent years and has progress considerably within the context of local treatment for lung diseases, by virtue of enhanced local targeting and reduced systemic side effects with the administration of minute drug dosages.

The present review is an attempt to provide some information concerning naso-pulmonary drug delivery system such as advantages, disadvantages, mechanism of drug absorption, anatomy of nasal cavity and respiratory tract, factors affecting nasal drug absorption, dosage form, novel drug formulations and recent advancement of nasal delivery system.

KEYWORDS: Naso-Pulmonary drug delivery; Nose; peptides and proteins; vaccines; mucociliary clearance; nasal pulmonary; respiratory tract; anatomy and physiology; recent advancement; bioavailability.

INTRODUCTION

Nasal therapy, has been recognized form of treatment in the Ayurvedic systems of Indian medicine, it is also called "NASAYA KARMA". 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 content. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration.

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. The nasal route 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.

The nasal delivery seems to be a favorable way to circumvent the obstacles for blood-brain barrier (BBB) allowing the direct drug delivery in the bio phase of central nervous system (CNS) active compounds. It has

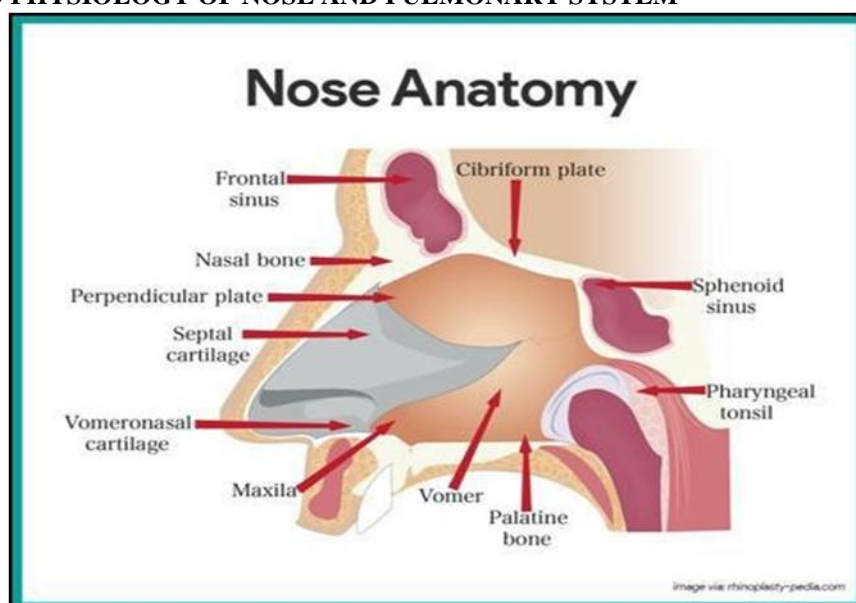
also been considered to the administration of vaccines. Pulmonary drug delivery is the inhalation of drug formulation through mouth and the further deposition of inhaled pharmacological agents in lower airways. Pulmonary delivered drugs are rapidly absorbed except large macromolecules drugs, which may yield low bioavailability due to enzymatic degradation and/or low mucosal permeability.

Pulmonary bioavailability of drugs could be improved by including various permeation enhancers such as surfactants, fatty acids, and saccharides, chelating agents and enzyme inhibitors such as protease inhibitors. The most important issue is the protein stability in the formulation: the dry powder formulation may need buffers to maintain the pH, and surfactants such as Tween to reduce any chance of protein aggregation. The

stabilizers such as sucrose are also added in the formulation to prevent denaturation during prolonged storage. The respiratory tract is one of the oldest routes used for the administration of drugs. Over the past decades inhalation therapy as established itself as a valuable tool in the local therapy of pulmonary diseases such as asthma or COPD (Chronic Obstructive Pulmonary Disease).

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.

ANATOMY AND PHYSIOLOGY OF NOSE AND PULMONARY SYSTEM



Nose: - The nose is the complex multifunctional organ. The nose is the primary entrance of the respiratory track.

External Nose: - The external nose is a pyramidal structure, situated in the mid face, with its base on the facial skeleton and its apex projecting anterior. The paired nasal bones form the external nose superiorly and two sets of paired cartilage inferiorly. The upper lateral cartilages provide the shape of the middle third of the nose and support for the underlying nasal valve. During periods of increased nasal breathing, such as during exercise, an increase in the activity of the dilating muscles occurs and aids in increasing the nasal airway patency.

Vestibule: -The first part of the respiratory tract to contact the external environment is the vestibule. Unlike the remaining nasal cavity, the vestibule is lined with stratified squamous epithelium. The epithelium of the nasal vestibule changes into pseudo stratified columnar

epithelium. The vestibule also contains thermo receptors that are not found in the portion of the nasal cavity lined by respiratory epithelium. The vestibule is the most important area for sensing nasal airflow.

Nasal Valve and Airflow: -The nasal valve lies just posterior to the nasal vestibule. It is bounded laterally by the caudal end of the upper lateral cartilage, medially by the septum, and inferiorly by the lower rim of the pyriform aperture. A widened area of the septum in this region, called the nasal septal swell body or septal turbinate, is considered part of the expansile vascular tissues of the nose. The nasal septal swell body mucosa is a highly glandular structure with moderate proportion of venous sinusoids that appears to contribute functionally to the area of the valve.

Nasal Septum: - The nasal septum divides the nasal cavity into two separate compartments, increasing the total mucosal surface area. It consists of an anterior

cartilaginous portion, which provides support for the nasal tip, and a posterior bony portion formed by the perpendicular plate of the ethmoid and the vomer. The percentage of nasal septal deformities changes with age. A multinational study has shown that septal deformities are present in approximately 90% of adult patients. A straight septum is twice more frequent in females than in males.

Turbinates: -The turbinates are three, rarely four, scroll-like projections from the lateral nasal wall. The lower two, referred to as the inferior and middle turbinates, are functionally the most significant. Each turbinate consists of a bony frame with overlying respiratory epithelium. Like the nasal septum, this aid in increasing the mucosal surface area of the nasal cavity to approximately 100 to 200 cm². The inferior turbinate has an important role in the defence of the lungs and the physiology of the nose. Trimming of the anterior portion of the inferior turbinate can lead to a decrease in the total nasal resistance to airflow by enlarging the nasal valve, but this should be considered only after potential causes for its enlargement have been investigated.

Histology: -The nasal lining has a mucosal epithelial layer with an underlying sub mucosal layer. The mucosa consists of pseudostratified columnar epithelium containing goblet cells, ciliated and nonciliated columnar cells with microvilli, and, occasionally, intraepithelial mast cells, eosinophils, and lymphocytes. The epithelial cells provide a protective barrier, and they produce inflammatory substances and the secretory portion of immunoglobulin IgA. The seromucous glands account for the largest proportion of nasal secretions. These glands are located throughout the nasal cavity, but the greatest concentration resides in the anterior nasal cavity. Depending on the cell type, these glands secrete either a serous or a mucous secretion.

Mucociliary Clearance: - Mucociliary transport is the mechanism by which the nasal cavity clears itself of secretions and trapped particulates. The two major components of this system are the mucous blanket and the ciliated epithelial cells. (12.np [<https://en.m.wikipedia.org/wiki/Lung>])

Lungs: - The lungs are the primary organs of the respiratory system in humans. In mammals and most other vertebrates, two lungs are located near the backbone on either side of the heart. Their function in the respiratory system is to extract oxygen from the atmosphere and transfer it into the bloodstream, and to release carbon dioxide from the bloodstream into the atmosphere, in a process of gas exchange. They are conical in shape with a narrow rounded apex at the top, and a broad concave base that rests on the convex surface of the diaphragm. The apex of the lung extends into the root of the neck, reaching shortly above the level of the sternal end of the first rib. The lungs stretch from close to the backbone in the rib cage to the front of

the chest and downwards from the lower part of the trachea to the diaphragm. The left lung shares space with the heart, and has an indentation in its border called the cardiac notch of the left lung to accommodate this. The cardiac impression is an indentation formed on the surfaces of the lungs where they rest against the heart. Both lungs have a central recession called the hilum at the root of the lung, where the blood vessels and airways pass into the lungs. There are also bronchopulmonary lymph nodes on the hilum.

Lung regions: -The respiratory tract starts at the nose and terminates deep in the lung at an alveolar sac. There are a number of schemes for categorizing the various regions of the respiratory tract.

Right lung:-The right lung has both more lobes and segments than the left. It is divided into three lobes, an upper, middle, and a lower lobe by two fissures, one oblique and one horizontal.

Left lung:-The left lung is divided into two lobes, an upper and a lower lobe, by the oblique fissure, which extends from the costal to the mediastinal surface of the lung both above and below the hilum.

Nasopharyngeal region: - This is also referred to as the “upper airways”, which involves the respiratory airways from the nose down to the larynx.

Tracheo-bronchial region: - This is also referred to as the “central” or “conducting airways”, which starts at the larynx and extends via the trachea, bronchi, and bronchioles and ends at the terminal bronchioles.

Alveolar region: - This is also referred to as the “respiratory airways”, “peripheral airways” or “pulmonary region”, comprising the respiratory bronchioles, alveolar ducts and alveoli.

Pulmonary epithelium: - The lung contains more than 40 different cell types, of which more than six line the airways. The diversity of pulmonary epithelia can be illustrated by examining its structure at three principal levels.

The bronchi: - These are lined predominantly with ciliated and goblet cells. Some serous cells, brush cells and Clara cells are also present with few Kulchitsky cells.

The bronchioles: - These are primarily lined with ciliated cuboidal cells. The frequency of goblet and serous cells decreases with progression along the airways while the number of Clara cells increases.

The alveolar region: -This is devoid of mucus and has a much flatter epithelium, which becomes the simple squamous type, 0.1–0.5 µm thick.

Ciliated cells: - In the trachea bronchial region, a high proportion of the epithelial cells are ciliated such that there is a near complete covering of the central airways by cilia. Towards the periphery of the tracheobronchial region, the cilia are less abundant and are absent in the alveolar region. The ciliated cells each have about 200 cilia with numerous interspersed microvilli, of about 1–2 μm in length. The cilia are hair-like projections about 0.25 μm in diameter and 5 μm in length. [7.np, <https://en.m.wikipedia.org/wiki/Lung>]

Major Functions of the Respiratory System

1. Maintaining hemostasis (acid-base balance) of arterial blood
2. Maintaining heat exchange
3. Removing waste (carbon dioxide) from body tissues
4. Supplying oxygen to the body.

ADVANTAGES OF PULMONARY DRUG DELIVERY

1. It is needle free pulmonary delivery.
2. It requires small and fraction of oral dose.
3. Low concentration in the systemic circulation is associated with reduced systemic side effects.
4. Rapid Onset of action
5. Avoidance of gastrointestinal upset
6. Degradation of drug by liver is avoided in pulmonary 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

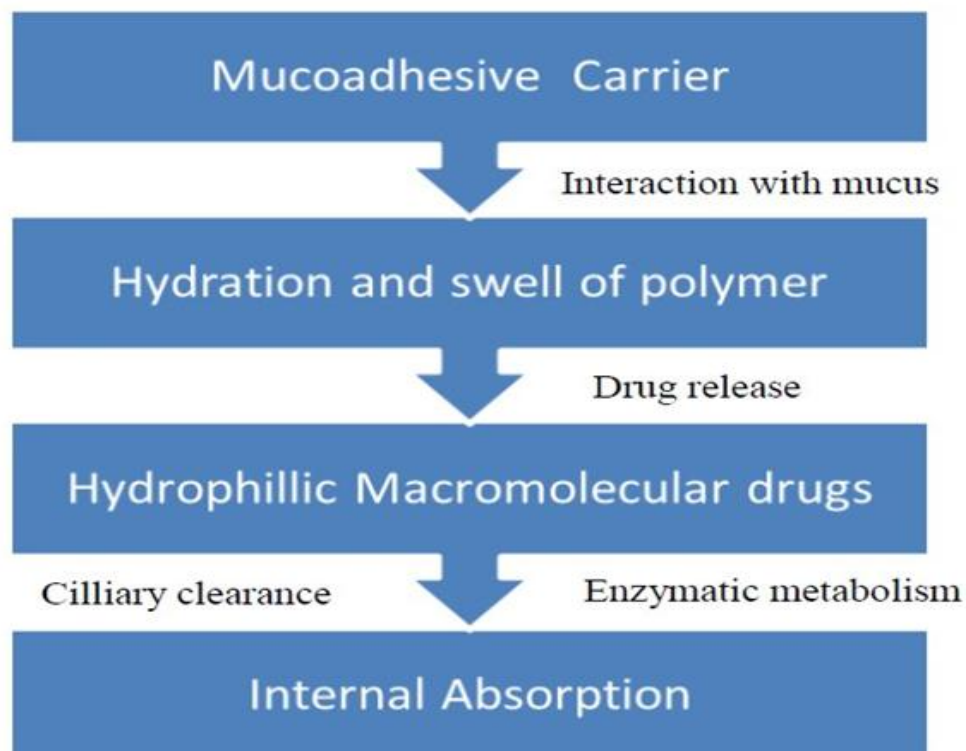
long term therapy, when compared with parenteral medication.

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 OF PULMONARY DRUG DELIVERY

1. Oropharyngeal deposition gives local side effect.
2. Patient may have difficulty using the pulmonary drug devices correctly.
3. Drug absorption may be limited by the physical barrier of the mucus layer.
4. Various factors affect the reproducibility on drug delivery on the lungs, including physiological and pharmaceutical barrier.
5. The lungs are not only accessible surface for drug delivery complex but also delivery devices are required to target drug delivery.
6. 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.
7. Certain surfactants used as chemical enhancers may disrupt and even dissolve membrane in high concentration.
8. 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.

MECHANISM OF DRUG ABSORPTION IN NASAL DRUG DELIVERY



Two mechanisms have been considered predominantly out of several mechanisms that have been proposed.

The first involves an aqueous route of transport, which is also known as the paracellular route. Key feature of this mechanism involves:

This route is slow and passive.

- There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds.
- Poor bioavailability was observed for a drug with a molecular weight greater than 1000 Daltons.
- The second involves transport through a lipoidal route is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. For examples, chitosan, a natural biopolymer from shellfish, opens tight junctions between epithelial cells to facilitate drug transport.

DOSAGE FORM IN NASO-PULMONARY DRUG DELIVERY SYSTEM

1. Nasal drops

They are the most convenient and simple system developed for nasal drug delivery. Nose drops can be delivered with a squeezy or by a pipette a bottle. These pharmaceuticals formulations are often recommended for treating local conditions, which include suffering some challenges such as microbial growth, mucosal dysfunction, and non-specific loss of the nose or lower back. The featured disadvantage of this system is the lack of the dose precision, and therefore, nasal drops may not be useful for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.^[9-14]

2. Nasal sprays

Solution and suspension are formulated into nasal sprays. Availability of metered dose pumps and actuators, a nasal spray can deliver an exact dose from 25 to 200 μm . The morphology particles size (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.^[9, 10, 13, 15]

3. Nasal gels

Until the recent development of precise dosing device, there was not a lot of interest during this system. Nasal gels are high viscosity thickened solutions or suspensions. The benefits 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 using soothing/emollient excipients, and target to mucosa for higher absorption.^[9, 13, 15, 16 17]

4. Nasal powder

This dosage form may be formulated if solution and suspension dosage forms cannot be formulated, for

example, due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of superior stability and preservative of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particle size, aerodynamic properties, and nasal irritancy of the active drug and excipients. Local application of the drug is another advantage of this system.^[9, 13, 15, 18, 19, 20]

5. Liposomes

These are phospholipid vesicles composed by bilayer enclosing one or more aqueous compartments, in these compartments drug can be entrapped or adsorbed.

6. Microspheres

Microsphere has an important role in nasal drug delivery with enhancing absorption, sustained release, and also has great importance because it protects the drug from enzymatic degradation.^[21]

7. 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. 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.^[22]

8. 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. 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. 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.^[23, 24]

9. 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 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.^[25]

10. 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 disaggregation 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.^[26]

11. 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.

12. 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 dose range per actuation, dose consistency, dose accuracy, protection of the contents and that they are quickly ready for use.

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 :

A. Physiochemical properties of drug

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

B. Nasal Effect

1. Membrane permeability.
2. Environmental pH.
3. Mucociliary clearance.
4. Cold, rhinitis.

C. Delivery Effect

1. Formulation (Concentration, pH, osmolarity)
2. Delivery effects
3. Drugs distribution and deposition.
4. Viscosity.

RECENT FORMULATIONS OF PULMONARY DRUG DELIVERY

- Insulin by aerosol.
- Nicotine aerosol for Smoking cessation. Alpha 1 Antitrypsin.
- Aerosols for Angina. Gene therapy via aerosol.
- In cancer chemotherapy. Pentamidine aerosol.
- Gentamycin aerosol. Ribavirin aerosol.
- Pulmonary delivery of lower molecular weight heparin. Controlled delivery of drugs to lungs.
- Pulmonary delivery of drugs for bone disorders.

FUTURE SCOPE

The intranasal route is an accessible alternative route for drug administration. This route provides future potential for several drugs through the development of safe and efficacious formulations for simple, painless and long term therapy. Despite the various challenges faced by pulmonary drug delivery system, several peptide and protein drugs are currently investigated for potential systemic absorption through pulmonary system, which includes insulin, calcitonin, luteinizing- hormone-releasing hormone (LHRH) analogs, granulocyte colony-stimulating factor (rhG-CSF), and human somatotropin (hGH). Despite considerable clinical experience with aerosolized macromolecules, there have been no serious safety issues to date, nor have there been significant problems with throat irritation or cough. Much has been investigated and far more are to be investigated for the recent advancement of nasal drug

delivery system.

CONCLUSION

The nasal cavity has a large surface area and a highly vascularized mucosa. Drugs absorbed by the rich network of blood vessels pass directly into the systemic circulation, thereby avoiding the firstpass metabolism. A growing body of evidence relating to nasal drug delivery suggests it might use for challenging drugs which can facilitate the pharmaceutical manufacturing and drug delivery challenges.

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