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A REVIEW ON NASOPUIMONARY DRUG DELIVERY SYSTEM

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ABSTRACT

Nasopulmonary delivery system (NPDS) has produced a significant interest as a simple, reliable, and promising approach for the systemic administration of pharmaceuticals. The intranasal route can improve patient convenience, comfort, and compliance because it is basically painless and simple for the physician or patient to use. Higher drug absorption occurs through nasopulmonary route owing to large surface area, high vascularity, avoidance of hepatic first pass metabolism, and gastrointestinal tract destruction. The intranasal route has been identified as one of the foremost investigated area within the field of pharmaceutical research for the delivery of polar elements, hormones, vaccines, proteins, and peptides. Because the nasal mucosa offers several advantages for targeted delivery, a range of therapeutic substances can be used intranasally to elicit local, systemic, and central nervous system (CNS) effects. At present, NPDS has been investigated widely for direct drug delivery to the brain and CNS for rapid therapeutic action. Over the recent years, significant progress has been made in the treatment of lungs disease with local targeted delivery and reduced systemic side effects through the use of drugs in small doses. This chapter attempts to provide an overview on NPDS including its advantages, disadvantages, anatomy of the nasal cavity and airways, mechanism/factors affecting of drug absorption, intranasal dosage forms, newer drug formulations, and recent advancements in the field.

KEY WORDS

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

INTRODUCTION

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 Sign 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 .It can be a form of either topical administration or systemic administration, as the drugs thus locally delivered can go on to have either simply local or systemic effects.

Intranasal and pulmonary drug delivery offer advantages for compounds with poor oral bioavailability, such as peptides, proteins, and polar drugs. Intranasal administration bypasses the blood-brain barrier, allowing direct delivery of CNS-active compounds. Pulmonary delivery, via inhalation, rapidly absorbs drugs except large macromolecules, which may require permeation enhancers (surfactants, fatty acids, saccharides, chelating agents, and enzyme inhibitors). Key considerations include protein stability, pH maintenance, and prevention

of denaturation. The pulmonary route's large absorptive area, thin mucosal membranes, and good blood supply make it ideal for local and systemic therapy, particularly for respiratory diseases like asthma and COPD.[1]

ADVANTAGES :

Intranasal Delivery:

- Bypasses blood-brain barrier
- Suitable for CNS-active compounds
- Ideal for poor oral bioavailability compounds

Pulmonary Delivery:

- Rapid absorption, Good blood supply
- Large absorptive area (up to 100m²),Thin mucosal membranes (0.1 µm)
- Suitable for respiratory diseases (asthma, COPD),Requires permeation enhancers for large macromolecules

DISADVANTAGES

- Pathological conditions such as allergies and cold may alert significantly the nasal bioavailability .
- The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet early established.
- Relative inconvenient to patient when compared to oral delivery systems since they possibility of some irritation.

Anatomy and physiology of nose and Pulmonary system

The nasal cavity consists three main regions

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.

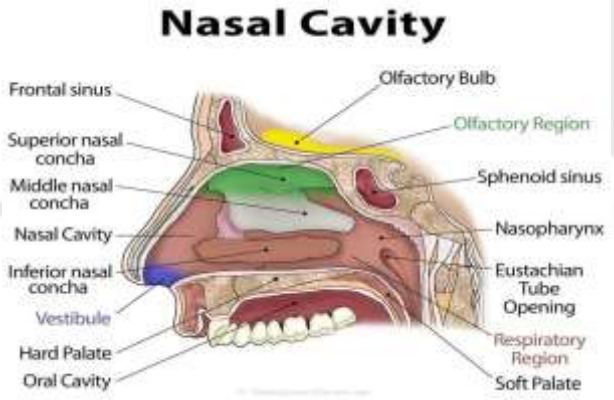

Fig.1.Anatomy & physiology of nose

3. Olfactory region

- Small area in the roof of the nasal cavity of about 10 cm2 is exposed to neurons thus facilitate it across the cerebro-spinal fluid.Drug
- 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.
- Mucussecretion is composed of 95%-water,2%-mucin,1%-salts,1%-of other proteins Such as albumin, lysozyme and lactoferrinand 1%-lipids.

PULMONARY SYSTEM

Vestibule: The vestibule is the first area of the respiratory system to come into touch with the outside world. The vestibule is lined by stratified squamous epithelium, in contrast to the rest of the nasal cavity. Airflow and the Nasal Valve: The nasal valve is located just behind the nasal vestibule. It is bordered inferiorly by the lower rim of the pyriform aperture, medially by the septum, and laterally by the caudal end of the upper lateral cartilage.
Nasal Septum: This structure increases the overall mucosal surface area by dividing the nasal cavity into two distinct compartments. It is composed of a posterior bony element made up of the perpendicular plate of the ethmoid and the vomer, and an anterior cartilaginous piece that supports the nasal tip. Turbinates: These are three, and occasionally four, projections that resemble scrolls.

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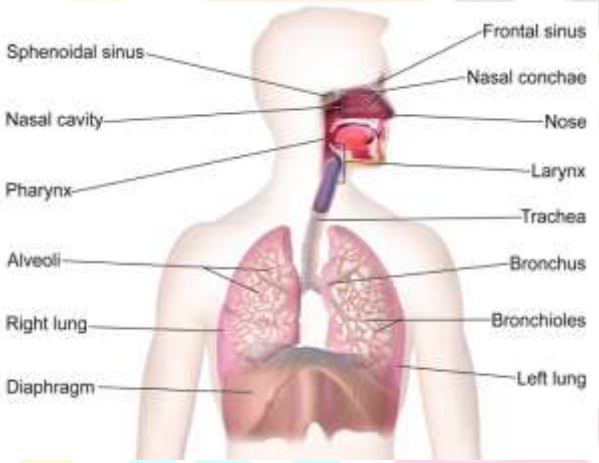


Fig. 2. Anatomy & physiology of respiratory system

Turbinates: The lateral nasal wall has three, and in rare cases, four, scroll-like projections called turbinates. In terms of function, the two lower turbinates—known as the inferior and middle turbinates—are the most important. Every turbinate has a bony structure.

lungs: The main components of the human respiratory system are the lungs. Mammals and the majority of other vertebrates have two lungs, one on each side of the heart, close to the backbone. In the respiratory system, they are responsible for the extraction of oxygen from the atmosphere and its subsequent transfer into the bloodstream, as well as the gas exchange process that releases carbon dioxide from the bloodstream into the ambient.

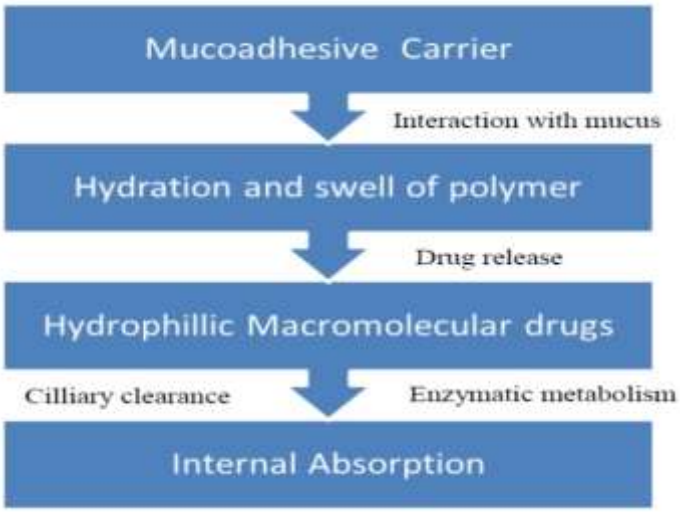
The bronchi are primarily lined by goblet and ciliated cells. Along with a small number of Kulchitsky cells, there are also some serous, brush, and Clara cells.

The ciliated cuboidal cells that line the bronchioles constitute the main component. As the airways advance, the amount of Clara cells rises while the frequency of goblet an

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.[2,3,4,5]

MECHANISM OF DRUG ABSORPTION IN THE NASOPULMONARY DRUD DELIVERY SYSTEM

- Two mechanisms have been considered generally 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.[15]



- 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
- Paracellular (intercellular) : slow and passive absorption of peptides and proteins associated with intercellular and tight junctions.
- Transcellular(intracellular) : Transport of lipophilic drugs passive /Active diffusion
- Transcytotic : particle taken into a vesicles and transferred to the cell [17,6,7]

PATHWAY FOR DRUG DELIVERY VIA NASAL ROUTE

- Nasal cavity: The initial entry point for the drug.
- Olfactory route: Pathway for drugs to reach the brain directly.
- Brain tissue: Target organ for certain drugs.
- Cerebrospinal fluid (CSF): Another potential pathway for drugs to reach the brain.
- Circulation: Drugs entering the bloodstream for systemic distribution.
- Tissues/Organs: Target sites for the drug's action.
- Elimination: Routes through which the drug is removed from the body.[3,29,23]

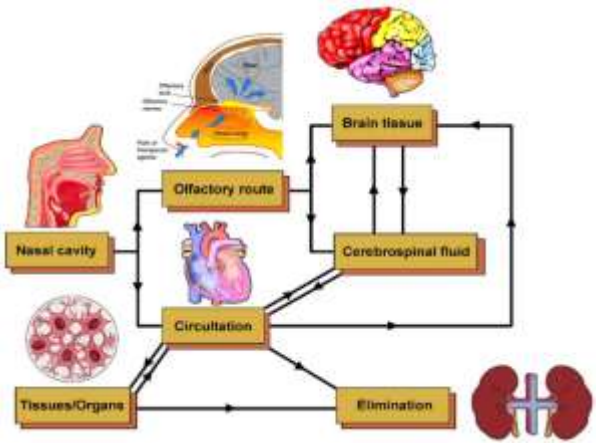


Fig. 3. Pathways for drug delivery via nasal route

FACTORS INFLUENCING NASOPULMONARY DRUG DELIVERY SYSTEM

Several factors have an effect on the general bioavailability of medication that square measure administered through the nasal route. The factors may be touching to the physiochemical properties of the medication, the anatomical and physiological properties of the cavum and therefore the sort and characteristics of chosen nasal medication delivery system. These factors play key role for many of the medication so as to achieve therapeutically effective blood levels once nasal administration. The factors influencing nasal drug absorption square measure represented as follows.

1. Physiochemical properties of drug.
    - Molecular size
    - Lipophilic-hydrophilic balance.
2. Enzymatic degradation in cavum.
    - Nasal result
    - Membrane permeability
3. Environmental pH
    - Mucociliary clearance
    - Cold, rhinitis, Delivery result
    - Formulation (Concentration, pH, osmolality) Delivery effects.[11,12,28]

DOSAGE FORM IN NASO-PULMONARY DRUG DELIVERY SYSTEM

1. Nasal Drops:

- Convenient and simple

- Suitable for local conditions (e.g., allergies, congestion)

- Challenges: microbial growth, mucosal dysfunction, dose precision

- Advantage: efficient deposition of human serum albumin

2. Nasal Sprays:

- Solution and suspension formulations

- Metered dose pumps and actuators provide exact dosing (25-200 µm)

- Particle size and viscosity determine pump/actuator choice

3. Liposomes:

- Phospholipid vesicles encapsulating drug in aqueous compartments
- Enhance absorption, protect from degradation

4. Microspheres:

- Enhance absorption, sustained release
- Protect drug from enzymatic degradation
- Important role in nasal drug delivery

Key Benefits:

- Targeted delivery for local conditions
- Enhanced absorption and bioavailability
- Protection from degradation and precise dosing.

Applications:

- Allergies .

5. Rhinyle Catheter:

- Delivers drops to specific nasal cavity region
- Catheter filled with formulation, blown into nose via mouth
- Accurate dosing, mainly for experimental studies

6. Compressed Air Nebulizers:

- Device converts liquid medication into inhalable mist
- Uses compressed air, oxygen, or ultrasonic power
- Breaks up solutions/suspensions into small aerosol droplets
- Commonly used for respiratory treatments (e.g., asthma, COPD)

Nebulizer Benefits:

- Targeted delivery to respiratory tract
- Rapid onset of action
- Reduced side effects
- Effective for corticosteroids and bronchodilators (e.g., salbutamol, ipratropium)

7.Squeezed Bottle:

- Used for decongestants
- Simple plastic bottle with jet outlet
- Contamination risk due to air intake
- Dose accuracy and deposition vary with administration mode

- Not recommended for children due to difficulty controlling dose

8. Insufflators:

- Deliver drug substances for inhalation

- Use straw or tube with drug substance and optional syringe

- Particle size increased due to insufficient disaggregation

- High coefficient of variation for initial deposition areas

- Often use pre-dosed powder doses in capsules

9. Dry Powder Inhalers (DPIs):

- Deliver dry powder formulations for local or systemic effect

- Contain solid drug, suspended or dissolved in non-polar propellant

- Commonly used for respiratory diseases (asthma, COPD, bronchitis)

- Also used for diabetes mellitus treatment

10.Pressurized Metered-Dose Inhalers (MDIs)

Deliver specific amount of medication to lungs as aerosolized burst

- Commonly used for asthma, COPD, and other respiratory diseases

Medications:

- Bronchodilators, Corticosteroids, Combination therapies

- Mast cell stabilizers (e.g., cromoglicate, nedocromil)[10,13,14]

FORMULATION OF INHALERS:

Dry power inhalers:

- The dry-powder-inhalers are designed to deliver drug/excipients powder to the lungs.
- Dry powder inhalers (DPls) are devices through which a dry powder formulation of an active drug is delivered for lo cal 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.
- Excipients used in DPI are used as carrier for Active Pharmaceutical Ingredient (API). Most commonly used carrier is Lactose Monohydrate.[27]

ACTIVE INGREDINT	BRAND	MANUFACTURE	COUNTRY
Terbutalin 0.25mg	Bricanyl	Astrazeneca	UK
Salbutamol	Salbutamol dry powder inhales	Cipla limited	India
Fluticasone propionate	Flixotide	Glaxo smithkalin	UK

Table.1. Dry powder inhalers markated drugs

Formulation of DPI mainly includes following three steps;

a. API Production The important requirement of API in case of DPI is particle size. Particle size of drug should be less than 5 um. / It should be in the range of 2-5 pm.

b. Formulation of API with or without carriers.

- The part of carrier in DPI is enhancing the flow property of powder. After drug and carrier have separately been brought to their desired forms, they are combined in the blending

c. Integration of the formulation into device

- After the formulation has been blended, it is filled into capsules.
- Currently there are two types:
- * Unit dose devices: * Multi dose Devices:
- 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.[18]

Metered Dose inhalers (MDI)

- A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs. It is the nmost 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.
- Pressurized metered aerosols may be formulated as either solutions or suspensions of drug in the liquefied propellant.
- Compared with suspension formulations, solution MD0s offer the benefits of homogenous formulation.
- The basic requirements for formulation of MD0s are containers, propellants, and metering valve.
- Filling Metered Dose inhaler : flled by propellant pressure. liquefying at reduced temperature or elevated pressure .
- Additional propellants is then added at the same temperature. [22]

➢ ACTIVE INGREDINT	BRAND	MANUFACTURE	COUNTRY
Salbutamol 100mg	Asthalin	Cipla	India
Albuterol	Ventolin	Glaxosmithkline	India
Fluticasone50mg	Flixotide	Glaxosmithkline	New zealand

Table.2.Meterd dose inhaler markated products

NASAL SPRAYS

- Most of the pharmaceutical nasal preparations Aerosole on the market containing solutions, emulsions or suspensions are delivered by metered-dose pump sprays .
- Nasal sprays, or nasal mists, are used for the nasal delivery of a drug or drugs, either locally to generally alleviate cold or allergy symptoms such as nasal congestion or systemically.
  Although delivery methods vary, most nasal sprays function by instilling a fine mist into the nostril by action of a hand-operated pump mechanism.
- The three main types available for local effect antihistamines, corticosteroids, and topical decongestants
- Metered- dose pump sprays include the container, the pump with the valve and the actuator.
- The dose accuracy of metered-dose pump sprays is dependent on the surface tension and viscosity of the formulation.
- For solutions with higher viscosity, special pump and valve combinations are on the market. [19,20]

Some marketd product in india

Fig. 4. Markated products in india

Pressurized Metered-Dose Inhalers (MDIs)

Deliver medication to the lungs as a short burst of aerosolized medicine. They are commonly used to treat respiratory diseases such as asthma and COPD. MDIs contain bronchodilators, corticosteroids, combination therapies, and mast cell stabilizers. The advantages of MDIs include their portability, wide dosage range, dose consistency, protection of contents, and quick readiness for use. This results in rapid relief from symptoms,

targeted delivery to the lungs, and reduced side effects. MDIs are a popular and effective treatment option for respiratory diseases, offering convenience, precision, and rapid relief.

AEROSOLS : Aerosol preparations are stable mixtures of solid particles and liquid droplets suspended in a gas. Drug delivery via aerosols relies on three deposition mechanisms:

1. Gravitational sedimentation (larger particles)

2. Inertial impaction (larger particles)

3. Diffusion (smaller particles, reaching peripheral lung regions)

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.
- Nebulizers are used in aerosol drug delivery produce a poly-disperse aerosol where the drug delivered in the particles size range 1-5 um in diameter.
- Most Nebulizers use compressed air for atomization, but some use ultrasonic energy.
  There are two basic types:

  1) Air jet

  2)Ultrasonic nebulizer

1)Jet Nebulizer:

- This uses compressed gas to make an aerosol (tiny particles of medication in the air).
  Jet nebulizer.
- bulizers are applicable for acute and domiciliary treatment of various respiratory diseases, pediatric and adult medical practices.
- These types of nebulizers required 2-10 L\min withdraw medication a capillary tube from the reservoir of the nebulizer.
- It may cause generate a wider range of particles which blasted into One or more baffles (to convert larger particles to smaller particles) out of suspension and return them to nebulizer:

2) Ultrasonic Nebulizer.

- This makes an aerosol through high frequency vibrations.
- The particles are larger than with a jet nebulizer.
- This nebulizer generates vibrations, which are transferred to solution surface that would create waves, and those waves produce aerosol. We can say that these types of nebulizers are large volume nebulizers to deliver hypertonic saline for sputum induction.
- Ultrasonic nebulizers work on the principle that converts electrical energy to high-frequency vibrations using a transducer.

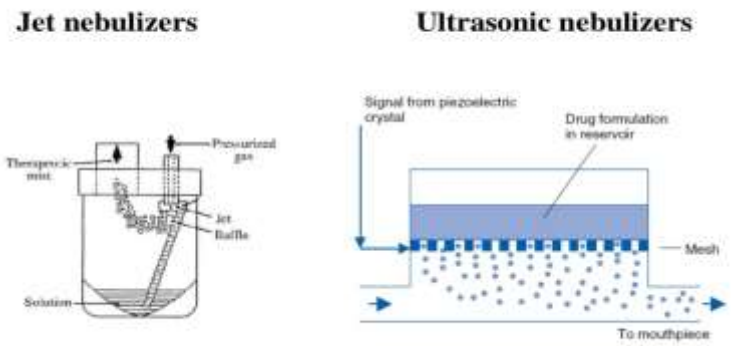


Fig.5. Jet nebulizer,ultrasonic nebulizer

Metered Dose Inhalers (MDI)

- They can be given in the form of suspension or solution.
- Particle size of less than 5 microns.
- Used to minimize the number of administrations errors. It can be deliver measure amount of medicament accuratly

- **Fig.6. Metered dose inhaler**

Advantage of MDI

- It delivers specified amount of dose.
- Small size and convenience.
- Usually inexpensive as compare to dry powder inhalers and nebulizers.
- Quick to use.
- Multi dose capability more than 100 doses available

Disadvantages of MDI

- Require propellants
- Difficult to deliver high doses
- Additional cost

- Possible dosing error

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.Thedrug 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 flowproperties 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.

Advantages

- Less need for patient co-ordination.
- Less formulation problems.
- Dry powders are at a lower energy state, which reduces the rate of chemical degradation.

Disadvantages

- Dependency on patient's inspiratory flow rate and profile.
- Greater potential problems in dose uniformity.
- More expensive than pressurized metered dose inhalers.
- Not available worldwide.[22]

RECENT ADVANCES

The DirectHaler™ Pulmonary device platform :

- DirectHaler™ Pulmonary is an innovative and new device for dry powder Each pre-metered, pre-filled pulmonary dose has its own DirectHaler™ Pulmonary device.
- The device is hygienically disposable and is made of only 0,6 grammes of Polypropylene.
- DirectHaler™ Pulmonary offers effective, accurate and repeatable dosing in an intuitively easy-to-use device format Sensitive powders Deep lung deliveryHigh drug payloadsNew types of combination dosing
- The powder dose is sealed inside the cap with a laminate foil strip,which is easily torn off for dose-loading into the PowderWhirl chamber, before removing the cap and delivering the Dose.
    - Sensitive powders
    - Deep lung delivery
    - High drug payloads
    - New types combinations.

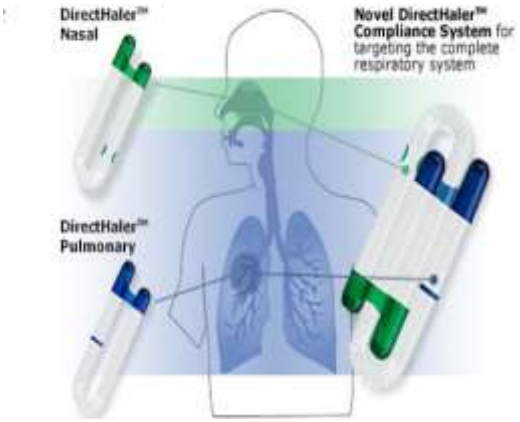
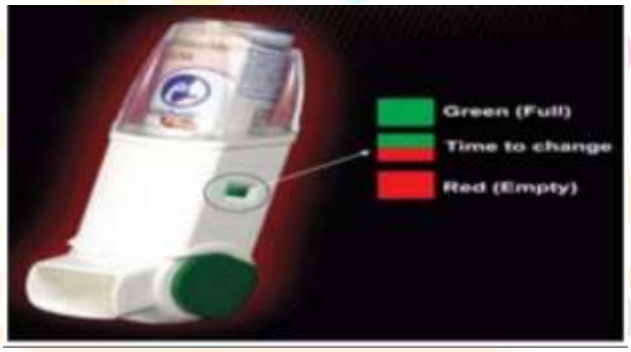


Fig.7Direct haler pulmonary device

Newer Development

Dr Reddy's launches 'Dose Counter Inhalers' in India Friday, April 16, 2010



Dr Reddy's Laboratories (DRL) has launched an innovation in the metered dose inhaler (MDI) space with launch of 'Dose Counter Inhalers (DCI) for the first time in India. This the first MDI in India that gives patients an advance indication of when the inhaler is going to be empty. DCI is a new drug delivery device with a single device having 120 metered doses. There is a window in the inhaler that changes color from green to red. Green indicates the inhaler is full and red indicates the inhaler is empty. Half green and half red in the window indicate it's time to change the inhaler.[30]

FUTURE PERSPECTIVES AND CHALLENGES

With several possible uses, NDDS is a drug delivery system that shows promise. NDDS has a bright future ahead of it, and in the years to come, major advancements in this subject should be expected.

The nasal drug delivery system (NDDS) holds great promise for the future. Expanded applications of nanotechnology will enhance drug solubility, permeability, and targeting, revolutionizing treatment options. Additionally, customized NDDS systems will cater to individual patient needs, considering factors like age, sex, and health status. Furthermore, NDDS will facilitate the delivery of complex medications, such as proteins and vaccines, which are challenging to administer through conventional channels.

However, safety profiles and regulatory issues must be addressed. As medical devices, NDDS are subject to FDA regulations in the United States. To ensure approval, they must meet FDA safety and efficacy standards. While NDDS generally have a good safety profile, common side effects include nosebleeds, coughing, headaches, sneezing, dry nose, and nasal mucosa irritation. Adhering to strict regulations and maintaining strong safety profiles is essential for improving patient outcomes and advancing medication administration. Effective regulation ensures the safe and effective development of NDDS, ultimately enhancing patient care.[21]

APPLICATIONS OF NASOPULMONARY DRUG DELIVERY SYSTEMS

Because they may effectively target both the upper and lower respiratory tract, nasopulmonary drug delivery systems have great potential for a variety of therapeutic applications.One possibleuse is in the management of respiratory conditions such cystic fibrosis, asthma, and (COPD) chr0nic obstructive pulmonary device.
There are numerous possible uses for nasal drug delivery systems (NDDS), such as:

Applications:

1. Local delivery to nose and lungs for respiratory disorders (infections, allergies, COPD, asthma)

2. Systemic delivery for rapid absorption or poorly absorbed oral medications

3. Direct delivery to the brain for brain tumors, Parkinson's, Alzheimer's

Respiratory Disorders Treatment:

1. Asthma: bronchodilators, corticosteroids, anti-inflammatory agents

2. COPD: bronchodilators, other medications

3. Cystic fibrosis: antibiotics, improved lung function

4. Lung cancer: targeted chemotherapy, reduced side effects

Additional Research:

1. Diabetes

2. Pain management

3. Neurological disorders

NDDS offer targeted and efficient treatment options for various diseases, enhancing patient outcomes and quality of life.[13,14]

Regulatory considerations

Nasal spray approved by FDA

Today, the U.S. Food and Drug Administration approved neffy (epinephrine nasal spray) for the emergency treatment of allergic reactions (Type I), including those that are life-threatening (anaphylaxis), in adult and pediatric patients who weigh at least 30 kilograms (about 66 pounds).

“Today’s approval provides the first epinephrine product for the treatment of anaphylaxis that is not administered by injection. Anaphylaxis is life-threatening and some people, particularly children, may delay or avoid treatment due to fear of injections,” said Kelly Stone, MD, PhD, Associate Director of the Division of Pulmonology, Allergy and Critical Care in the FDA’s Center for Drug Evaluation and Research. “The availability of epinephrine nasal spray may reduce barriers to rapid treatment of anaphylaxis. As a result, neffy provides an important treatment option and addresses an unmet need.”[25]

Evaluation of Nasal drug delivery

In vitro studies

- In the case of nasal powders : Particle size , melting point and angle repose and carr's index
- In case of nasal gels : mucoadhessive strength and flow property.
- In case of nasal spray : Clarity of liquid, sterilization and content of drug delivery etc.

- In case of nasal drops : Clarity test , sterilization.

In vivo studies

- Various animal compartment models are Used for In vivo evaluation study.
- Most convenient model is anesthetized rat model.
- For most non peptide drugs the results obtained in rats can accurately reflect The absorption profile in human.
- Some other animal models

1)Rabbit model

2)Dog model

3)monkey model etc.[16,24,25]

CONCLUSION

Nasal Drug Delivery Systems (NDDS) hold tremendous promise for the future. With its non-invasive administration, rapid absorption, and bypass of first-pass metabolism, the nasopulmonary route offers numerous benefits. The nasal cavity's rich blood supply and extensive surface area make it an ideal channel for systemic medication delivery.

Despite its potential, NDDS faces challenges such as nasal mucociliary clearance and limited drug permeability. However, ongoing advancements in formulation technologies and nasal drug delivery devices are poised to overcome these hurdles.

As research continues to evolve, NDDS is expected to play a significant role in drug delivery, offering:

- Targeted treatment for respiratory disorders

- Systemic delivery for various diseases

- Direct brain delivery for neurological conditions

- Improved patient outcomes and quality of life

The future of NDDS looks bright, with anticipated major breakthroughs in the years to come.[8,9]

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