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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. 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 intra nasally for topical, Systemic and central nervous system action. 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 formulation and recent advancement of nasal delivery system.

KEYWORDS: Naso-Pulmonary drug delivery, Mucociliary clearance, First pass metabolism, Proteins, Peptides.

1. INTRODUCTION

Nasal route of drug delivery 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. 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 muco-ciliary clearance mechanism. For many years, drugs have been administered nasally for both topical and systemic action.[1,2]

Topical administration includes the treatment of congestion, rhinitis, sinusitis and related allergic or chronic conditions. Prominent therapeutic classes of drugs delivered are decongestants for cold nasal symptoms and antihistamines and corticosteroids for allergic rhinitis The intranasal administration of drugs is an effective way for the systemic availability of drugs as compared to oral and intravascular routes of administration. It provided fast and extended drug absorption than oral and parenteral administration.[3,4]

Advantages

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.

2. ANATOMY AND PHYSIOLOGY OF NASAL CAVITY

The nasal cavity consists three main regions[5,6]

1) Nasal vestibule
2) Respiratory region

Major drug absorption.

15-20 % of the respiratory cells covered by layer of long

Cilia size 2-4 μm.

3) Olfactory region

Small area in the roof of the nasal cavity of about 10cm2

Drug is exposed to neurons thus facilitate it across the cerebrospinal fluid

- Normal pH of the nasal secretions in adult 5.5-6.5.
- Infants and young children 5.0- 6.7.
- Nasal cavity is covered with a mucous membrane. Mucus secretion is Composed of 95%-water, 2%-mucin, 1%-salts, 1%-of other proteins Such as albumin, lysozyme and lactoferrin and 1% of lipids.

3. MECHANISM OF DRUG ABSORPTION

Paracellular (intercellular): Slow and passive absorption of peptides and Proteins associated with Intercellular spaces and tight junctions.[6]

Transcellular: Transport Of lipophilic drugs passive diffusion/active transport.[7]

Transcytotic: Particle is taken into a vesicle and transferred to the cell.[8]

4. FORMULATION APPROACHES FOR NASOPULMONARY DRUG DELIVERY SYSTEM

Nasal gel

Nasal Drops

Nasal sprays

Nasal Powder

Liposome

Microsphere

4.1. Nasal drops

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. The main disadvantage of this system is the lack of the dose precision and therefore nasal drops may not be suitable for prescription products. It has been reported that nasal Drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.[9]

4.2. Nasal sprays

Both solution and suspension formulations can be formulated into Nasalsprays. Due to the availability of metered dose pumps and actuators, a nasal Spray can deliver an exact dose from 25 to 200 µm. The particles size And morphology (for suspensions) of the drug and viscosity of the Formulation determine the choice of pump and actuator assembly.[10]

4.3. Nasal powder

This dosage form may be developed if solution and suspension dosage Forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of Preservative and superior stability of the formulation. However, the Suitability of the powder formulation is dependent on the solubility, Particles size, aerodynamic properties and nasal irritancy of the active drug and /or excipients. Local application of drug is another advantage of this system.[11]

4.4. Liposomes

Liposomal Nasal solutions can be formulated as drug alone or in Combination with pharmaceutically acceptable excipients. Administered to the respiratory tract as an aerosol or solution for a Nebulizer, or as a microfine powder for insufflation, alone or in Combination with an inert carrier such as lactose, the particles of the Formulation have diameters of less than 50 microns.[12]

4.5. Microspheres

Specialized systems becoming popular for designing nasal products, as it provides prolonged contact with the nasal mucosa. Microspheres (in the powder form) swell in contact with nasal mucosa to form a gel and control the rate of clearance from the nasal Cavity. Thus increases the absorption and bioavailability by adhering to the nasal mucosa and increase the nasal residence time of drug.[13]

5. EVALUATION TESTS

5.1. Mucoadhesive testing

A 1x1 cm piece of goat nasal mucosa was tied to a glass slide using thread. Micro particles spread on the tissue specimen and the prepared glass slide was hung on one of the groves of a USP tablet disintegration test apparatus. The tissue specimen was given regular up and down movements in the beaker of the disintegration apparatus containing phosphate buffer pH6.4.Time required for complete washing of microparticles was noted.[13]

5.2. In vitro drug diffusion study

The drug diffusion from different formulation was determined using treated cellophane membrane and Franz diffusion cell. Drug was placed on cellophane membrane in the donor compartment contained phosphate buffer (pH 6.4). Samples were analyzed spectrophotometrically.[14]

5.3. In vitro drug release studies of the gels

1 ml of the gel was taken into a small test tube. The open end of the Test tube was closed with the nasal membrane of the pig by tying it With a thread. Then this was placed in a beaker containing the media. Measurement of Gelation Temperature (T1) and Gel Melting Temperature (T2): A 2ml aliquot of gel was taken in a test tube, immersed in a water bath. The temperature of water bath was increased slowly and left to equilibrate for 5min at each new setting.[15]

6. APPLICATION[15-17]

Currently the majority of intranasal products on the market are targeted toward local relief or the prevention of nasal symptoms. The trend toward the development of intranasal products for systemic absorption should rise considerably over the next several years. The development of these products will be in a wide variety of therapeutic areas from pain management to treatment for erectile dysfunction.

However, the primary focus of intranasal administration, correlated with increasing molecular scientific knowledge and methods, will be the development of peptides, proteins, recombinant products, and vaccines. The nasal cavity provides an ideal administration site for These agents because of its accessibility, avoidance of hepatic first-pass metabolism, and large vascular supply.

Future technologies in the intranasal arena will be concentrated on improved methods for safe, efficient delivery systems primarily for molecular agents, but also for numerous therapeutic categories.

6.1. Delivery of non-peptide Pharmaceuticals

Adrenal corticosteroids

- Sex hormones: 17ß-estradiol, progesterone, norethindrone, and Testosterone.
- Vitamins: vitamin B
- Cardiovascular drugs: hydralazine, Angiotensin II antagonist, Nitroglycerine, isosobide dinitrate, propranolol.
- CNS stimulants: cocaine, lidocaine
- Narcotics and antagonists: bupemorphine, naloxone

6.2. Delivery of peptide-based pharmaceuticals

- Peptides and proteins are hydrophilic polar molecules of High molecular weight, poorly absorbed. Absorption enhancers like surfactants, glycosides, cyclodextrin and glycols increase the bioavailability. Examples are insulin, calcitonin, pituitary hormones etc.

6.3. Delivery of diagnostic drugs

- Phenol sulfonphthalein is used to diagnose kidney function. Secretin for Pancreatic disorders of the diabetic patients.

6.4. Delivery of Vaccines through Nasal Routs

- Anthrax and influenza are treated by using the nasal vaccines, prepared by using the recombinant Bacillus anthracis protective antigen (rPA) and chitosan respectively.

6.5. Delivery of Drugs to Brain through Nasal Cavity

Conditions like Parkinson's disease, Alzheimer's disease or pain.

7. DELIVERY OF DRUGS THROUGH THE RESPIRATORY TRACT[17,18]

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

The conducting airway 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 bronchioles. The respiratory region consists 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. Themajor task of the lungs is gas exchange, by adding oxygen to, and removing carbon dioxide from the blood passing the pulmonary capillary bed.

Aerosol preparations are stable dispersions or suspensions of solid material and liquid droplets in a gaseous medium. The drugs, delivery By aerosols is deposited in the airways by: gravitational sedimentation, inertial impaction, and diffusion. Mostly larger drug particles are deposited by first two mechanisms in the airways, while the smaller Particles get their way into the peripheral region of the lungs by following diffusion.

There are three commonly used clinical aerosols

1. Jet or ultrasonic nebulizers,
2. Metered–dose Inhaler (MDI)
3. Dry-powder inhaler (DPI)

Devices

Nebulizers

Nebulizers are widely used as aerosolize drug solutions or suspensions for drug delivery to the respiratory tract and are particularly useful for The treatment of hospitalized patients. Delivered the drug in the form of mist.

There are two basic types

1) Air jet
2) Ultrasonic nebulizer

Dry powder inhalers (DPI): DPIs are bolus drug delivery devices that contain solid drug in a dry Powder mix (DPI) that is fluidized when the patient inhales. DPIs are typically formulated as one-phase, solid particle blends. The Drug with particle sizes of less than 5µm is used. Dry powder formulations either contain the active drug alone or have a Carrier powder (e.g. lactose) mixed with the drug to increase flow Properties of drug. DPIs are a widely accepted inhaled delivery dosage form, particularly In Europe, where they are currently used by approximately 40% of asthma patients.

Unit-Dose Devices Single dose powder inhalers are devices in which a powder containing Capsule is placed in a holder. The capsule is opened within the device And the powder is inhaled.

Multidose Devices: This device is truly a metered-dose powder delivery system. The drug Is contained within a storage reservoir and can be dispensed into the Dosing chamber by a simple back and forth twisting action on the base of the unit

Metered Dose Inhalers (MDI)

Used for treatment of respiratory diseases such as asthma and COPD.

They can be given in the form of suspension or solution.

8. 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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