DRUG DELIVERY TO RESPIRATORY SYSTEM

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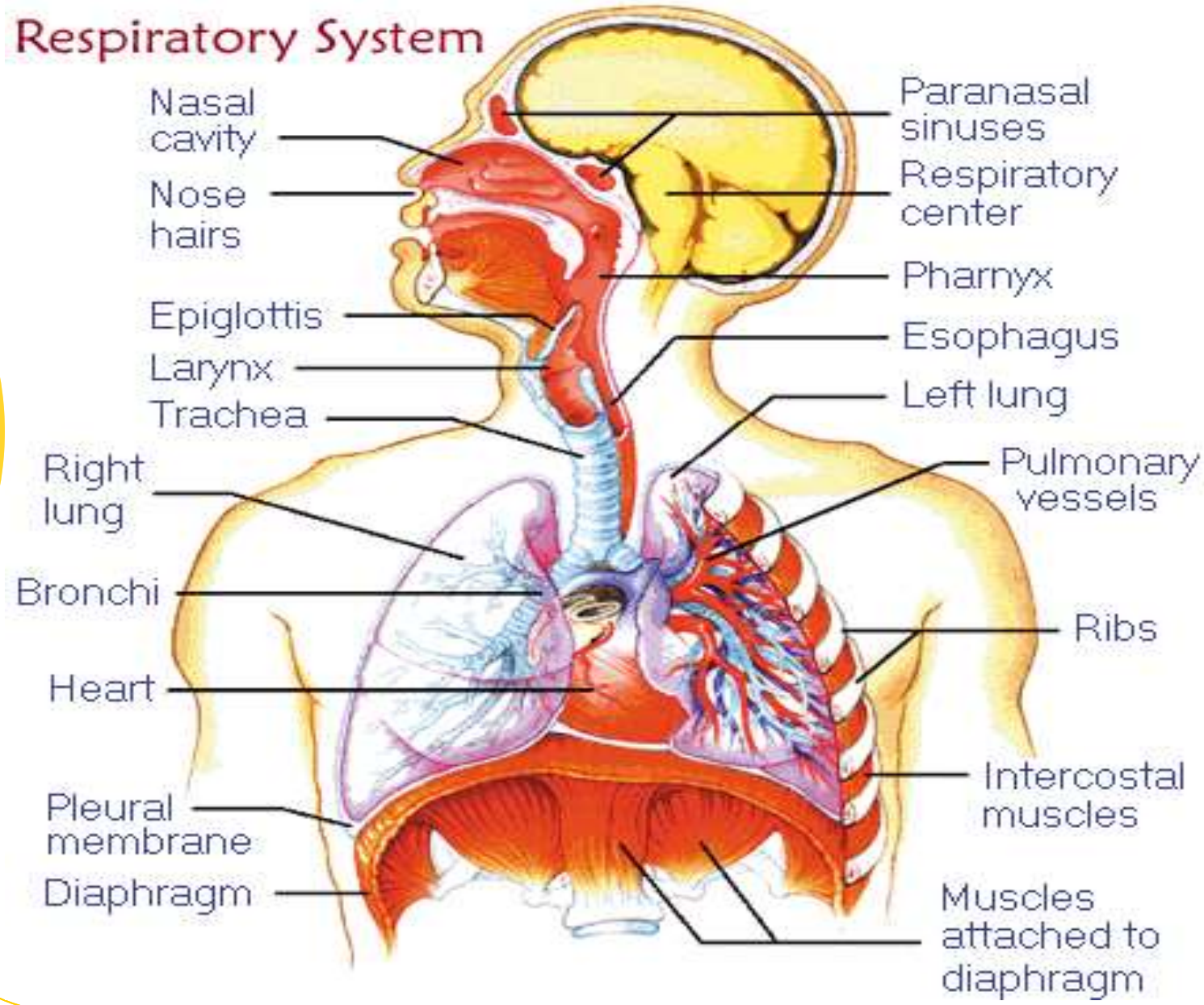
General Respiratory Anatomy and Physiology

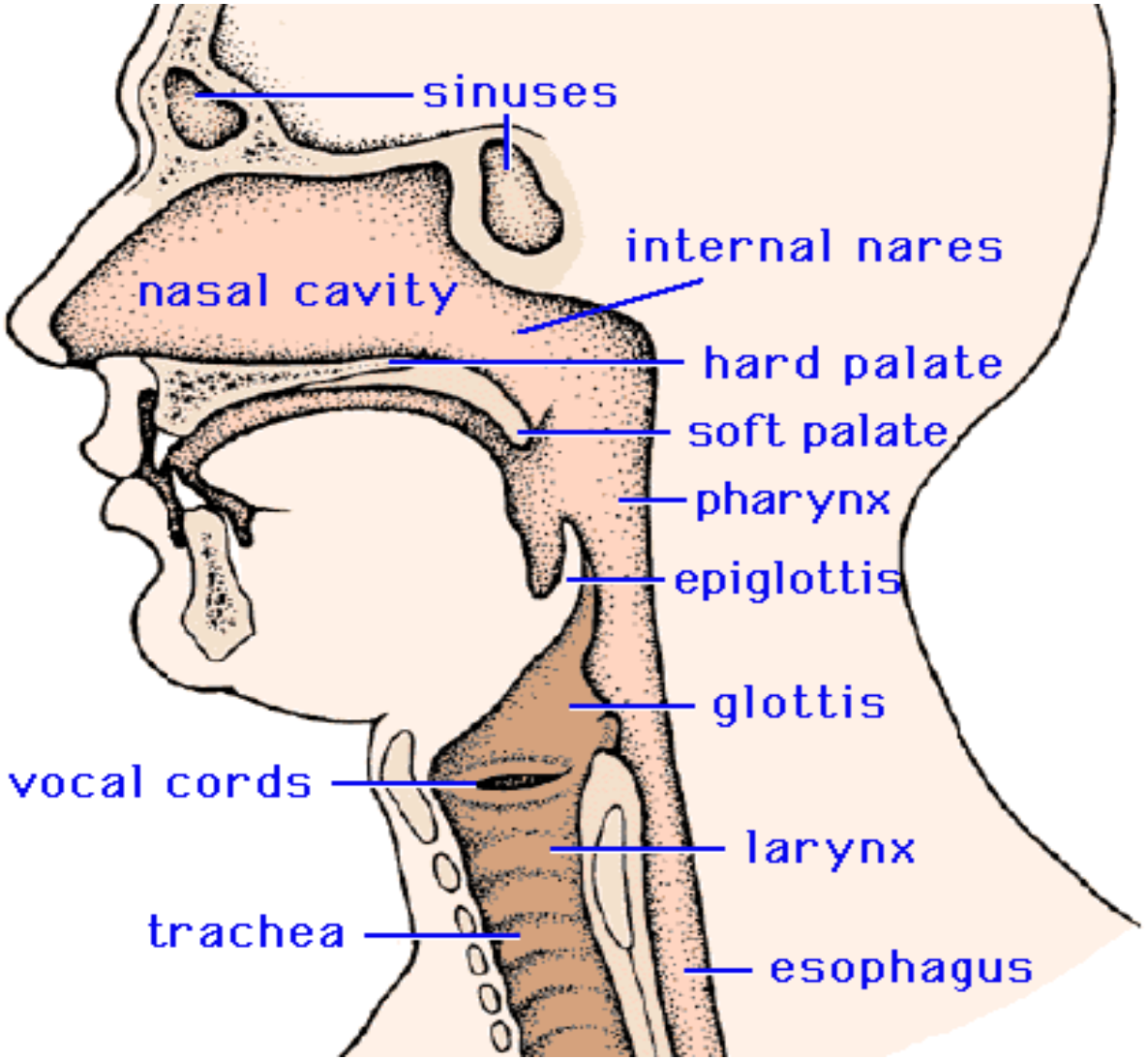
A. The respiratory system is comprised of the upper airway and lower airway structures.

B. The upper respiratory system filters, moistens and warms air during inspiration

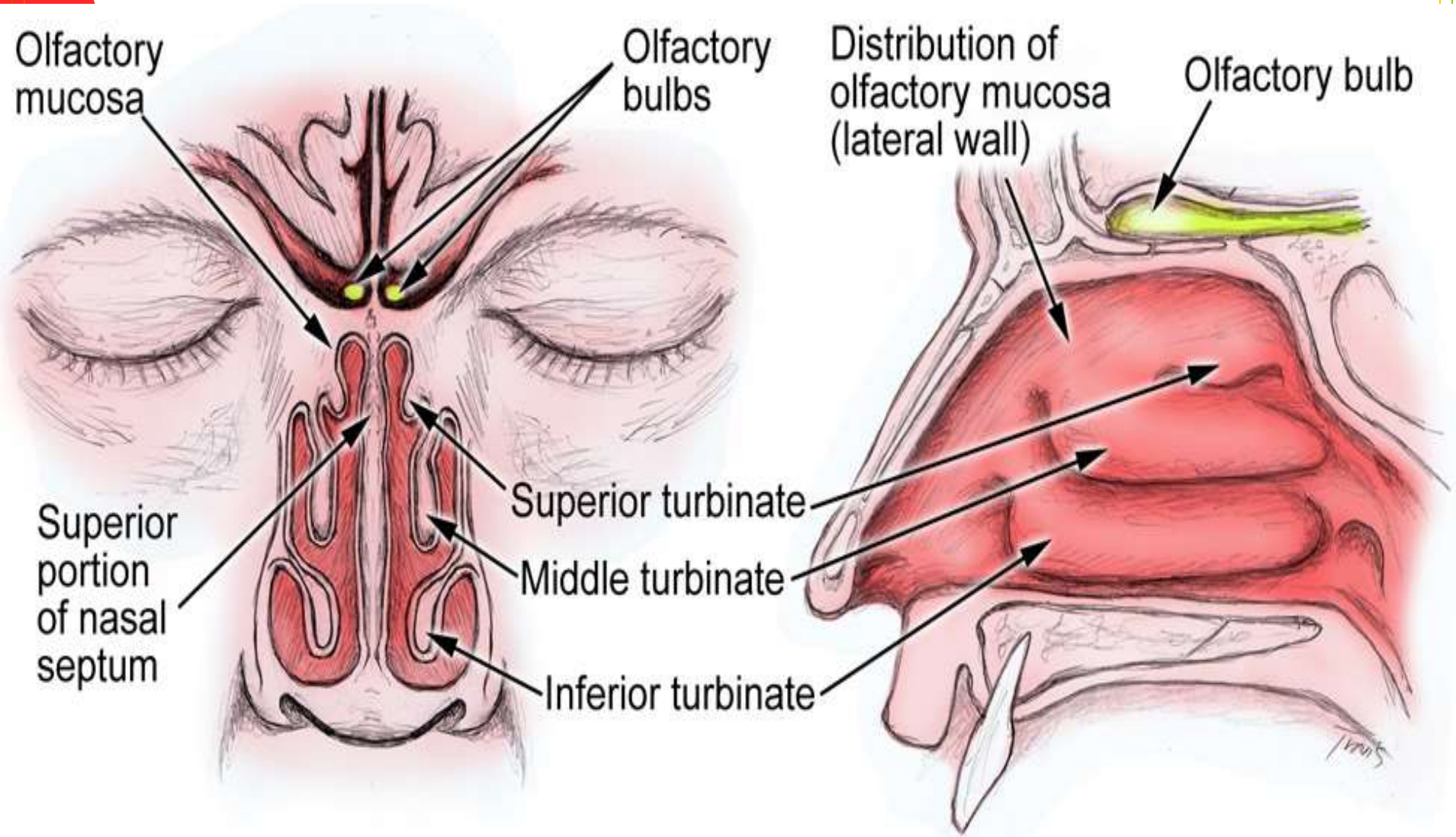
C. The lower respiratory system enables the exchange of gases to regulate serum PaO_2 (partial pressure of oxygen in arterial blood) , $PaCO_2$ (partial pressure of carbon dioxide in arterial blood) and Ph (partial pressure of hydrogen in blood) .

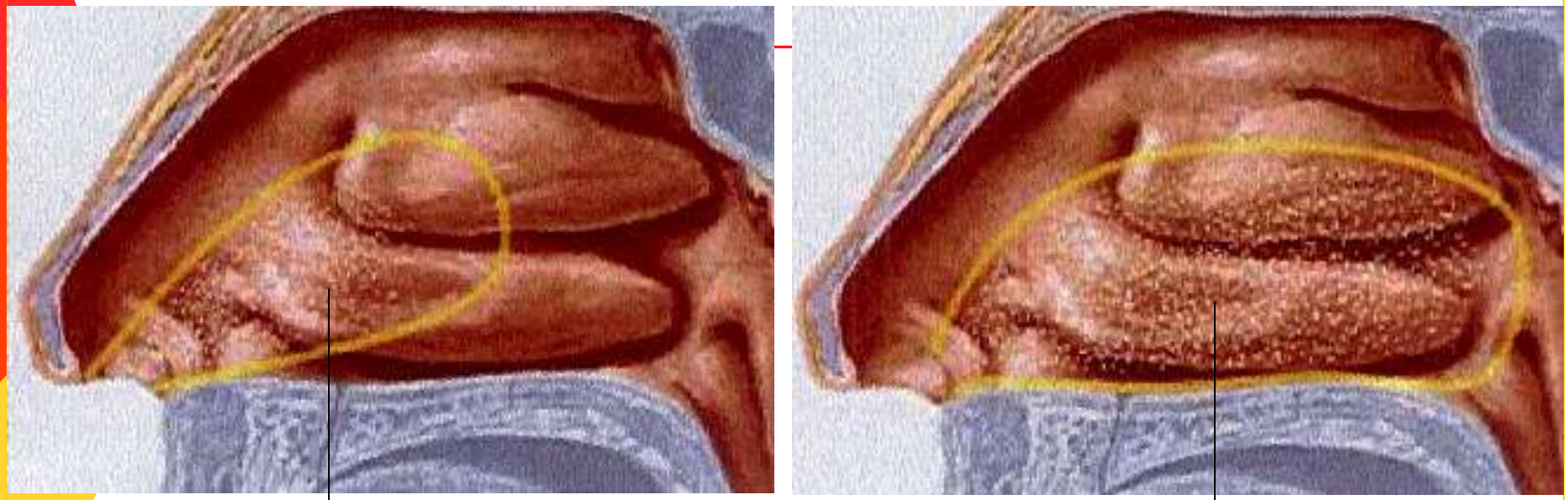

Respiratory System
Nasal cavity
Nose hairs
Epiglottis
Larynx
Trachea
Right lung
Bronchi
Heart
Pleural membrane
Diaphragm
Paranasal sinuses
Respiratory center
Pharnyx
Esophagus
Left lung
Pulmonary vessels
Ribs
Intercostal muscles
Muscles attached to diaphragm

UPPER RESPIRATORY TRACT



ANOTOMY OF HUMAN NASAL CAVITY





Site of drug spray & absorption

Advantages of Nasal Drug Delivery System

1) Drug degradation that is observed in the gastrointestinal tract is absent.
2) Avoidance of Hepatic first – pass metabolism..
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) Direct transport into systemic circulation and CNS is possible

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) Convenient for the patients, especially for those on long term therapy, when compared with parenteral medication.

8) Good penetration, especially lipophilic, low molecular weight drugs through the nasal mucosa. For instance the absolute nasal availability of fentanyl is about 80%.

LIMITATIONS

1) The histological toxicity of absorption enhancers used in nasal drug delivery system is not yet clearly established.
2) Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritation.
3) Nasal cavity provides smaller absorption surface area when compared to GIT.
4) Volume that can be delivered into nasal cavity is restricted to 25–200 µl.
5)Normal defense mechanisms like mucocillary clearance and ciliary's beating affects the permeability of drugs

Therapeutic class of drugs

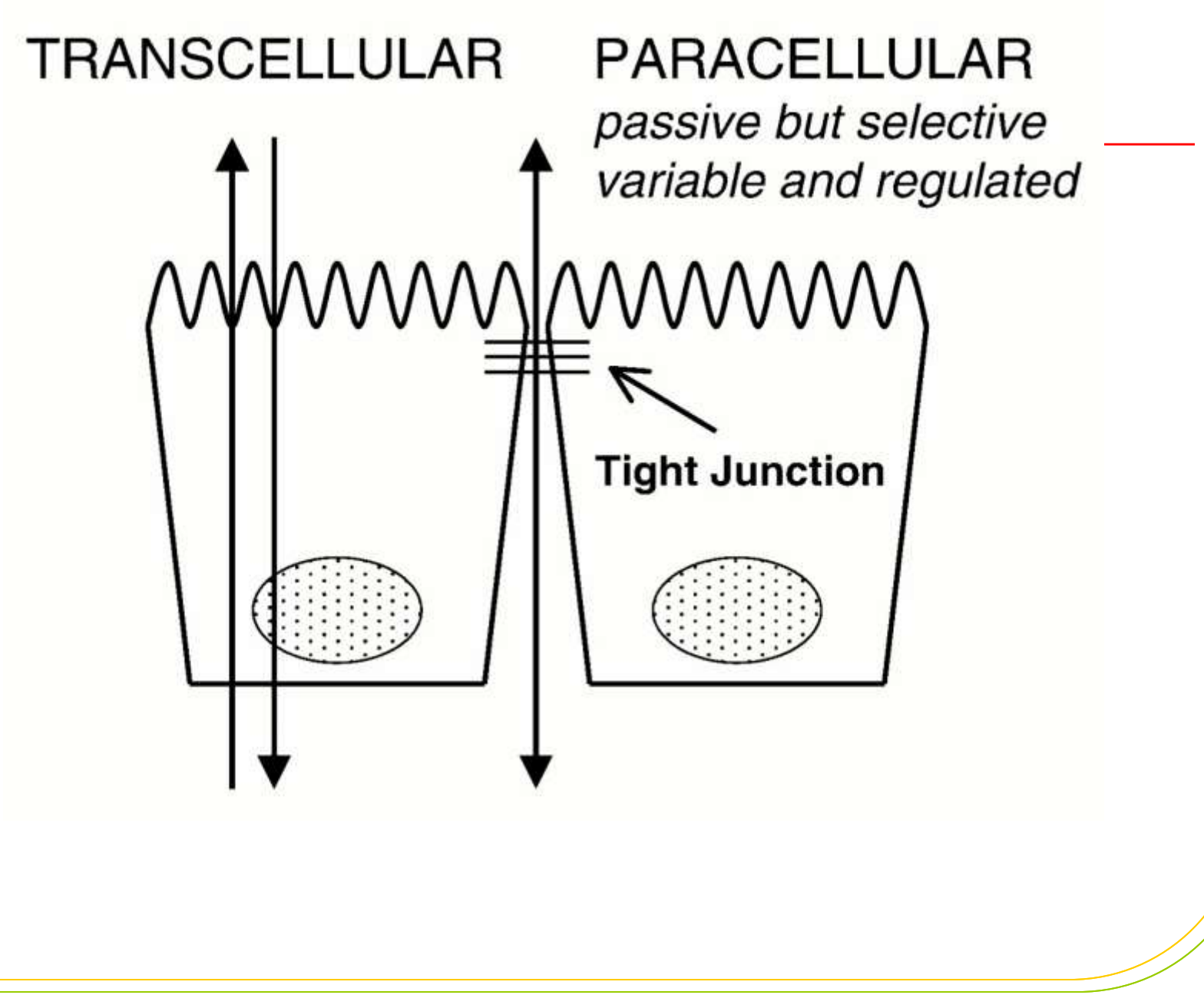
1. β_2 adrenergic agonists
2. Corticosteroids
3. Antiviral
4. Antibiotics
5. Antifungal
6. More recently, vaccines

MECHANISM OF DRUG ABSORPTION

- The first step in the absorption of drug from the nasal cavity is passage through the mucus. Small, uncharged particles easily pass through this layer. However, large or charged particles may find it more difficult to cross.
- The following two mechanisms have been considered predominantly to explain nasal absorption

1. Paracellular route
2. Transcellular process

1. The first mechanism involves an aqueous route of transport, which is also known as the paracellular route. This route is slow and passive. Poor bioavailability was observed for drugs with a molecular weight greater than 1000 Daltons.
2. The second mechanism involves transport through a lipoidal route that is also known as the transcellular process and is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity.


TRANSCELLULAR
PARACELLULAR
passive but selective
variable and regulated
Tight Junction

Factors effecting the bioavailability of drugs following intranasal administration

- **Physiological factors**
  - Speed of mucous flow
  - Blood flow
  - Pathological conditions of Nasal Cavity
  - Change in Physiological State
- **Dosage form factors**
  - Concentration of active drug
  - Physicochemical properties of drug
  - pH, Viscosity & Lipophilicity of drug
- **Administration factors**
  - Volume administered
  - Site of deposition
  - Mechanical loss into esophagus & other regions

NASAL PHYSIOLOGICAL FACTORS

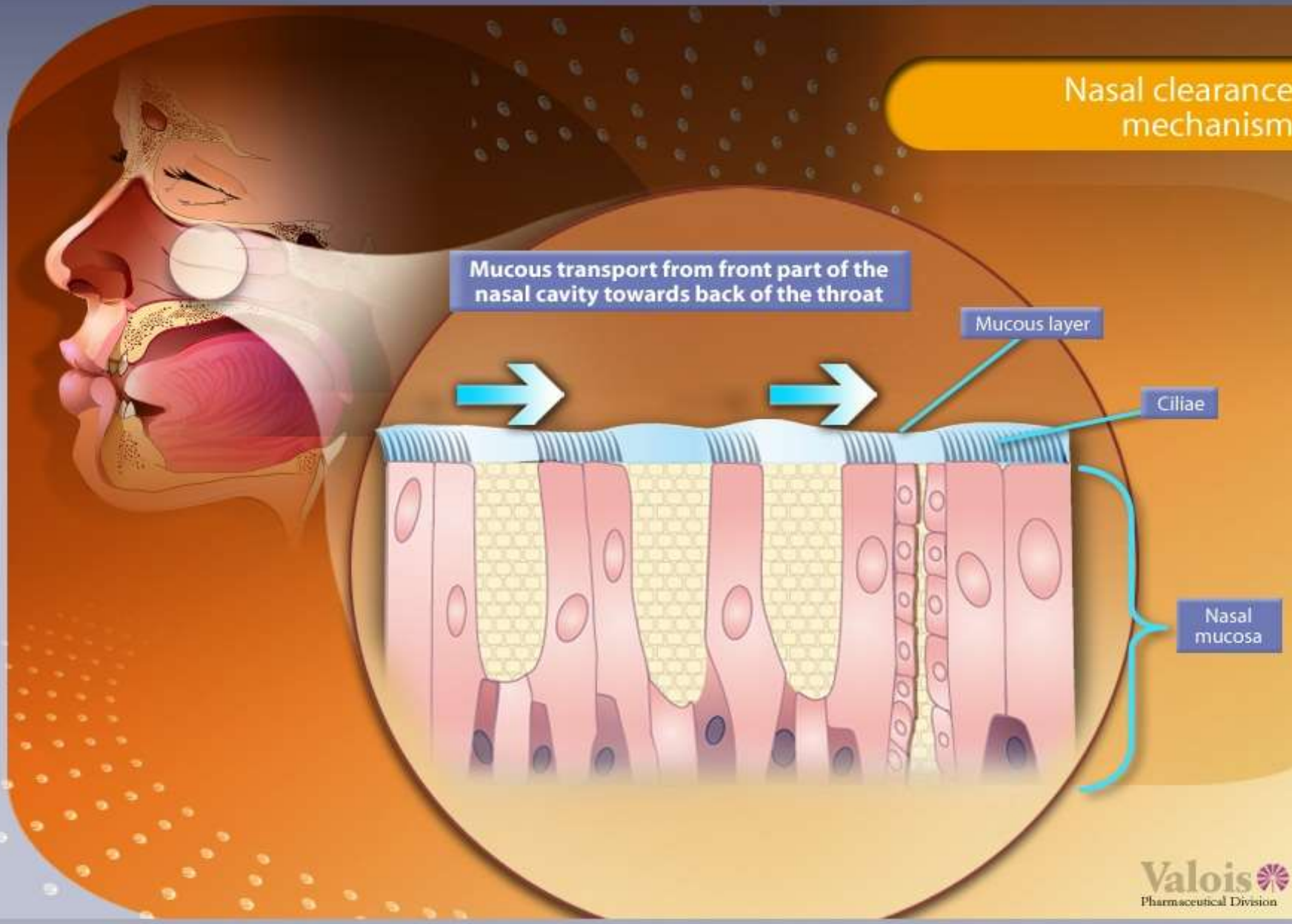
- ***Blood flow***

As the blood flow rate increases the amount of drug that reaches the general circulation also increases.

Mucociliary clearance (MCC)

One of the functions of the upper respiratory tract is to prevent noxious substances (allergens , bacteria , viruses , toxins etc) from reaching the lungs . When such materials adhere to , or dissolve in the mucus lining of the nasal cavity , they are transported towards the nasopharynx for eventual discharge into the GIT. Clearance of this mucus and the absorbed / dissolved substances is called the MCC.

Nasal clearance mechanism



Valois
Pharmaceutical Division

FORMULATION FACTORS

pH, Concentration,

The pH of the nasal formulation should be adjusted to 4.5-6.5.
Concentration gradient plays very important role in the absorption / permeation process of drug through the nasal membrane due to nasal mucosal damage.

Viscosity

A higher viscosity increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation.
At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.

Osmolarity

Drug absorption can be affected by tonicity of the formulation. Shrinkage of epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity.

FACTORS RELATED TO DRUG

Molecular weight, lipophilicity and pKa

- On increasing lipophilicity, the permeation of the compound normally increases through nasal mucosa.
- In general, the passage across biomembranes is affected not only by lipophilicity/hydrophilicity, but also by the amount of drug existing as uncharged species. This depends on the drug pKa and the pH of the absorption site (5.0-6.5 in human nasal mucosa)
- Large particles (> 7 microns) will be lost in the gastrointestinal tract
- Small particles (< 3 microns) will be lost in exhaled breathe
- Intermediate particles (3 to 7 microns) reach the actual site of action

- Since the rate of absorption for most compounds is rapid, the extent of absorption is dependent on physiological factors such as rate of nasal secretion, ciliary movement and metabolism.

- The greater the rate of nasal secretion and the faster the ciliary movement, the smaller the bioavailability will be

Pharmacokinetics of Nasal Absorption

- The bioavailability of drug following intranasal route is given as

$$Ae = \frac{(AUC)_{i.n}\ (Dose)_{i.v}}{(AUC)_{i.v}\ (Dose)_{i.n}}$$

Zero order Kinetics

$$dX_B/dt = Ko - Ke\ X_B$$

where Ko is Zero order absorption rate constant
Ke is overall elimination constant

$$Cp = Ko/Cl\ (1 - e^{-ket})$$

where Cl is total body clearance
t time interval following drug administration

- First order kinetics

$$dX_B/dt = F\ X_{IN}\ Ka - Ke\ K_B$$

where Ka is first order absorption rate constant
F is fraction of applied dose absorbed
X_{IN} is amount of drug administered to absorption site
X_B is the amount of drug in central compartment
Ke is overall elimination constant

$$Cp = \frac{F\ XO_{IN}\ Ka}{V(\ Ka-Ke)} \left(e - {}^{K_e t} - e^{-k\ a^t} \right)$$

where XO_{IN} is initial dose applied to site of absorption at time zero

Nasal Administration

- The drugs employed for nasal delivery can be classified as
  1. Drugs administered for local action
  2. Drugs administered for systemic effects

Profile of an ‘ideal’ drug candidate for nasal delivery

- Appropriate aqueous solubility to provide the desired dose are about 0.25 to 0.3 ml per nostril.
- Appropriate nasal absorption properties
- No nasal irritation from the drug
- Low dose. Generally, below 25 mg per dose
- No toxic nasal metabolites
- Suitable stability characteristics

Formulation Excipients

SOLUBILIZERS

- Sometimes, it is necessary to use solubilizers in nasal formulations.
- One can use the conventional approach which includes the use of co-solvents. Some commonly used co-solvents include glycols, small quantities of alcohol.

BUFFER COMPONENTS

- Various conventional buffer systems can be used to buffer nasal formulations.
- It should be kept in mind that secretions can alter the formulation pH. A high buffer capacity is important to maintain in situ formulation pH.

ANTIOXIDANTS

- Depending upon the stability profile of a given drug in the formulation chosen, it may be necessary to use antioxidants to prevent drug degradation.
- Typically, sodium metabisulfite, sodium bisulfite, are used. Usually, antioxidants are used in small quantities and they may not affect drug absorption or cause any nasal irritation.

PRESERVATIVES

- Nasal formulations usually contain preservatives to protect them from microbial contamination.
- Parabens, benzalkonium chloride and benzoyl alcohol are some typically used preservatives.

HUMECTANTS

- To avoid any nasal irritation by formulation humectants are usually added to formulations.
- Some common humectants used include glycerin, sorbitol, and mannitol.

GELLING /VISCOFYING AGENTS

- Some formulations need to be gelled or made more viscous as formulation viscosity can affect drug absorption.

ENHANCEMENT IN NASAL ABSORPTION

Generally, the absorption enhancers act via one of the following mechanisms

- Inhibit enzyme activity.
- Reduce mucus viscosity or elasticity.
- Decrease mucociliary clearance.
- Open tight junctions.
- Solubilize or stabilize the drug.

General Approaches

1. Viscosity Modifiers
2. Absorption Enhancers
3. Bio adhesive Polymers
4. Colloidal Drug Delivery Systems

VISCOSITY MODIFIERS

- Increase nasal residence time of formulation and thus drug.
- Spray solutions with 0.25% methyl cellulose for administration of Desmopression and HPMC in other formulations.

ABSORPTION ENHANCERS

- Penetration enhancers act by increase in membrane fluidity by extracting proteins from nasal membrane & creating hydrophilic pores, altering the properties of mucous layer, facilitating the leaking of lipids and by opening the tight junctions between epithelial cells

Mucoadhesive drug delivery systems

- MCC is one of the most important limiting factors for nasal drug delivery, because it reduces the time allowed for drug absorption.
- Thus, improving nasal drug absorption can also be achieved prolonging the contact time between drug and nasal mucosa.
- Mucoadhesion implies the attachment of the drug delivery system to the mucus, involving an interaction between mucin and a synthetic or natural polymer called mucoadhesive.
- Mucoadhesives mostly used in intranasal drug delivery are chitosan, alginate and cellulose or its derivatives.
- Some of them may present other important characteristics which also enhance drug absorption.
- For example, chitosan is mucoadhesive and also causes a transient widening of epithelial tight junctions.

PERMEATION ENHANCER	EXAMPLE
Surfactants	Laureth -9
Bile salts	Deoxycholate
Chelators	EDTA, Citric acid
Fatty acid salts	Oleic, Lauric etc
Cyclodextrins	α- β- Cyclodextrins
Particulate carriers	Microspheres

COLLOIDAL CARRIERS

Ex: Starch, Dextran , Albumin etc

BIOADHESIVE POLYMERS

- They increase the time of contact between the delivery system and mucosa via bioadhesion
- Release the drug in controlled and sustained manner
- Protects the drug from enzymatic degradation in nasal cavity

Types of dosage forms and delivery systems

NASAL DROPS

- Advantage of this type of delivery is that it is perhaps the simplest and most convenient form of administering drug formulations into the nose.
- Disadvantage of this is that an exact amount of the formulation cannot be delivered.
- This dosage form was most popular

in the past because no

metered dose nasal devices

were available

SOLUTION SPRAYS

- As more sophisticated drug delivery devices became available, especially, metered dose nasal actuators, solution formulations were packaged in such delivery systems.
- Today, spray solutions are most commonly delivered through metered dose nasal actuator systems. These systems can deliver actuation volumes as low as 25 µl.

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SUSPENSION SPRAYS

- Suspension dosage forms are also administered by using the metered dose nasal actuator systems .
- The actuator may have to be designed according to the specific needs taking into consideration the particle size and morphology of the drug particles

GELS

- Gels are either thickened / gelled solutions or suspensions of drugs delivered by metered dose gel devices.

Gels can offer the following advantages over other dosage forms

- Gels reduce anterior leakage of the drug out of the nasal cavity
- Gels also help localize formulation on the thereby providing a better chance for the drug to be absorbed.

NASAL DELIVERY DEVICES

Common devices are

- Droppers
- Squeeze bottles
- Spray pumps / atomizers (Accuspray Nasal Atomizer, MAD (Mucosal Atomization Device, nasal)
- Gel applicators
- Nasal Nebulisers (Sinus Nebuliser Rhino Clear)
- Pressurized Metered Dose Inhalers (pMDIs) Nasal (Ex: Landmark®)
- Disposable Unit/Bi-dose dispensing devices
- Powder Dispensing Systems

Pulmonary Drug Delivery

- Drug delivery to or via the respiratory tree for the treatment of diseases has been long standing objective.

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 are 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

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.

- Generally, lung physiological investigations show that the airway and alveolar epithelia, not the interstitium and the endothelium, constitute the main barrier that restricts the movement of drugs and solutes from the airway lumen into the blood circulation.

1. Transcellular diffusion
2. Paracellular diffusion
3. Carrier-mediated transport
4. Vesicle-mediated transcytosis
5. Efflux transport

- Drug delivery to or via respiratory tree for the treatment of diseases like asthma, bronchitis has been a long standing objective.

- Drug delivery to the lungs can be achieved by two mechanisms, one is by aerosol drug delivery and second one is by direct instillation.

1.AEROSOLS

2.Nebulizers

3.Metered Dose Inhalers

They are the dosage forms containing therapeutically active ingredients that are packaged under pressure in a sealed container and are released as a fine mist of spray upon activation of a suitable valve system4.

Basic components

- 1. The container
- 2. Propellants
- 3. Product concentrate (containing API)
- 4. Valve and Actuators.

AEROSOLS

- Aerosols delivery systems consists of finely divided liquid droplets or solid particles in a gaseous suspension.
- Pharmaceutical aerosols may be classified as **space spray** and **surface coating** aerosols.
- **Space spray** disperse drug as a finely divided spray with particles less than 50μ in size and are suitable pulmonary drug delivery.
- Surface coating aerosols generate coarse and wet particles and are not suitable for pulmonary delivery.

- Limitations of aerosols include low patient compliance, drug metabolism, cost.
- The inhalation drug delivery systems are classified into

1. Nebulizers.
2. Metered dose inhalers.
3. Dry powder inhalers.

- The design of these systems is influenced by physicochemical properties of drug, target population and clinical objective to be met.

Nebulizers

- These are designed with aqueous solutions or suspensions .
- Normally water is used to prepare nebulizer solution and cosolvents like glycerine, ethanol andpropylene glycol may also be used.
- Nebulizers are classified as pneumatic type and electric type.
- For medical applications the pneumatic nebulizers can be jet or hydrodynamic while electric are ultrasonic type.

- The type of nebulizer and its operation determine the output and particle size of the aerosol generated.
- The droplets generated from nebulizers vary in size from1-10 μ.
- The advantages of nebulizers are the adjustment of flow rate with the inhalation rate of patient, large quantity of drug can be delivered through continuous nebulization.

Nebulizers

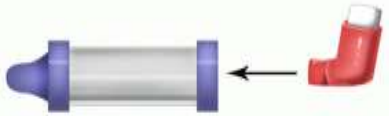
- In jet nebulizers, an aerosol is prepared by a high velocity air stream from a pressurized source directed against a thin layer of liquid solution.
- Ultrasonic nebulizers include the vibration of a piezoelectric crystal aerosolizing the solution.
- The nebulizer can transport more drugs to the lungs than MDI or DPI, the most common disadvantage of nebulizer are lack of possibility, higher costs of drug delivery as a result of the larger need for assistance from healthcare professionals, and the need for higher drug doses to achieve a therapeutic result.

NEBULIZERS

METERED DOSE INHALERS

How to Use a Metered-Dose Inhaler with a Spacer

1. Shake the medicine.

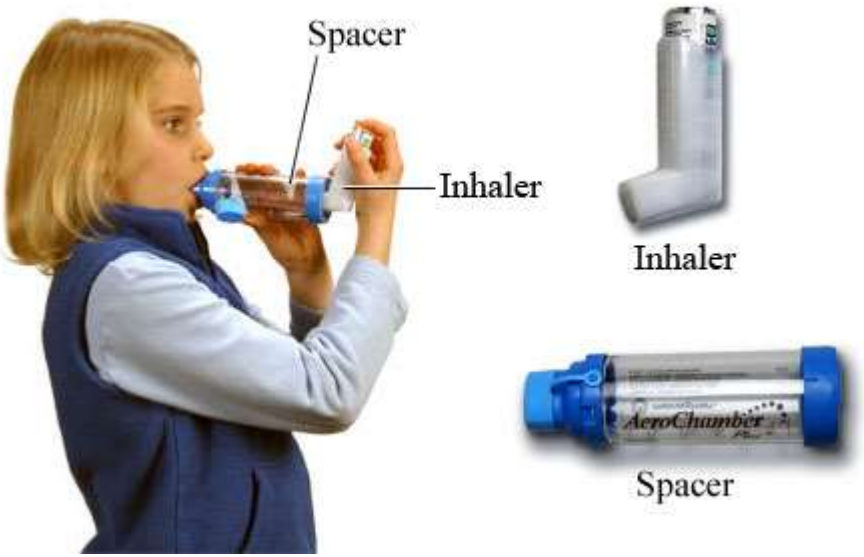


2. Insert the mouthpiece of the inhaler into the rubber-sealed end of the spacer.

3. Breathe all of the air out of your lungs. Then put the spacer into your mouth between your teeth. Make a tight seal around the mouthpiece with your lips.

4. Press the metered-dose inhaler down once to release a spray of medicine. The medicine will be trapped in the spacer. Breathe in slowly and deeply.

5. Hold your breath for at least 5 to 10 seconds. Breathe out slowly.

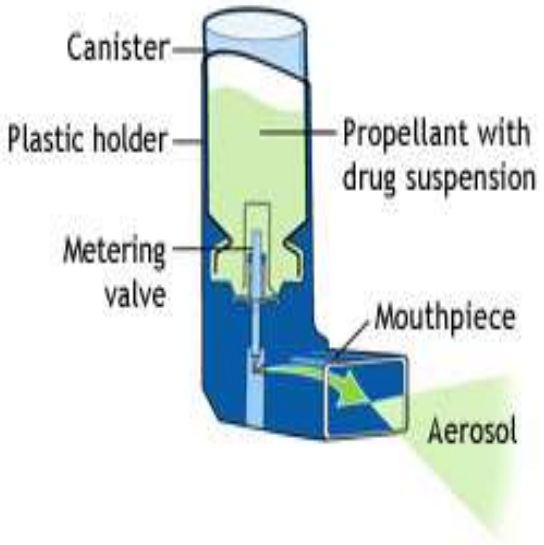

Spacer
Inhaler
Inhaler
AeroChamber
Spacer

Meterd Dose Inhalers

- MDI are sophisticated and safe dosage forms that can deliver accurate doses.

A typical MDI is composed of 4 components.

- The base formulation
- The container
- The metering valve
- The actuator or Mouth peice



Drug Targeting to Respiratory Tract

Physical targeting Or Site Specific targeting

- Non Spherical elongated Particles
- Salts And Precipitates
- Colloidal carriers

Chemical targeting