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Review Article

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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. 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.The pulmonary drug delivery system offers several merits over other drug delivery systems and therefore, this delivery route has been in prime focus for various applications like local and systemic therapeutics delivery.

KEYWORDS: Naso-Pulmonary drug delivery, mucociliary clearance, nasal, pulmonary, respiratory tract.

I. INTRODUCTION[1]

In ancient times the Indian Ayurvedic system of medicines used nasal route for administration of drug and the process is called as "Nasya". Intranasal drug delivery is now recognized to be a useful and reliable alternative to oral and parenteral routes. Undoubtedly, the intranasal administration of medicines for the symptomatic relief and prevention or treatment of topical nasal conditions has been widely used for a long period of time. Nasal administration is a route of administration in which drugs are insufflated through the nose. The nasal delivery seems to be a favourable 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.

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. Over the past decades inhalation therapy has established itself as a valuable tool in the local therapy of pulmonary diseases such as asthma or COPD(Chronic Obstructive Pulmonary Disease)

II. ANATOMY AND PHYSIOLOGY OF NASAL DRUG DELIVERY SYSTEM[2][3]

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, i.e. nasal vestibule, olfactory region and respiratory region. The surface area in the nose can be enlarged about 150 cm by the lateral walls of the nasal cavity which 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. The main nasal airway have the narrow passages, usually 1-3 mm wide, and these narrow structures are useful to nose to carry out its main functions. The nasal cavity is covered with a mucous membrane which can be divided into two areas; non-olfactory and olfactory epithelium. The non olfactory area includes the nasal vestibule which is covered with skin-like stratified squamous epithelium cells, the respiratory region, which has a typical airways 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 the mucus as mucus granules which are swelling in the nasal fluid to contribute to the mucus layer.

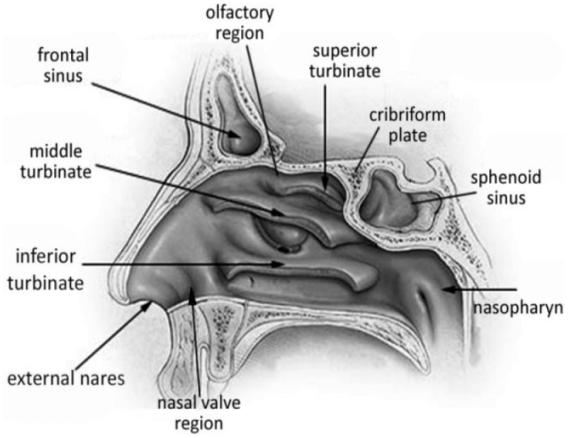

Figure 1: Nasal Cavity.

Normal pH of the nasal secretions in Adults: 5.5-6.5; Infants and Young Children: 5.0-6.7. Nasal Cavity is covered with a mucous membrane. Mucus secretion composed of 95% water, 2% Mucin, 1% Salts, 1% of other proteins such as Albumin, Lysozyme and Lactoferrin and 1% Lipids.

III. MECHANISM OF ABSORPTION[4]

- Paracellular (intercellular) Slow and passive absorption of peptides and proteins associated with intercellular spaces and tight junctions.
- Transcellular: Transport of lipophitic drugs passive diffusion/active transport.
- Transcytotic: Particle is taken into a vesicle and transferred to the cell.

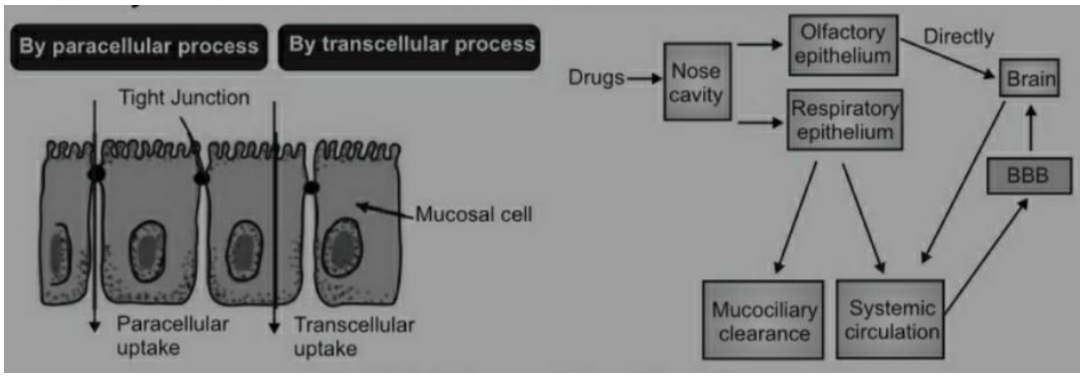

Figure 2: Pathway of drug absorption.

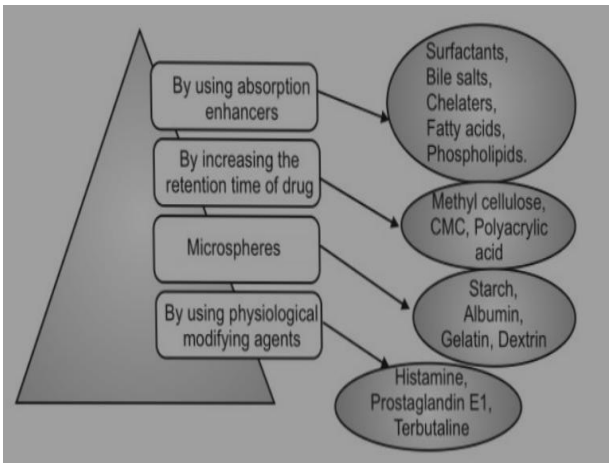

Figure 3: Enhancement of drug absorption.

IV. ADVANTAGES OF NASAL DRUG DELIVERY SYSYEM[5]

- Hepatic first pass metabolism avoided.
- Rapid drug absorption and quick onset of action.
- Bioavailability of larger drug molecules can be improved by means absorption enhancer.
- Drugs possessing poor stability G.I.T fluids given by nasal route.
- Easy and convenient.
- Easily administered to unconscious patients.

V. DISADVANTAGES[5]

- Pathologic conditions such as cold or allergies may alter significantly the nasal bioavailability.
- The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
- Relatively inconvenient to patients when compared to oral delivery systemssince there is a possibility of nasal irritation.
- Nasal cavity provides smaller absorption surface area when compared to GIT.

VI. PULMONARY DRUG DELIVERY SYSTEM[6]

The respiratory tract is one of the oldest routes used for the administration of drugs. Over the past decades, inhalation therapy has established itself a valuable tool in the local therapy of pulmonary diseases such as; asthma and COPD (Chronic Obstructive Pulmonary Disease).

- This type of drug application in the therapy of these disease is a clear form of targeted drug delivery The popularly marketed products are inhalation aerosol products for local pulmonary effects
- The drug used for asthma and COPD, for eg, agonists such as Salbutamol (albuterol) Terbutalin formoterol, corticosteroids such as Budesonide, Flixotide or Beclomethasone and mast cell

stabilizers such as Sodium cromoglycate or nedrocromi.

- The latest and probably one of the most promising applications of pulmonary drug administration is

1. Its use to achieve systemic absorption of the administered drug substances.
2. Particularly for those substances that exhibit a poor bioavailability when administered by the oral route, for eg peptides or proteins, the respiratory tract might be convenient port of entry.

VII. ANATOMY OF RESPIRATORY TRACT[7][8]

- The human respiratory system is a complicated organ system of very close structure function relationships The system consisted of two regions

1. The conducting system
2. The respiratory region

- The airway is further divided into many folds nasal cavity and the associated sinuses, and the nasopharynx oropharynx larynx trachea, bronchi and bronchiales
- The respiratory regions consist of respiratory bronchioles, alveolar ducts and alveolar sacs
- The human respiratory tract is a branching system of air channels with approximately 23 bifurcations from the mouth to the alveoli. The major task of the lungs is gas exchange, by adding oxygen to and removing carbon-di-oxide from the blood passing through the pulmonary capillary bed.

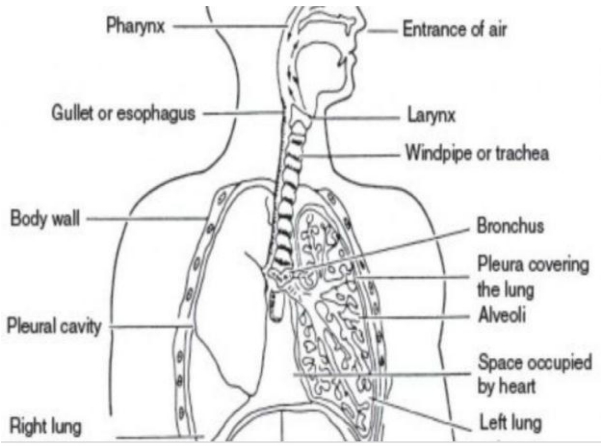

Figure 4: The respiratory tract.

VIII. ADVANTAGES OF PULMONARY DRUG DELIVERY SYSTEM[10]

- The dose needed to produce a pharmacological effect can be reduced
- Low concentrations in the systemic circulation are associated with reduced systemic side-effects
- Rapid onset of action.
- Avoidance of gastrointestinal upset Avoidance of metabolism.Intestinal And Hepatic First-pass

IX. DISADVANTAGES[10]

- Low efficiency and low amount of drugs delivered per puff.
- Targeting problems.
- Poor formulation stability of drugs.
- Immunogenicity problems with protein based drug.
- Rapid drug clearance by phagocytosis and mucociliary clearance.

X. MECHANISM OF PULMONARY DRUG DELIVERY SYSTEM[9]

The deposition of inhaled particles in the different regions of the respiratory system is very complex, and depends on many factors. Some of the factors influencing respiratory deposition include: • Breathing rate • Mouth or nose breathing • Lung volume • Respiration volume • Health of the individual • Bifurcations in the airways result in a constantly changing hydrodynamic flow field. Depending on the particle size, airflow, and location in the respiratory system, particle deposition occurs via on of the following principal mechanisms: Mechanism of particle deposition in air ways

- Inertial impaction
- Sedimentation
- Brownian diffusion

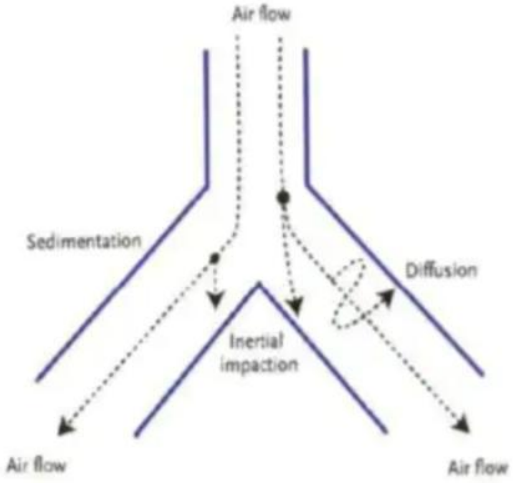

Figure 5: Particle deposition in air way.

XI. FORMULATIONS OF NASO PULMONARY DRUG DRLIVERY SYSYEM[10][11]

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 backchats been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

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.

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 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.

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. size, aerodynamic properties, and nasal irritancy of the active drug and excipients. Local application of the drug is another advantage of this system.

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.

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.

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, and Bronchodilators such as salbutamol (Albuterol USAN) are often used, and sometimes in combination with ipratropium.

Droplets

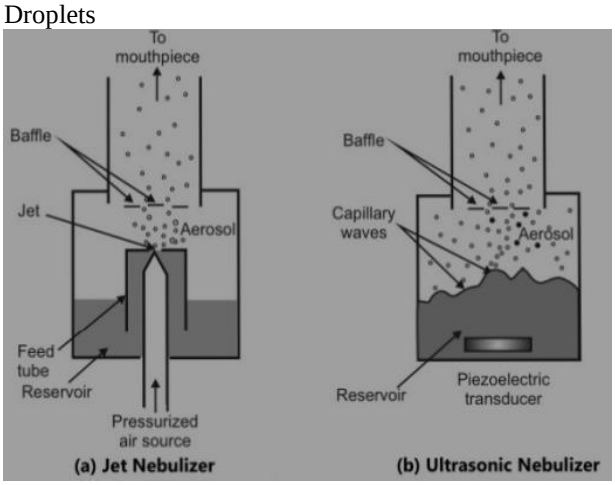

Figure 6: nebulizer.

9. Squeezed bottle

Squeezed nasal bottles are mainly used as delivery de-vice for decongestants. They include a smooth plastic bottle with a simple jet outlet. This procedure often results in contamination of the 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.

10. Insufflators

Insufflators are the devices to deliver the drug sub-stance for inhalation; it can be constructed by using a straw or tube which contains the drug substance and sometimes it contains syringe also. Many insufflator systems work with pre-dosed powder doses in capsules.

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-polarvolatile propellant or in dry powder inhaler that is fluidized when the patient inhales. These are commo nly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD and have also been used in the treatment of diabetes mellitus.

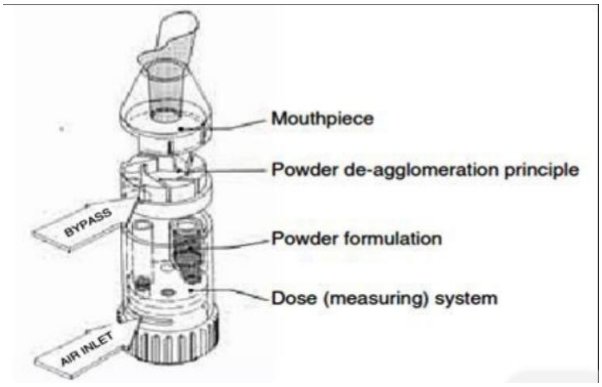

Figure 7: Dry powder inhaler.

12. Presurised 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 consistency, dose accuracy, protection of the contents and that they are quickly ready for use.Factors influencing osen nasal medicationdelivery system. These factors play key role for many of the medication so as to achievetherapeutically effective blood levels once nasal administration.

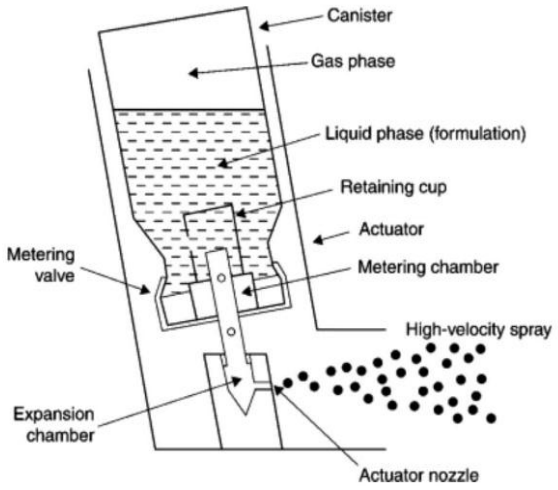

Figure 8: Meterd dose inhalers.

XII. EVALUATION OF PULMONARY DRUG DELIVERY SYSTEM[12][13]

1. *In vitro*

In this respect, in vitro models for pulmonary drug delivery studies propose another as It convey up fewer moral questions but also because they allow a fast screening of drugs. In both cellular models, it is significant that epithelial cells form a tense monolayer in order to characterize the natural epithelial barrier. Monolayer tension and reliability are classically assessed by measuring Tran's epithelial electrical resistance (TEER) and potential difference crosswise the monolayer. Monolayers of lung epithelial cells permit the categorization of drug transport and evaluation of potential drug and formulation toxicity.

2. *In –vivo*

Guinea-pigs have been generally used as an animal form of allergic asthma and infectious diseases (e.g., tuberculosis) since the airway anatomy and the respond to inflammatory stimuli are similar to the human case. In large mammals, the rate of mucus permission in millimetres per minute is elevated compared with small rodents. Though, huge mammals also have longer comparatively slow in humans.

XIII. FACTORS INFLURNCING NASAL DRUG ABSORPTION[14][15]

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 a The factors influencing nasal drug absorption square measure represented as follows.

1. Physiochemical properties of drug

- Molecular size.
- Lipophilic-hydrophilic balance.
- Enzymatic degradation in cavum.

2. Nasal result

- Membrane porosity.
- Environmental pH
- Mucociliary clearance
- Cold, rhinitis.

3. Delivery result

- Formulation (Concentration, pH, osmolality) Delivery effects
- Drugs distribution and deposition.

CONCLUSION

The general expansion of drug delivery system depends on its efficiency, superiority and protection and to attain such characteristic there is a requirement of reliable evaluation methods to test them. This review provides an in-depth investigation of the growth in the evaluation of pulmonary drug delivery systems

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