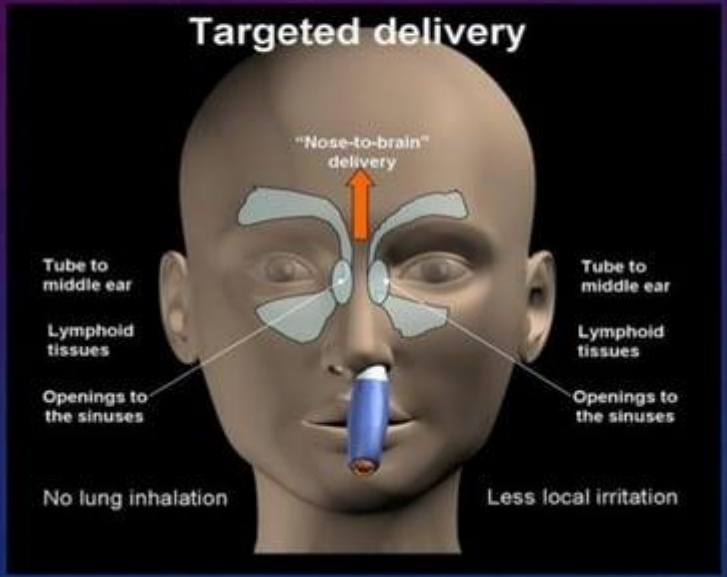
Nasal Drug Delivery



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 symptomatic relief and prevention or treatment of topical nasal conditions has been widely used for a long period of time.
- ✓ However, recently, the nasal mucosa has seriously emerged as a therapeutically viable route for the systemic drug delivery.

Introduction

- ✓ In general, among the primary targets for intranasal administration are pharmacologically active compounds with poor stability in gastrointestinal fluids, poor intestinal absorption and/or extensive hepatic first-pass elimination, such as peptides, proteins and polar drugs.
- ✓ 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 biophase of central nervous system (CNS)-active compounds.
- ✓ It has also been considered to the administration of vaccines.
- ✓ The pulmonary and nasal delivery of biologics is intuitively attractive; it is an easy, non-invasive administration route with readily targetable portals - the mouth and the nostrils.

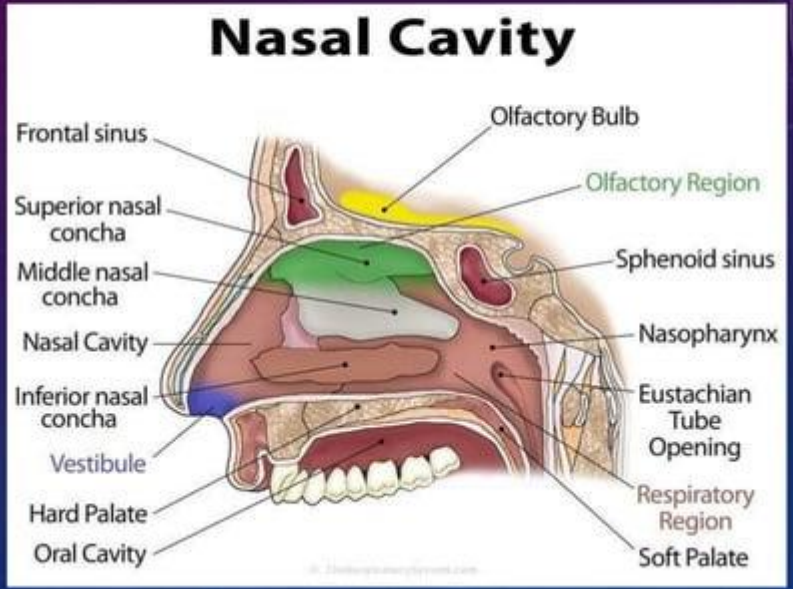
Advantages

- ✓ Hepatic first pass metabolism avoided.
- ✓ Rapid drug absorption and quick onset of action.
- ✓ Bioavailability of larger drug molecules can be improved by means of absorption enhancer.
- ✓ BA for smaller drug molecules is good.
- ✓ Convenient for long term therapy, compared to parenteral medication.
- ✓ Drugs possessing poor stability G.I.T fluids given by nasal route.
- ✓ Easy and convenient.
- ✓ Easily administered to unconscious patients.

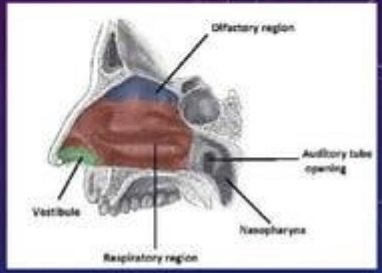
Disadvantages

- ✓ 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 systems since there is a possibility of nasal irritation.
- ✓ Nasal cavity provides smaller absorption surface area when compared to GIT.

Anatomy & Physiology of Nasal Cavity



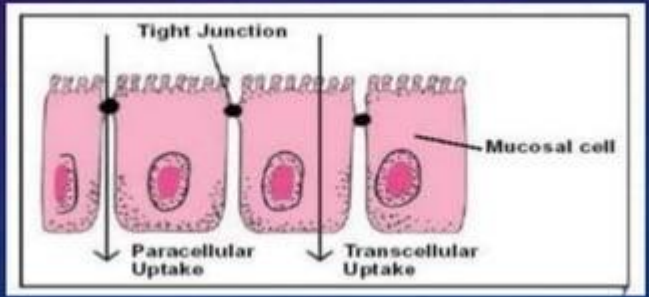
Parts of Nasal Cavity



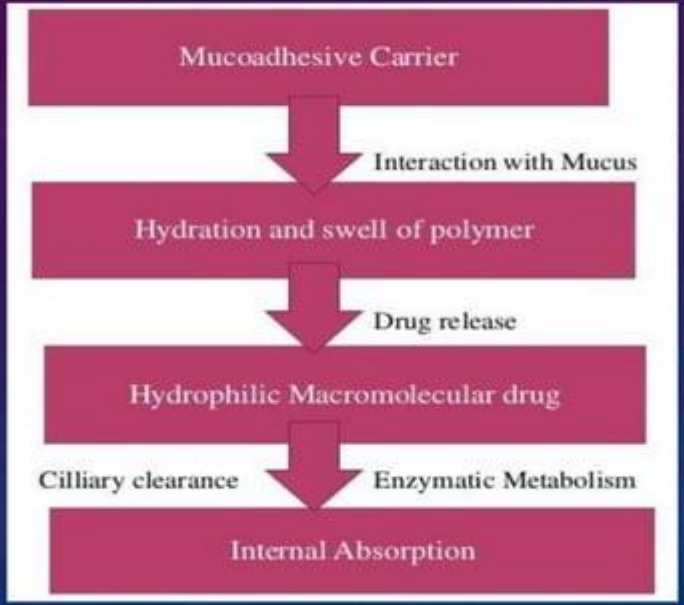
- ✓ The nasal cavity consists three main regions:
  - 1) Nasal vestibule
  - 2) Respiratory region
    - ✓ major drug absorption.
    - ✓ 15-20 % of the respiratory cells covered by layer of long
    - ✓ cilia size 2-4 μm.
  - 3) Olfactory region
    - ✓ small area in the roof of the nasal cavity of about 10 cm2
    - ✓ drug is exposed to neurons thus facilitate it across the cerebro-spinal 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% of water, 2% of mucin, 1% of salts, 1% of other proteins like albumin, lysozyme and lactoferrin and 1% of lipids.

Mechanism of Drug Absorption

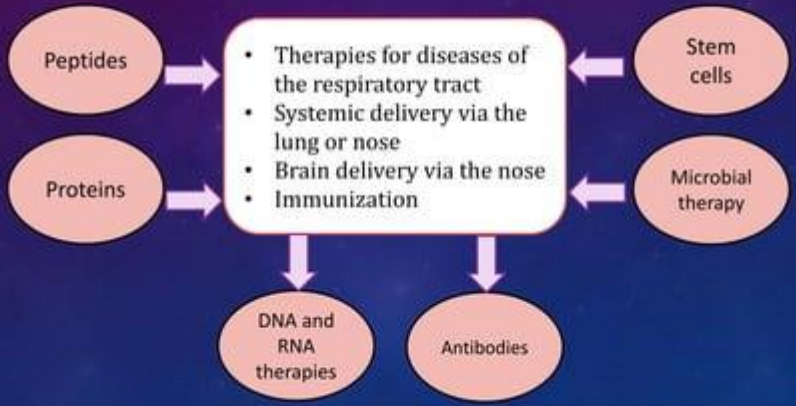
- ✓ Paracellular(intercellular) Slow and passive absorption of peptides and proteins associated with intercellular spaces and tight junctions.
- ✓ Transcellular: Transport of lipophilic drugs passive diffusion/active transport.
- ✓ Transcytotic: Particle is taken into a vesicle and transferred to the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



Mucoadhesive Nasal Drug Delivery



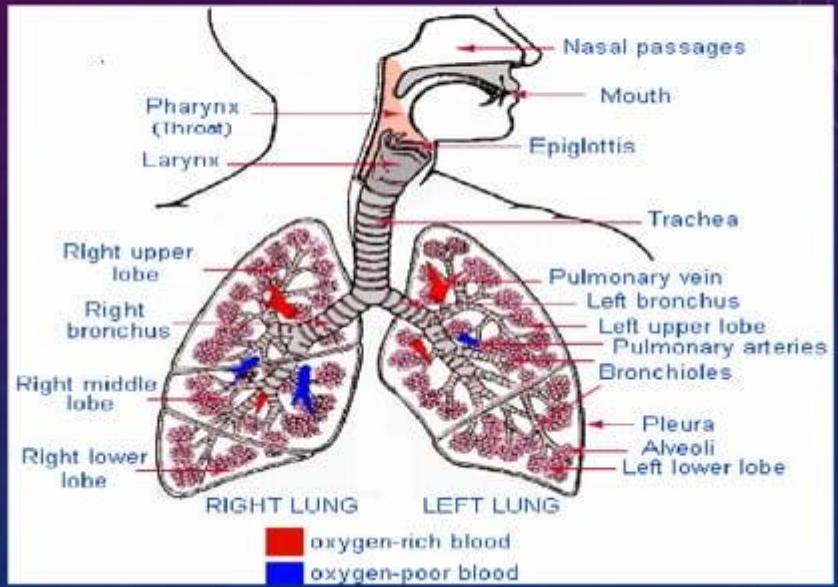
Potential for nasal and pulmonary delivery of biologics



Formulation Approaches

- ✓ Nasal gels
- ✓ Nasal Drops
- ✓ Nasal sprays
- ✓ Nasal Powder
- ✓ Liposome
- ✓ Microspheres

Pulmonary Drug Delivery System



Introduction: Pulmonary Drug Delivery System

- ✓ The respiratory tract is one of the oldest routes used for the administration of drugs.
- ✓ 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).
- ✓ This type of drug application in the therapy of these diseases is a clear form of targeted drug delivery.
- ✓ Currently, over 25 drug substances are marketed as inhalation aerosol products for local pulmonary effects and about the same number of drugs are in different stages of clinical development.

Introduction: Pulmonary Drug Delivery System

- ✓ The drug used for asthma and COPD e.g. β2-agonists such as salbutamol (albuterol), Terbutaline formoterol, corticosteroids such as budesonide, Flixotide or beclomethasone and mast-cell stabilizers such as sodium cromoglycate or nedocromil.
- ✓ The latest and probably one of the most promising applications of pulmonary drug administration is
- ✓ Its use to achieve systemic absorption of the administered drug substances.
- ✓ Particularly for those drug substances that exhibit a poor bioavailability when administered by the oral route, as for example peptides or proteins, the respiratory tract might be a convenient port of entry.

Advantages

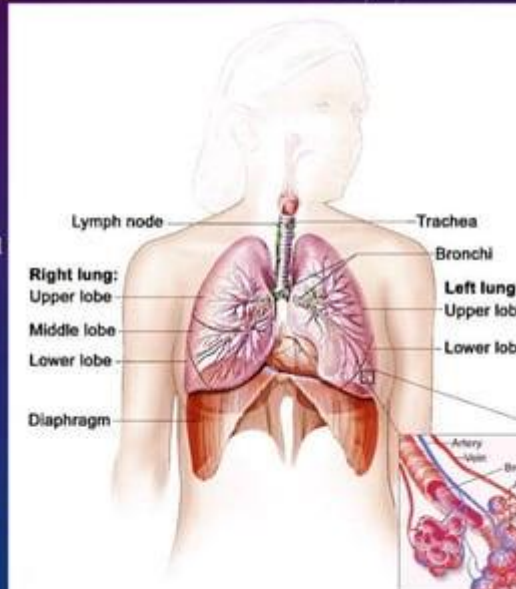
- ✓ It is needle free pulmonary delivery.
- ✓ It requires low and fraction of oral dose.
- ✓ Pulmonary drug delivery having very negligible side effects since rest of body is not exposed to drug.
- ✓ Onset of action is very quick with pulmonary drug delivery.
- ✓ Degradation of drug by liver is avoided in pulmonary drug delivery.

Disadvantages

- ✓ Stability of drug in vivo.
- ✓ Transport.
- ✓ Targeting specificity.
- ✓ Drug irritation and toxicity.
- ✓ Immunogenicity of proteins
- ✓ Drug retention and clearance.

The Respiratory Tract

- ✓ 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.
- ✓ The major task of the lungs is gas exchange, by adding oxygen to, and removing carbon dioxide from the blood passing the



Nasal sprays

- ✓ Both solution and suspension formulations can be formulated into nasal sprays.
- ✓ 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.

Types of nasal sprays and their benefits

- **Steroid nasal sprays**
  - A steroid nasal spray is an effective way of treating common nasal conditions.
  - In fact in cases of persistent, moderate or severe allergic rhinitis it is the first line of treatment.
  - A steroid nasal spray, if used as prescribed, will not cause a rebound effect or dependency.
  - It works topically on the nasal lining and is safe even if a small amount is swallowed and enters the bloodstream.

Types of nasal sprays and their benefits

- ✓ **Saline sprays and rinses**
  - ✓ Saline rinses and sprays are a safe and effective option for long-term relief of the symptoms of allergic rhinitis and chronic sinusitis.
  - ✓ These rinses and sprays use a salt solution to flush out the nasal cavity, which relieves nasal congestion.
- ✓ **Menthol nasal sprays**
  - ✓ A nasal spray with menthol-containing compounds can also be used for the temporary relief of nasal congestion.
  - ✓ This type of nasal spray works by acting on the menthol receptor in the nose but doesn't actually relieve nasal congestion, even though the patient may feel better.

Dry Powder Inhalers

- ✓ A dry powder inhaler (DPI) is a breath-activated device that aerosolizes a set dose of micronized drug in the solid state on an airstream.
- ✓ The DPI provides certain advantages regarding drug stability, ease of handling, and range of possible dose weights to be administered.
- ✓ A dry-powder inhaler (DPI) is a device that delivers medication to the lungs in the form of a dry powder.
- ✓ DPIs are commonly used to treat respiratory diseases such as asthma, bronchitis, emphysema and COPD although DPIs (such as Inhalable insulin) have also been used in the treatment of diabetes mellitus.

Dry Powder Inhalers

- ✓ DPIs are an alternative to the aerosol-based inhalers commonly called metered-dose inhaler (or MDI).
- ✓ The DPIs may require some procedure to allow a measured dose of powder to be ready for the patient to take.
- ✓ The medication is commonly held either in a capsule for manual loading or in a proprietary form inside the inhaler.
- ✓ Once loaded or actuated, the operator puts the mouthpiece of the inhaler into their mouth and takes a sharp, deep inhalation (ensuring that the medication reaches the lower parts of the lungs), 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.

Basic technique for using a DPI

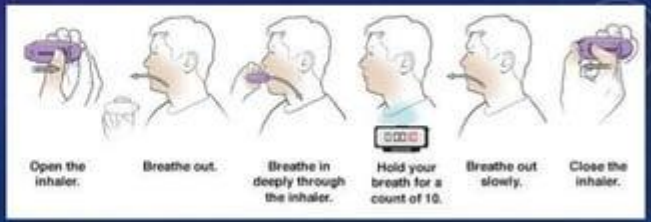
- ✓ Exhale away from device
- ✓ Put mouthpiece in your mouth
- ✓ Breathe in quickly

Advantages of DPI

- ✓ Breath-actuated
- ✓ Spacer not necessary
- ✓ No need to hold breath after inhalation
- ✓ Portable
- ✓ No propellant
- ✓ Less need for patient co-ordination.
- ✓ Less formulation problems.

Disadvantages of DPI

- ✓ Dependency on patient's inspiratory flow rate and profile.
- ✓ Device resistance and other design issues.
- ✓ Greater potential problems in dose uniformity.
- ✓ More expensive than pressurized metered dose inhalers.
- ✓ Not available worldwide
- ✓ Adequate inspiratory flow required for medication delivery
- ✓ May result in high pharyngeal deposition
- ✓ Humidity potentially causes powder clumping and reduced dispersal of fine particle mass

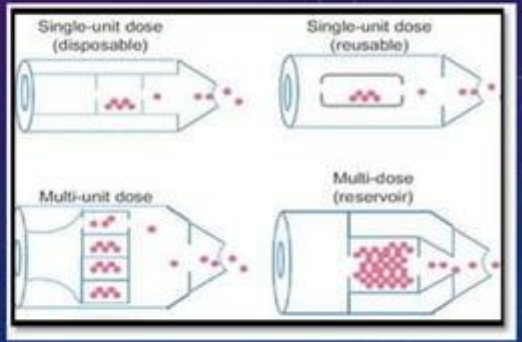


Unit-dose devices

- ✓ 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.

Multi-dose 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.



Marketed Products-DPI

- ✓ Aerolizer®
- ✓ Diskus®
- ✓ Ellipta™
- ✓ Flexhaler®
- ✓ Handihaler®
- ✓ Neohaler®
- ✓ Pressair™
- ✓ Rotahaler®
- ✓ Turbuhaler®
- ✓ Twisthaler®

Marketed Products DPI

Active Ingredient	Brand	Manufacturer	Country
Terbutaline 0.25mg	Bricanyl	AstraZeneca	UK
Beclometasone dipropionate 250mcg	Becloforte	Cipla Limited	India
Fluticasone propionate	Flixotide	GlaxoSmith Kline	United Kingom
Salbutamol	Salbutamol Dry Powder Capsules	Cipla Limited	India
Ipratropium Bromide 20 mcg	ATEM	Chiesi Farmaceutici	Italy
Xinafoate	Seretide Evohaler	GlaxoSmithKline	UK

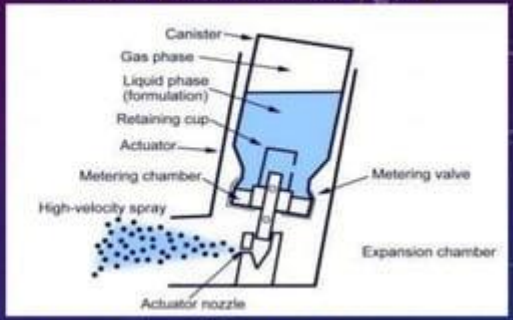
Metered Dose Inhalers

- ✓ Inhaled respiratory medications are often taken by using a device called a metered dose inhaler, or MDI.
- ✓ The MDI is a pressurized canister of medicine in a plastic holder with a mouthpiece.
- ✓ When sprayed, it gives a reliable, consistent dose of medication.
- ✓ A metered-dose inhaler is a small, hand-held device filled with medicine.
- ✓ It helps deliver a certain amount of medicine through the mouth and into the lungs.
- ✓ It is commonly used to treat breathing difficulties related to asthma, chronic obstructive pulmonary disease (COPD), and other respiratory problems.

Metered Dose Inhaler (MDI)

Advantages 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.
- ✓ Portability
- ✓ Multidose delivery capability
- ✓ Lower risk of bacterial contamination.



Disadvantages of MDI

- ✓ Difficult to deliver high doses.
- ✓ There is no information about the number of doses left in the MDI.
- ✓ Accurate co-ordination between actuation of a dose and inhalation is essential.
- ✓ Need for correct actuation and inhalation coordination.
- ✓ Oropharyngeal drug deposition.
- ✓ Possible flammability of hydrofluoroalkane (HFA) propellants.

Difference in MDI and DPI- Formulation Perspective

Formulation: MDI/DPI

MDI

- Propellant based (HFA/CFC)
- Solution/suspension
- Contains surfactant and lubricants
- Coordination necessary (newer developments address this question)

DPI

- Non-propellant based
- Solid particles
- Might contain lactose
- Patient controls inhalations (but lung function might affect deposition)

Comparison in MDI and DPI

MDI	DPI
High velocity aerosols	Aerosol velocity depends on inspiratory flow rate
Requires hand breath co-ordination	No hand breath co-ordination needed
Delivery of medicines independent of external factors	Delivery of medication largely dependent on external factors
Time consuming to teach	Easy to teach
Requires deep& slow breathing only	Requires high inspiratory flow>28L/min

Marketed Products MDI

Active Ingredient	Brand	Manufacturer	Country
Salbutamol pressurised inhalation (100µg)	Asthalin	Cipla	India
albuterol	Ventolin	GlaxoSmithKline	India
levalbuterol HCl	Xopenex	3M Pharmaceuticals	U.S.A.
Fluticasone50 µg	Flixotide	GlaxoSmithKline	New Zealand
Formoterol Fumarate12 mcg		Ultratech	India