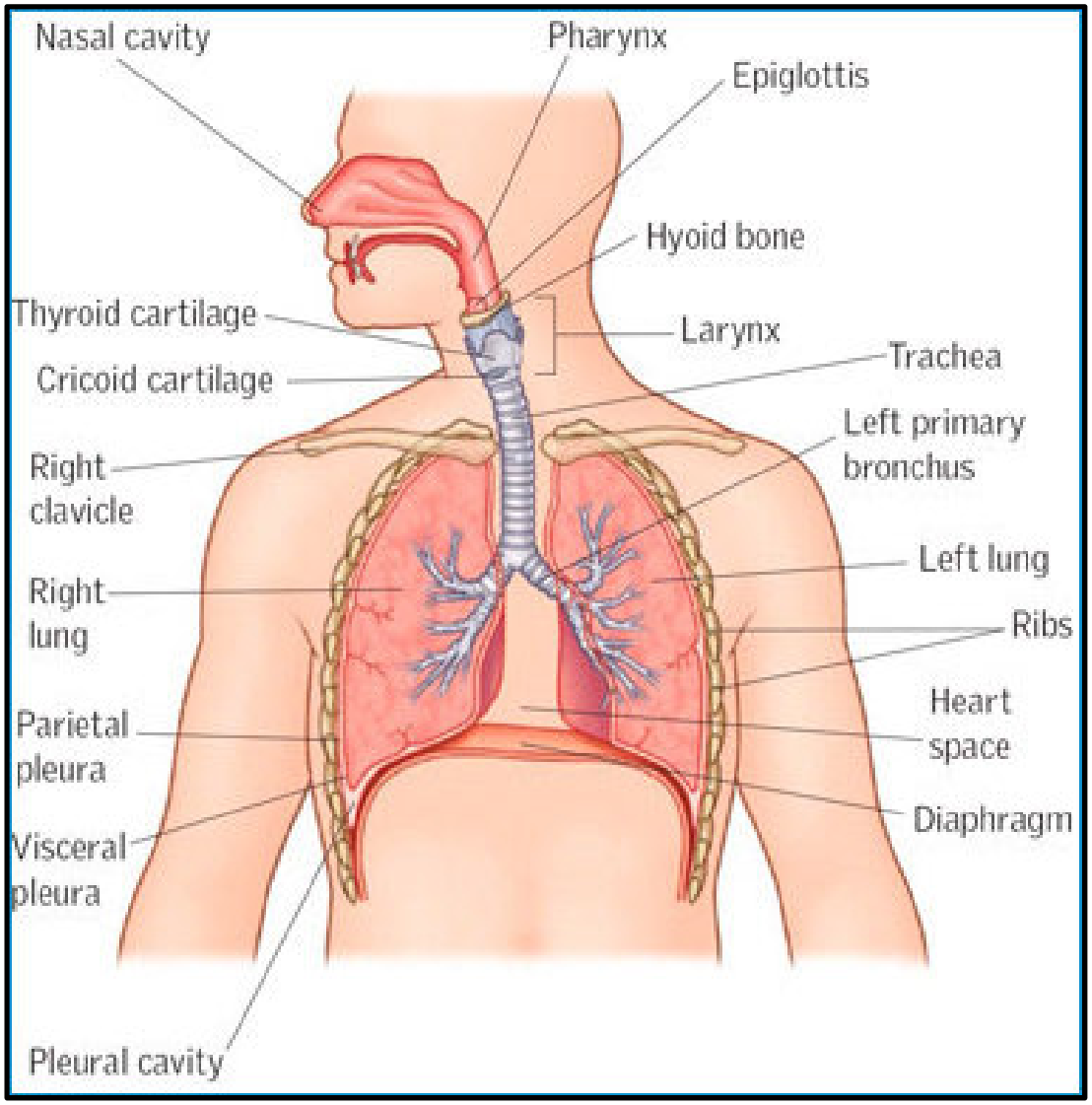
Pulmonary Drug Delivery



Presented By,
Dr. Dhaval Patel
Professor
SIPS, Gandhinagar

Introduction

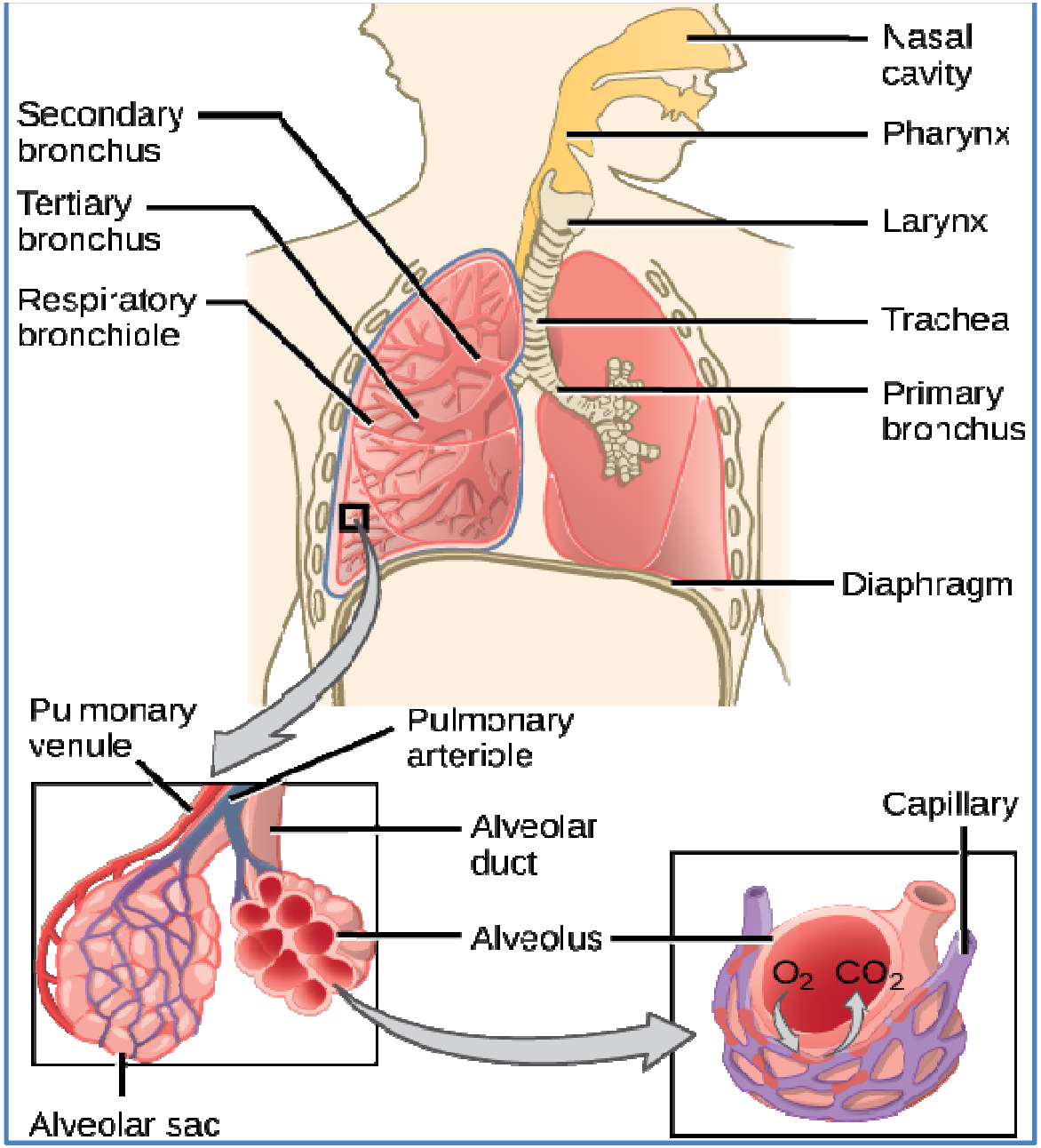
- Pulmonary route used to treat different respiratory diseases from last decade.
- The inhalation therapies involved the use of leaves from plants, vapours from aromatic plants, balsams, and myhrr.
- Pulmonary drug delivery is primarily used to treat conditions of the airways, delivering locally acting drugs directly to their site of action.
- Delivery of drugs directly to their site of action reduces the dose needed to produce a pharmacological effect.

Cont..

- 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.

Cont..

- The drugs which are administered by pulmonary route are not only for lungs delivery but it goes to systemic circulation and produce the effect where it is desired through out the body.
- Eg. A product containing ergotamine tartrate is available as an aerosolized dosage inhaler for the treatment of migraine & Volatile anesthetics, including, halothane, are also given via the pulmonary route.
- The drug used for asthma and COPD e.g..- β2-agonists such as salbutamol (albuterol), Terbutalin , formoterol, corticosteroids such as budesonide, Flixotide or beclomethasone and mast-cell stabilizers such as sodium cromoglycate or nedocromi



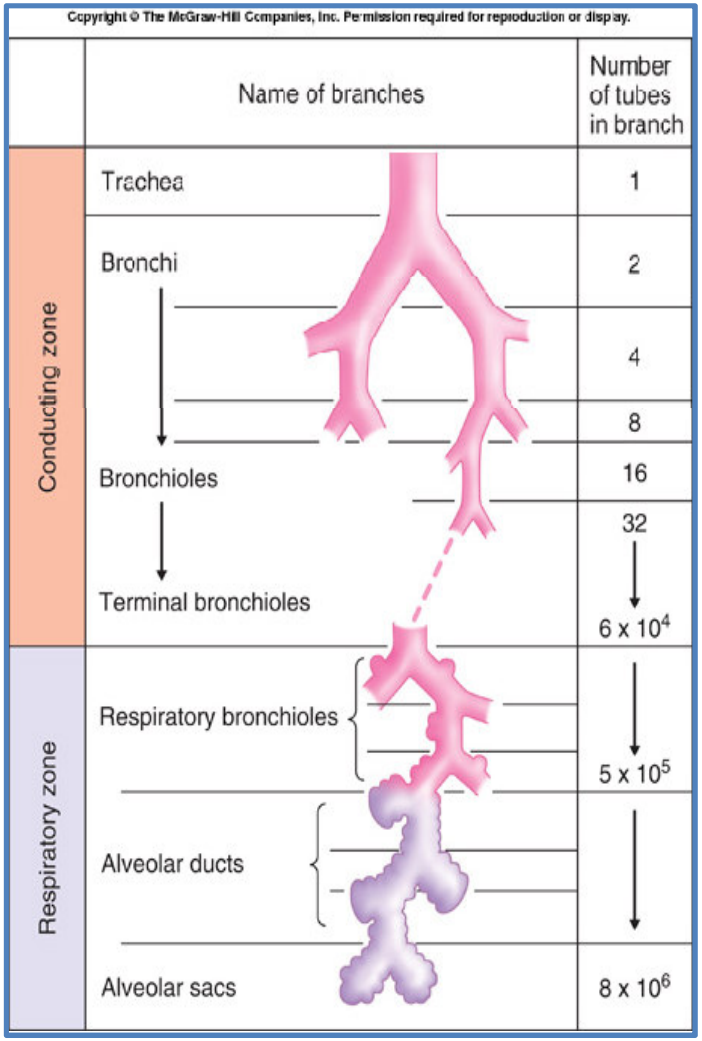
Anatomy and Physiology of Lungs

Anatomy and physiology of lungs

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

  1-the conducting airways

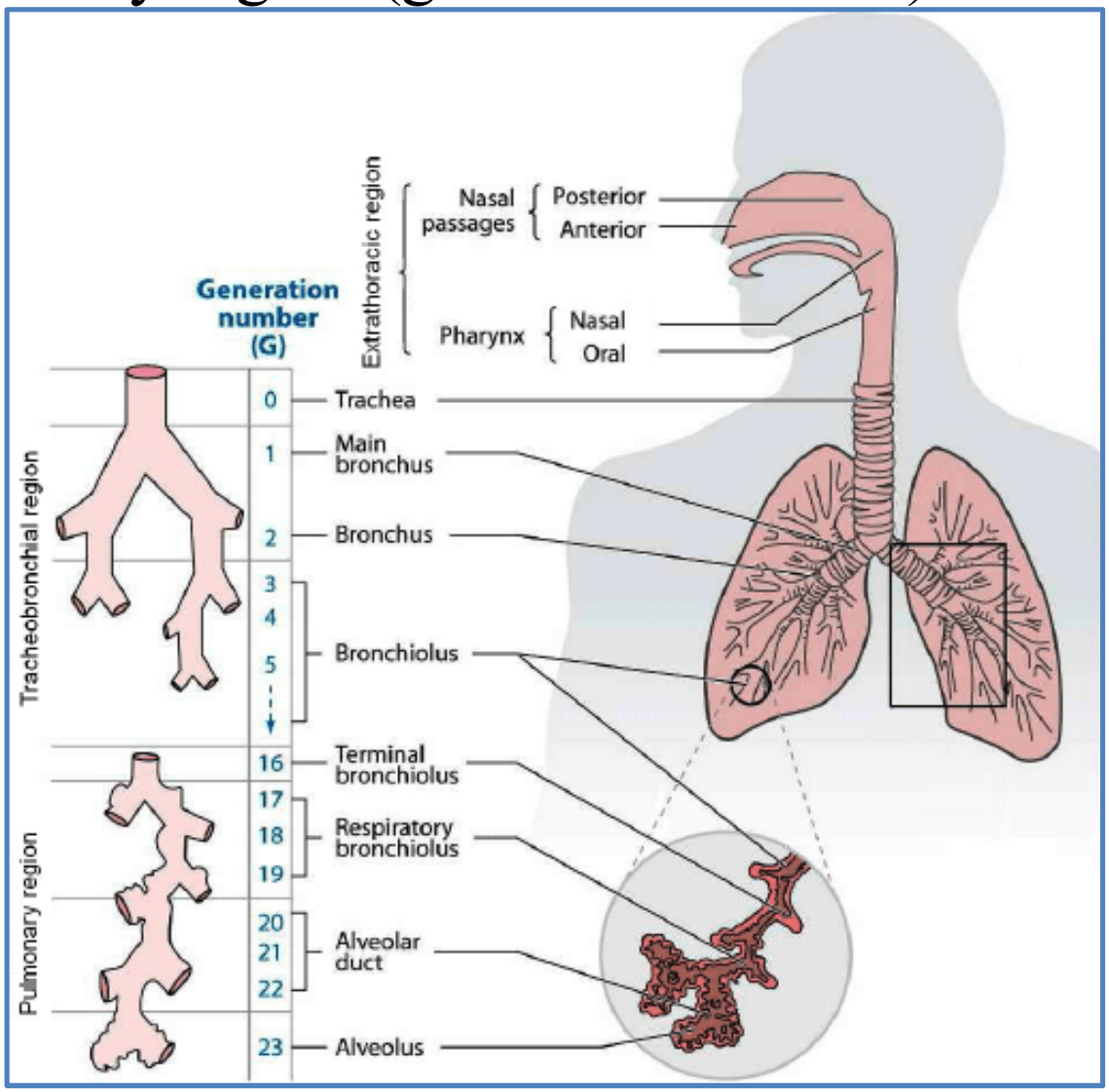
  2-the respiratory region



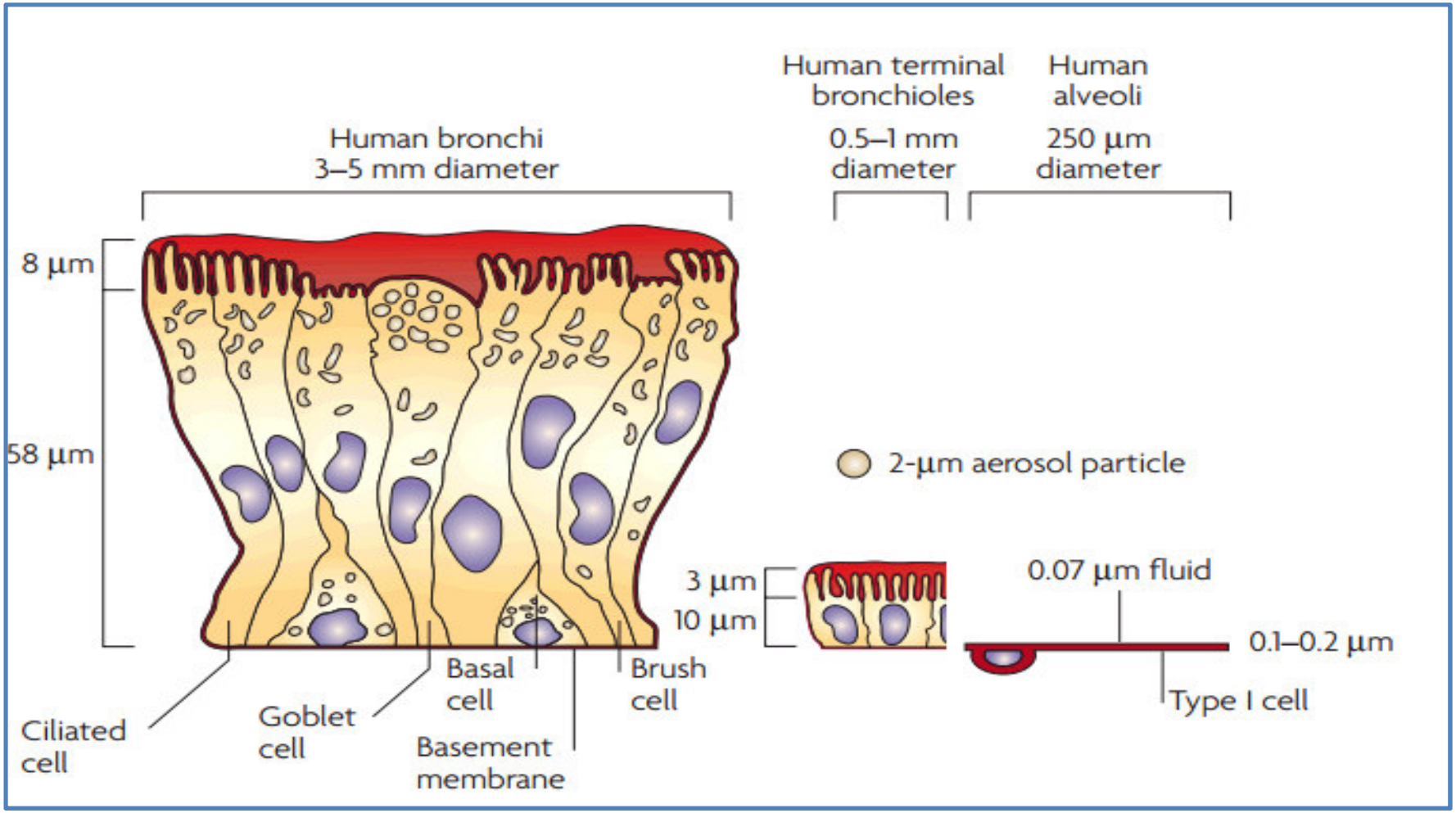
- The Conducting airway is further divided into many folds: nasal cavity and the associated sinuses, and the nasopharynx, oropharynx, larynx, trachea, bronchi, and bronchioles.
- The respiratory region consists of respiratory bronchioles, alveolar ducts, and alveolar sacs
- The human respiratory tract 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 pulmonary capillary bed.

Anatomical regions and airway generation model;

1. Tracheo-bronchial region (generations 0-16)
2. Pulmonary region (generations 17-23)



Type of Cells present in lungs

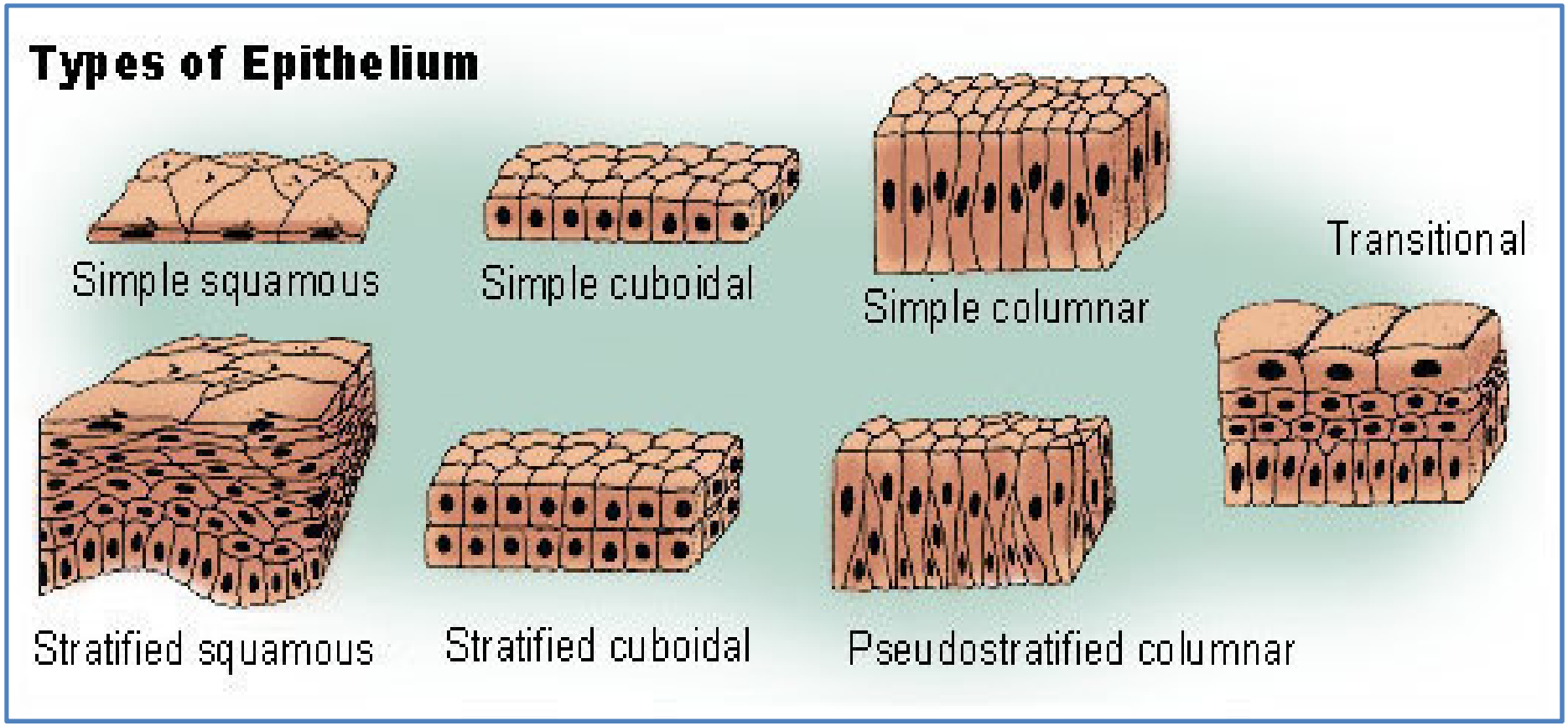


Pulmonary absorptive surfaces

- The airways (the trachea, bronchi and bronchioles) are composed of a gradually thinning columnar epithelium populated by many mucus and ciliated cells that collectively form the mucociliary escalator

- The airways bifurcate roughly 16–17 times before the alveoli are reached

- Inhaled insoluble particles that deposit in the airways are efficiently swept up and out of the lungs in moving patches of mucus, and for those deposited in the deepest airways this can be over a time period of about 24 hour


Types of Epithelium
Simple squamous
Simple cuboidal
Simple columnar
Transitional
Stratified squamous
Stratified cuboidal
Pseudostratified columnar

- The monolayer that makes up the alveolar epithelium is completely different. The tall columnar mucus and cilia cells are replaced primarily (>95% of surface) by the very broad and extremely thin (<0.1 μm in places) type 1 cells.

- Distributed in the corners of the alveolar sacs are also the progenitor cells for the **type 1 cells** and the producers of lung surfactant, the **type 2 cells.**

- The air-side surface of each of the 500 million alveoli in human lungs is routinely 'patrolled' by 12–14 alveolar macrophages, which engulf and try to digest any insoluble particles that deposit in the alveoli.

Pulmonary absorptive surfaces

- Insoluble, non-digestible particles that deposit in the alveoli can reside in the lungs for years, usually sequestered within macrophages.
- Molecules such as insulin are formulated either as liquids or in highly water-soluble aerosol particles that dissolve rapidly in the lungs and thereby largely avoid macrophage degradation.
- Protein therapeutics that are taken up by macrophages can be rapidly destroyed in the lysosomal 'guts' of the phagocytic cells.

Advantages of Pulmonary Delivery of Drugs To Treat Respiratory Disease

- Deliver high drug concentrations directly to the disease site
- Minimizes risk of systemic side effects
- Rapid clinical response
- Bypass the barriers to therapeutic efficacy, such as poor gastrointestinal absorption and first-pass metabolism in the liver
- Achieve a similar or superior therapeutic effect at a fraction of the systemic dose, (for example, oral salbutamol 2–4 mg is therapeutically equivalent to 100–200 μg by metered dose inhaler)
- A non-invasive, needle-free delivery system
- Suitable for a wide range of substances from small molecules to very large proteins

Advantages of Pulmonary Delivery of Drugs To Treat Respiratory Disease

- Enormous absorptive surface area (140 m^2) and a highly permeable membrane (0.2–0.7 μm thickness) in the alveolar region
- Large molecules with very low absorption rates can be absorbed in significant quantities; the slow mucociliary clearance in the lung periphery results in prolonged residency in the lung
- A less harsh, low enzymatic environment
- Avoids first-pass metabolism
- Reproducible absorption kinetics
- Pulmonary delivery is independent of dietary complications, extracellular enzymes, and inter-patient metabolic differences that affect gastrointestinal absorption.

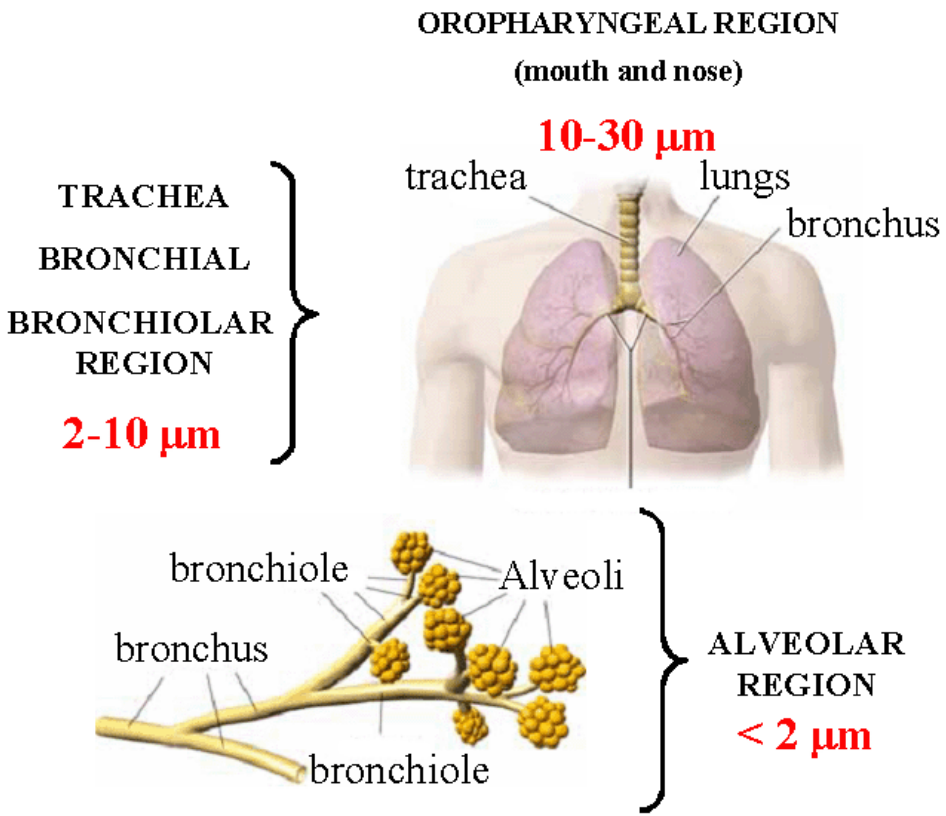
Disadvantages of pulmonary drug delivery

- Complex delivery devices are required to target drugs to the airways and these devices may be inefficient.
- Aerosol devices can be difficult to use
- Various factors affect the reproducibility of drug delivery to the lungs, including physiological (respiratory maneuver) and pharmaceutical (device, formulation) variables.
- Drug absorption may be limited by the physical barrier of the mucus layer and the interactions of drugs with mucus.
- Mucociliary clearance reduces the retention time of drugs within the lungs. Efficient drug delivery of slowly absorbed drugs must overcome the ability of the lung to remove drug particles by mucociliary transport.

Mechanisms of Deposition

- **Inertial impaction**
  - First 10 generations of lung
  - Tracheobroncial region and bends and bifurcations
  - Air velocity is high
  - Airflow is turbulent
  - Particles >10 microns deposited in oropharyngeal region
  - Delivered by DPI, forward velocity MDI
- **Gravitational sedimentation**
  - Last 5-6 generations of lung
  - Air velocity is low
- **Diffusion (Brownian motion)**
  - Alveolar region
  - Air velocity is negligible

Hygroscopic drugs swell as they come in contact with humidified air in lung (99.5%)



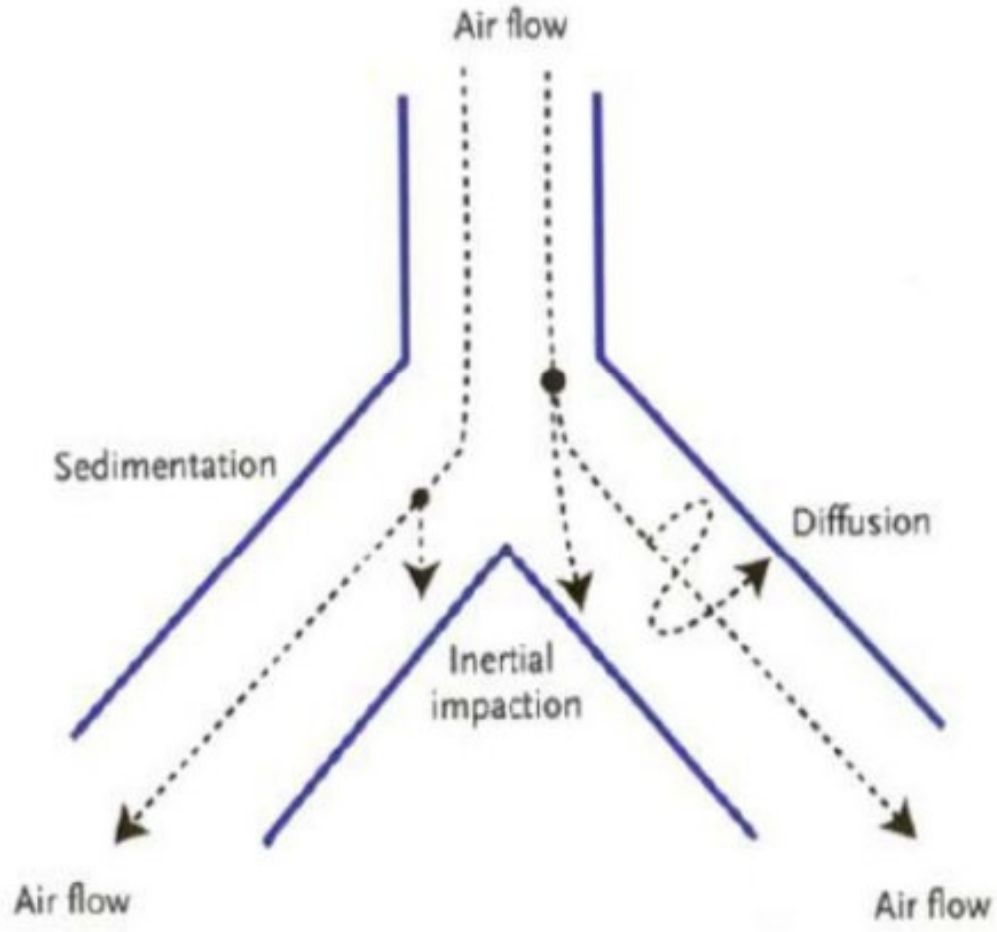
Factors affecting Pulmonary Drug Delivery

Mechanism of particle disposition in the airways:

- Inertial impaction
- Sedimentation
- Brownian diffusion

Mechanism of particle deposition in the airways

- Inertial impaction
- Sedimentation
- Brownian diffusion



- The inertial impaction occurs during the passage through the oropharynx and large conducting airways if the particles possess a certain mass and velocity.
- Inertial impaction can be partially influenced by hyperventilation and **does not occur when particles have a diameter below 3 mm.**
- These particles are subject to sedimentation by gravitational force which occurs in smaller airways and is influenced by breath-holding.
- **From a range below 0.5-1 mm, particles are deposited** by diffusion which is based on the Brownian motion.

Generally:-

- **Particles bigger than 10 µm** will have impact in the upper airways and are rapidly removed by swallowing, coughing and mucociliary processes.
- **The particles in the size range 0.5–5 µm** may break away from impaction in the upper airways and may deposit by sedimentation and impaction in the lower TB and A regions.
- If the aerosol particle size is **between the 3 and 5 µm** then deposition it mainly occur in the TB region.
- If the particles are **smaller than the 3 µm** then appreciable deposition in the A region is likely to occur.

Physiological factors affecting particle deposition in the airways:

- Lung morphology
- Inspiratory flow rate
- Co-ordination of aerosol generation with inspiration
- Tidal volume
- Breath holding
- Disease states

Lung Morphology

- Each successful production of the tracheobronchial tree produces airways of falling diameter and length.
- Every **bifurcation results in an increase possibility for impaction** and the decrease in airway diameter is associated with a smaller displacement necessary a particle to make contact with a surface.

Inspiratory flow rate

- When the inspiratory flow rate increases they enhance deposition by impaction in the first few generations of the TB region.
- The increase in flow not only increase particle momentum but also result in an increase in turbulence, mostly in the larynx and trachea, which itself will enhance impaction in the proximal tracheo-bronchial region.

Tidal Volume and Breath holding

Tidal volume:-

- An increased IFR will usually be connected with an enlarge in the volume of air inhaled in one breath, the tidal volume.
- Obviously **an increase in tidal volume will result in penetration of aerosol particles deeper into the TB and A regions** and a better chance for deposition inside these regions.

- **Breath holding:-**
- Increasing the time between the end of inspiration and the start of exhalation increase the time for sedimentation to occur.
- **Breath-holding is normally used to optimize pulmonary drug delivery.**

Disease states

- **Bronchial obstruction** as seen in different pulmonary disorders may associated with the **larger local airflows and turbulence** and this will result in localized deposition in the larger airways of the trachea-bronchial region.
- The **bronchoconstriction of asthma** has a more influence on exhalation than inhalation and thus deposition by sedimentation may be superior than normal.

Pharmaceutical factors affecting aerosol deposition

- Aerosol velocity
- Size and Shape
- Density
- Physical stability

Aerosol velocity

- The aerosols formed by nebulizers and dry powder inhalers (DPIs) are transported into the lung by entrainment on inspired air.
- In difference, pMDIs generate aerosol droplets with velocities greater than the inspiratory airflow and therefore the aerosol will have a greater affinity to impact in the oropharyngeal region.

Size and Shape

- The particle size is commonly expressed as the **aerodynamic diameter,** which is a variable depending on the shape, density and size of the object.
- If aerosols contain different particles, the size distribution is usually characterized by the **MMAD (Mass median Aerodynamic diameter).**
- Also, deposition is influenced by the particle source which **can be a solution, powder or suspension.**

- It was demonstrated that solution-based aerosols were characterized by 2-µm massmedian aerodynamic diameter (MMAD) particles whereas suspension-based aerosols displayed 4 -µm MMAD particles.
- A maximal alveolar deposition is reached with particle sizes of 3 µm and an increase of the MMAD leads to an inertial impaction based shift in deposition in larger airways.
- In this respect, the oropharyngeal deposition of an 8 -µm particle has a probability of about 50%, whereas it reaches approximately 100% for a 16 -µm particle

(Ref: Respiratory Medicine, Vol.97 (2003) 382-387)

Density

- Particles having densities less than 1 g/cm^{-3} (unit density) may have a mean physical diameter larger than the aerodynamic limit.
- **Most micronized drugs for inhalation will contain particle densities around 1, although materials created by freeze-drying or spray drying methods are likely to be appreciably less dense.**

Example

- Breath holding for 5-10sec on completion of inhalation, a low flow rate (less than 20 l/min), and an increase in the inhaled volume can lead to an increase in particle deposition, especially for particles with a diameter around 0.5 μm which are subject to sedimentary deposition
- In contrast, low flow rates of 15 l/min can lead to an increase in large conductance airway deposition of >3 μm particles due to inertial impaction

DRUG DELIVERY DEVICES

- 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)

- The basic function of these three completely different devices is to generate a drug-containing aerosol cloud that contains the highest possible fraction of particles in the desired size range.

Nebulizer

- Nowadays the many physicians are mostly use nebulizer for the treatment of acute asthma in an emergency care unit or for treating patients with severe asthma at home.
- A nebulizer is a device used to administer medication to patient in the form of a mist inhaled into the lungs
- It is commonly used in treating cystic fibrosis, asthma, and other respiratory diseases.

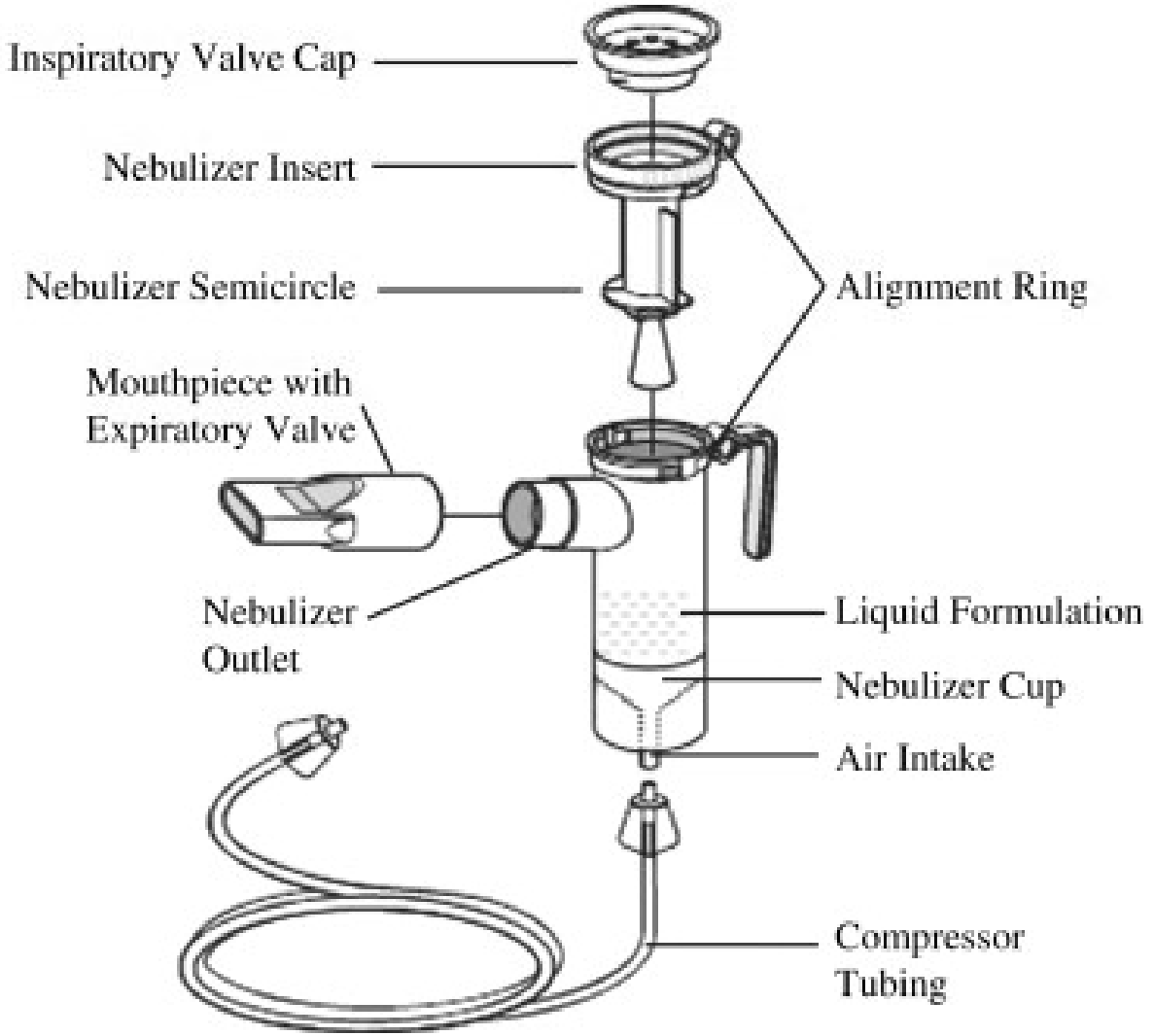
INDICATIONS FOR NEBULIZER

- Useful in children
- Handicapped person
- Seriously ill patients
- Ventilated patients
- Elderly individuals
- High doses can be given
- Combination drugs can be given

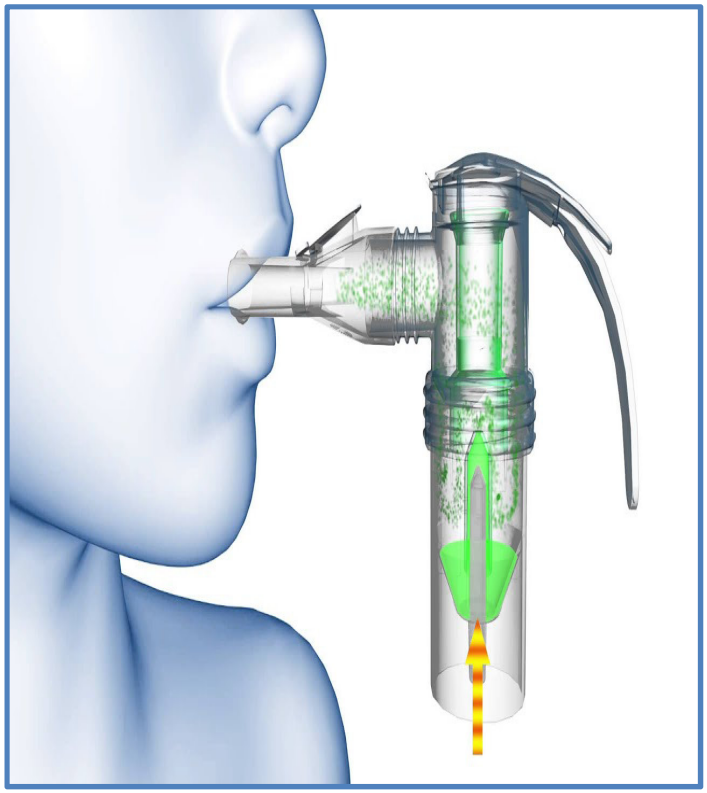
Types of Nebulizers

- There are two basic types of nebulizers:
- The jet nebulizer functions by the Bernoulli principle **by which compressed gas (air or oxygen) passes through a narrow orifice,** creating an area of low pressure at the outlet of the adjacent liquid feed tube. This results in the drug solution being drawn up from the fluid reservoir and shattering into droplets in the gas stream.
- The ultrasonic nebulizer uses a piezoelectric crystal, vibrating at a high frequency (usually 1–3 MHz), to **generate a fountain of liquid in the nebulizer chamber**; the higher the frequency, the smaller the droplets produced

Jet Nebulizer

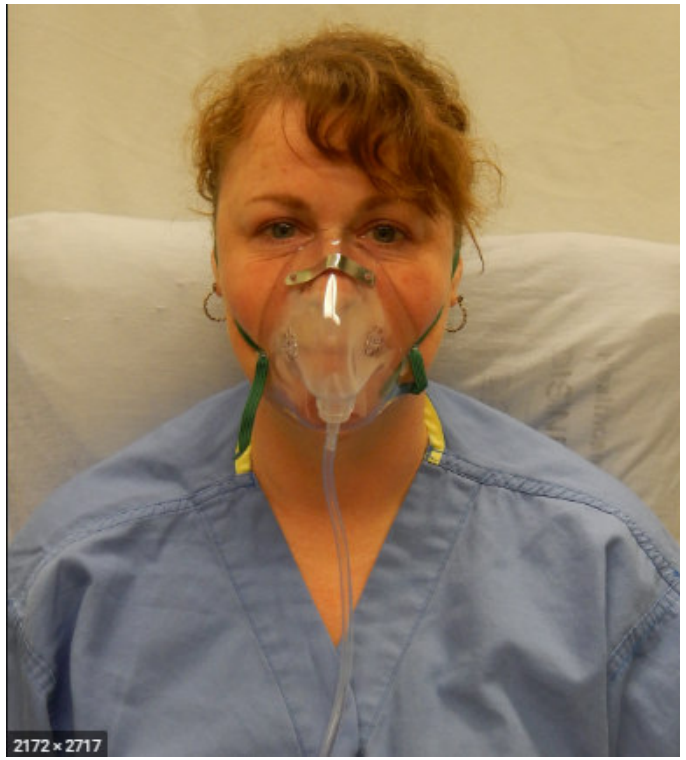


Jet Nebulizer



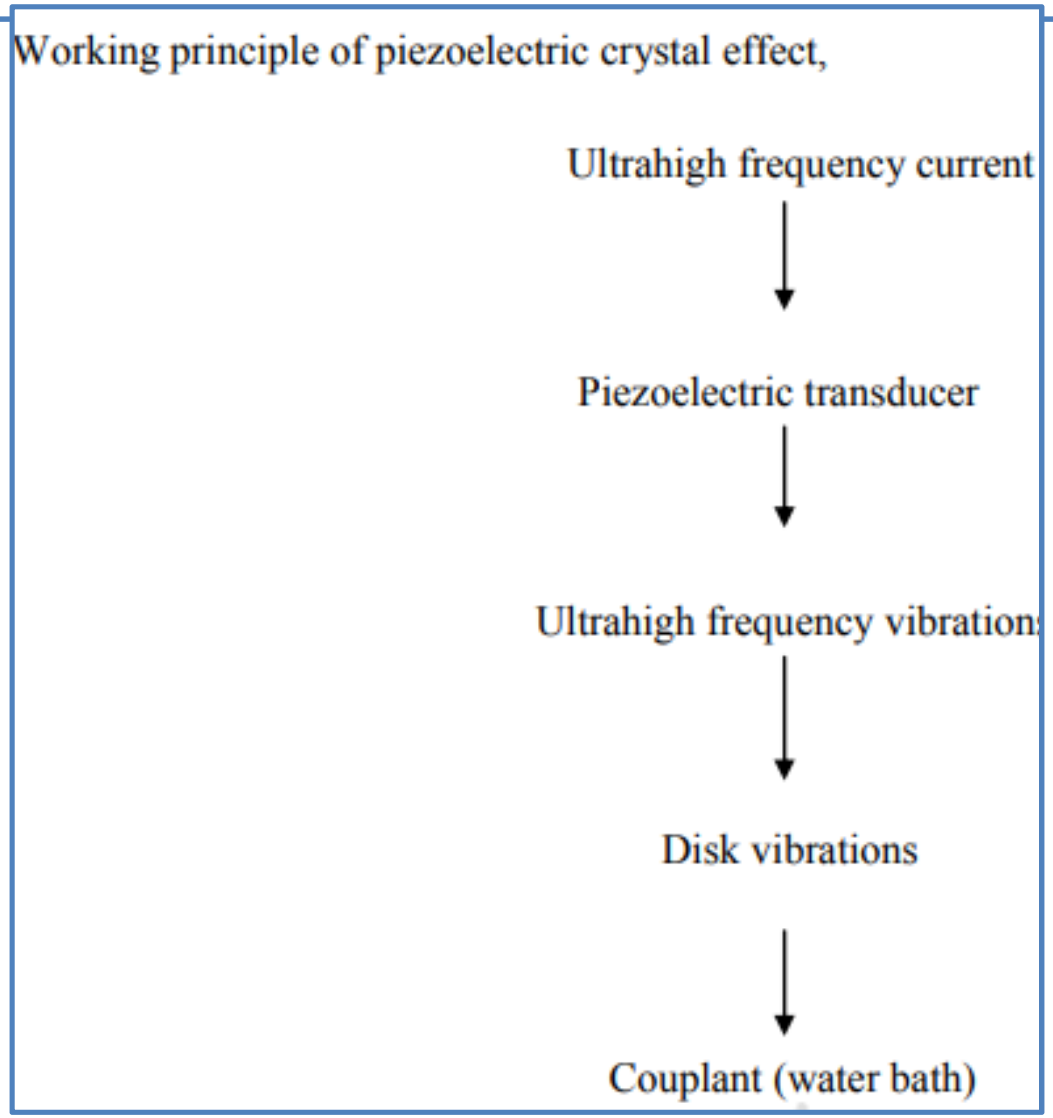
Ultrasonic nebulizer

- In ultrasonic type, aerosol droplets are produced through high-frequency vibrations of a piezoelectric crystal, for that the ultrasound waves are formed in it.



Working of Ultrasonic nebulizer

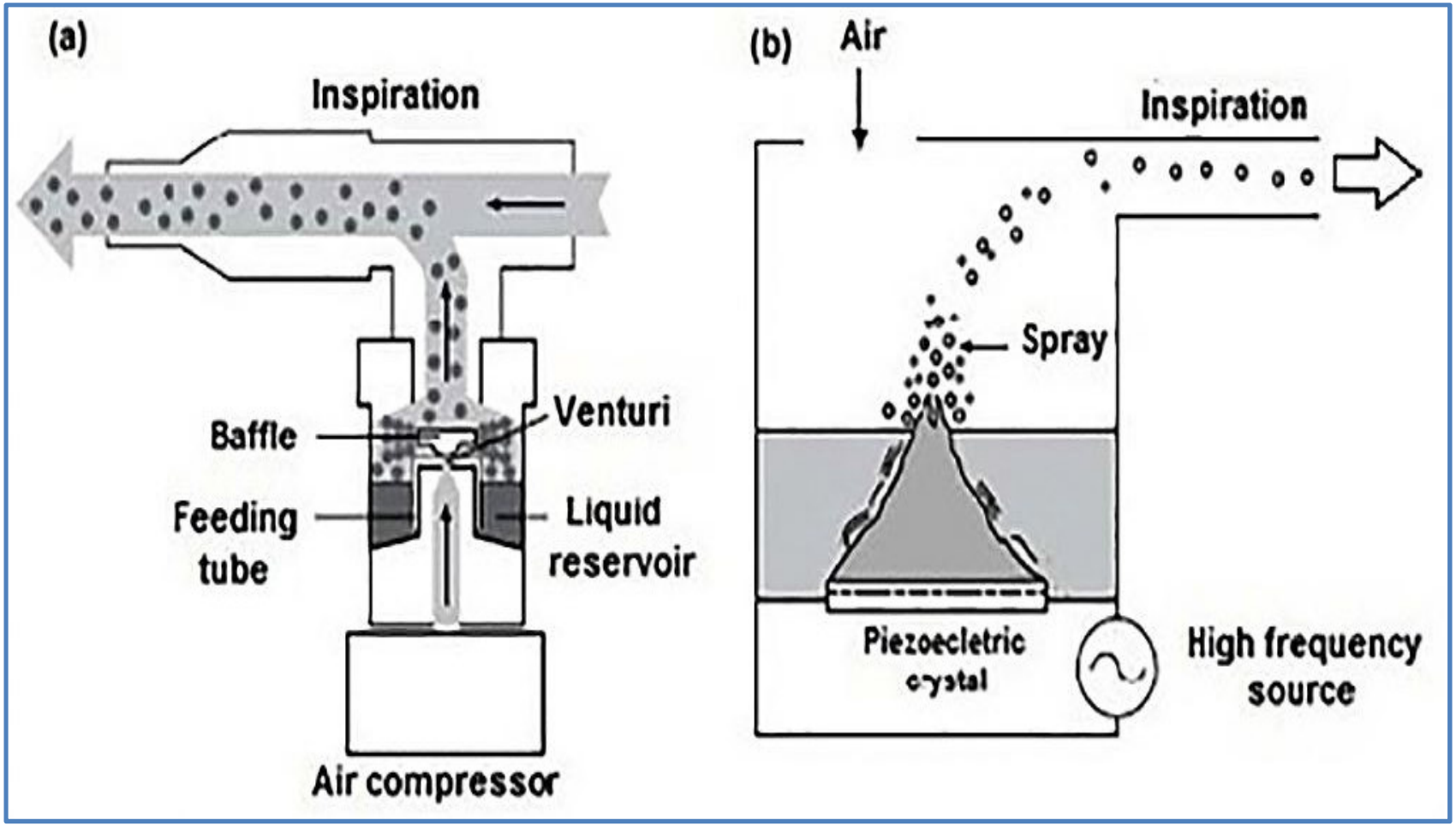
Working principle of piezoelectric crystal effect,



Features of ultrasonic nebulizers

- More expensive
- Heats up during operation, less noise
- Less Rx time
- Large average particle size
- Large output rate
- 0.5 to 3 micron-90% of the particle within range.

(a) Jet Nebulizer (b) Ultra sonic Nebulizer



commonly available nebulizers on the market are: Ventolin® (Salbutamol, ß2-mimetic bronchodilator), Bricanyl® (Terbutaline, ß2-mimetic bronchodilator), Atrovent® (Ipratropium, anticholinergic bronchodilator), Pulmozyme® (Dornase alpha, mucolytic) and Tobi® (Tobramycin, antibiotic).

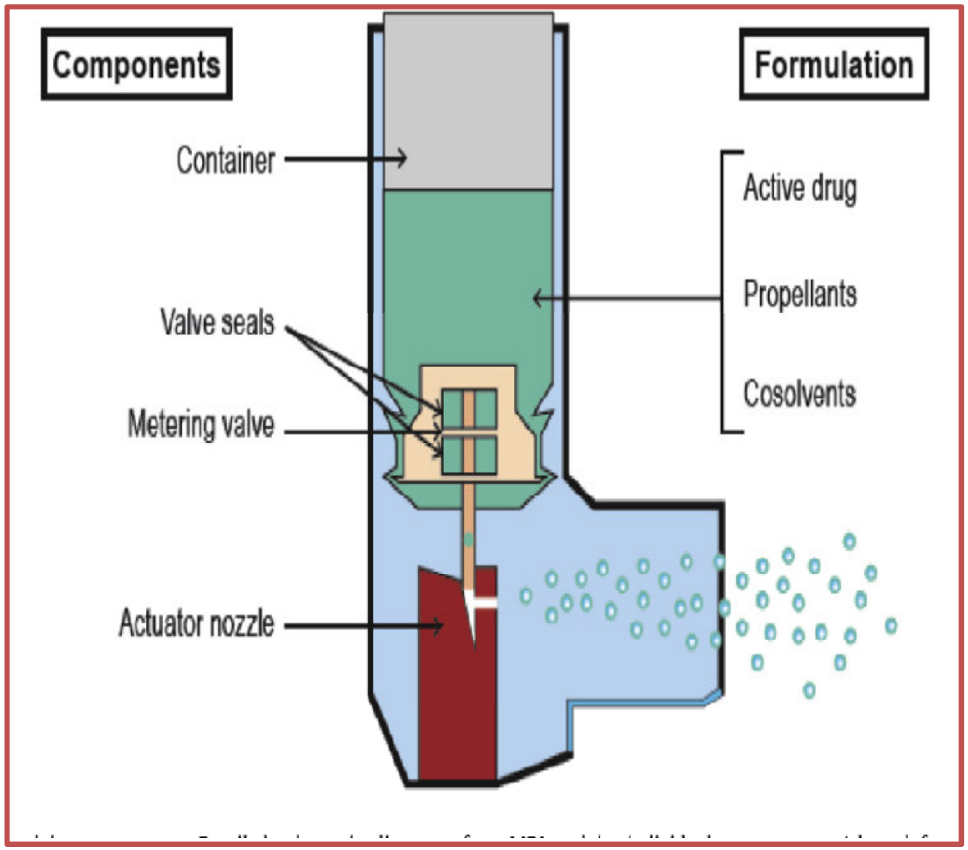
Metered Dose Inhaler (MDI)

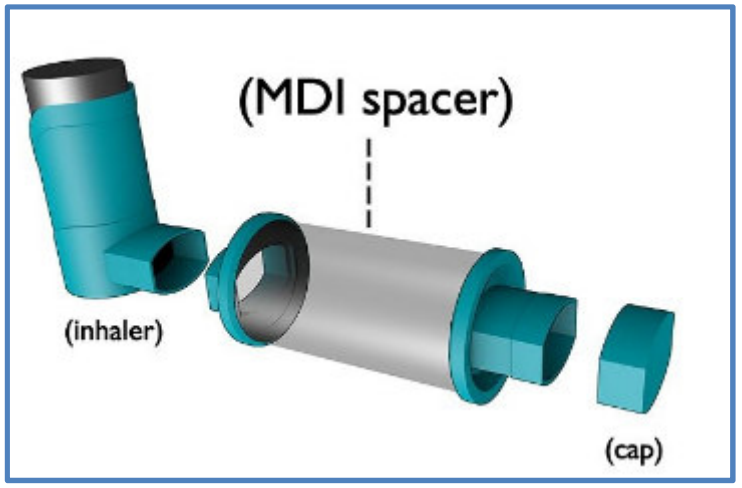
- These are the most common device for administration of aerosolized drugs.
- The pressurized metered-dose inhalation (pMDI) device was introduced to deliver asthma medications in a convenient and reliable multi-dose presentation
- The key components of the pMDI device are: container, propellants, formulation, metering valve, and actuator.
- The pMDI container must withstand high pressure generated by the propellant. Stainless steel has been used as a pMDI container material. **Aluminum is now preferred because,** compared to glass, it is lighter, more compact, less fragile, and light-proof.

- In this technique, a medication is mixed in a canister with a propellant, and the preformed mixture is expelled in exact measured amounts upon actuation of the device.
- Coatings on the internal container surfaces may be useful to prevent adhesion of drug particles and chemical degradation of drug.
- Popellants in pMDIs are liquefied, compressed gases that are in the gaseous phase at atmospheric pressure but form liquids when compressed.
- By using the spacer device it may solve the problem moderately the bulky size of the device can be prevention for patients who have need of use of MDIs outside their homes.

- In near the beginning 1990, attempts were actively made to reformulate MDIs as a result of the mandatory ban on the use of propellant chlorofluorocarbons (CFCs), which have been concerned in the depletion of the Earth's ozone layer.
- Optional propellants, such as hydrofluoroalkane 134a (HFA-134), have be extensively investigated for their potentials to change CFCs since 1990.

The Pressurized Metered-Dose Inhalation (pMDI) Device





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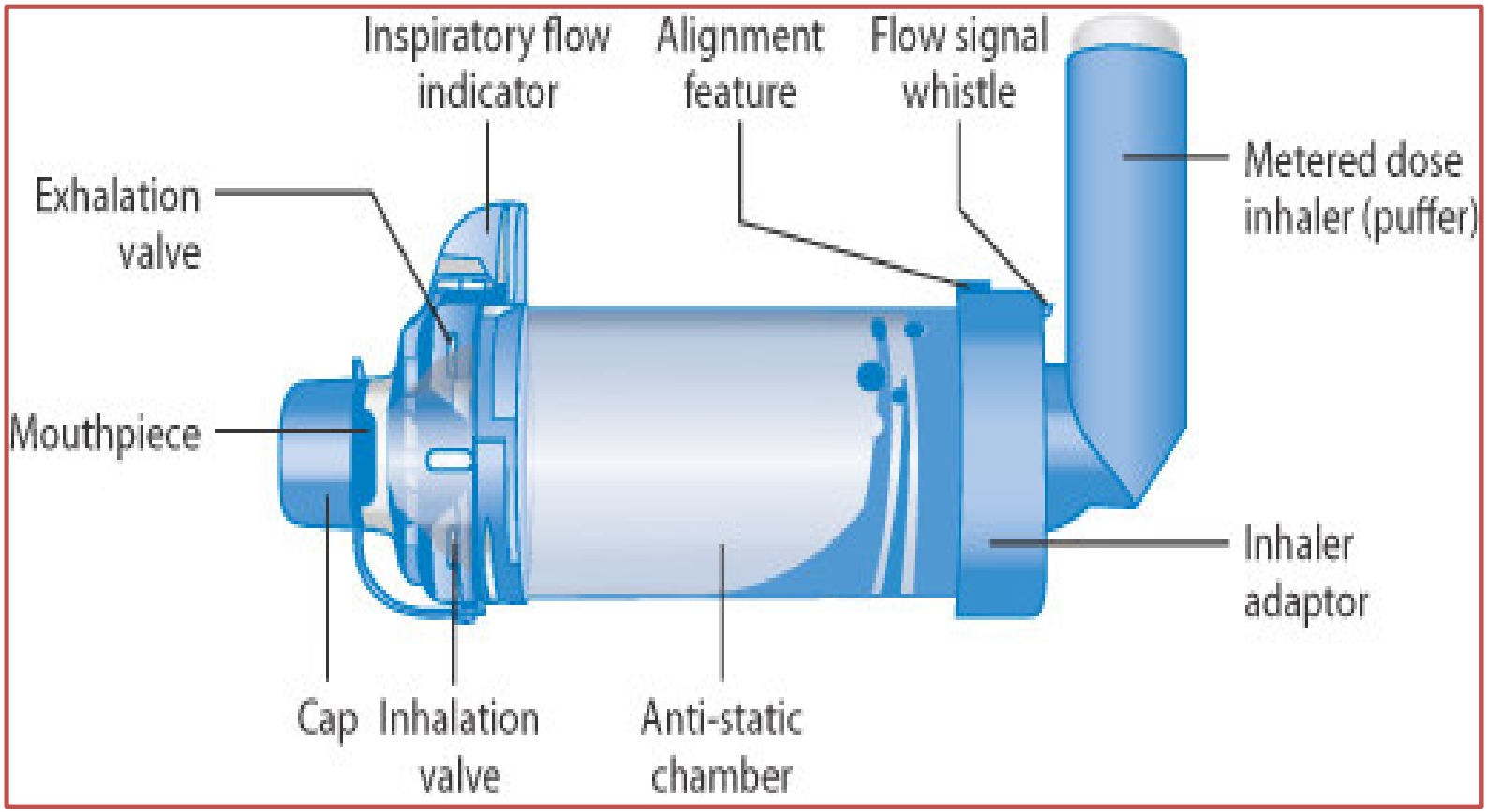


Advantage of MDI	Disadvantage of MDI
It delivers specified amount of dose.	Difficult to delivery high doses.
Small size and convenience.	There is no information about the number of dose left in the MDI
Usually inexpensive as compare to dry powder inhalers and nebulizers.	Accurate co-ordination between actuation of a dose and inhalation is essential.
Quick to use	

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..

Formulation aspect of DPI

- Lactose monohydrate is the most commonly used excipient (i.e., carrier) in DPI formulations.
- Mixtures of the lactose with drug are commonly described as ordered or interactive mixtures, which are simpler to handle during the manufacturing than micronized drug alone.
- The drug particles should loosely adhere to the lactose (carrier) particles and, during inhalation in the turbulent air stream which is produced, the drug particles detach from the lactose (carrier) particles and are made accessible for deposition into the lungs.

Formulation aspect of DPI

- The carrier also offers mass to the DPIs, which enhances the handling, dispensing, and actuation of the micronized drug, which is of actual significance for low dose DPIs such as steroids (typical dose per actuation: 50 μg to 500 μg).
- In order to confirm effective delivery of drug, it is crucial that adhesive forces between the drug and carrier are not so strong that separation from the carrier is prohibited.
- DPI formulation is greatly dependent on the particle size distribution, fine-lactose content, lactose source, the inhalation flow rate, and dispersion capacity of the respective DPI device.

Advantages of DPI	Disadvantages of DPI
Propellant-free.	Dependency on patient's inspiratory flow rate and profile.
Less need for patient co-ordination	Device resistance and other design issues.
Less formulation problems	Greater potential problems in dose uniformity.
Dry powders are at a lower energy state, which reduces the rate of chemical degradation	More expensive than pressurized metered dose inhalers
There is also not require to use spacers.	Not available worldwide Unit-Dose Devices

Single dose device:

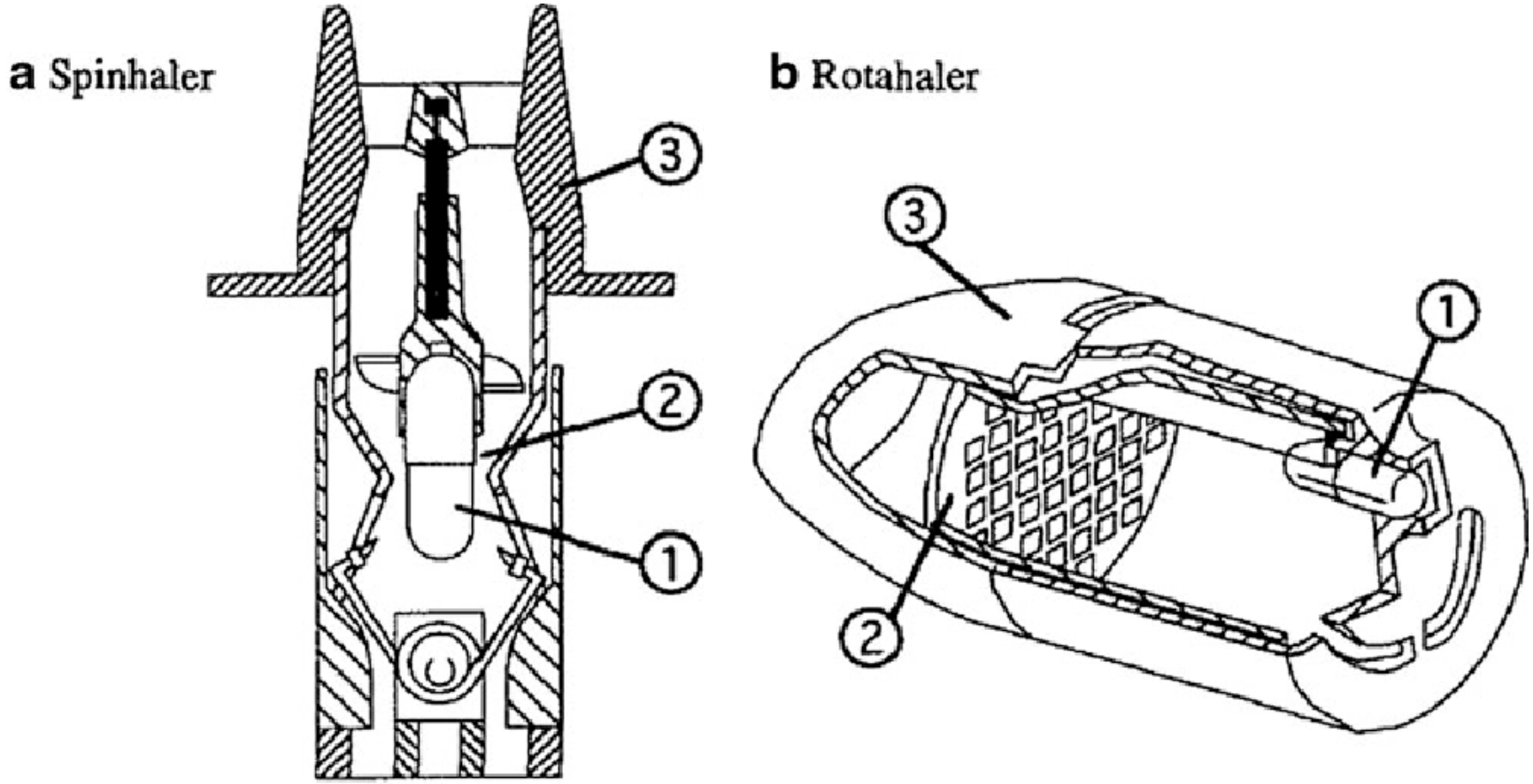
Inhalers are devices in which a powder containing capsule is placed in a holder. The capsule is opened within the device and the powder is inhaled.

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.

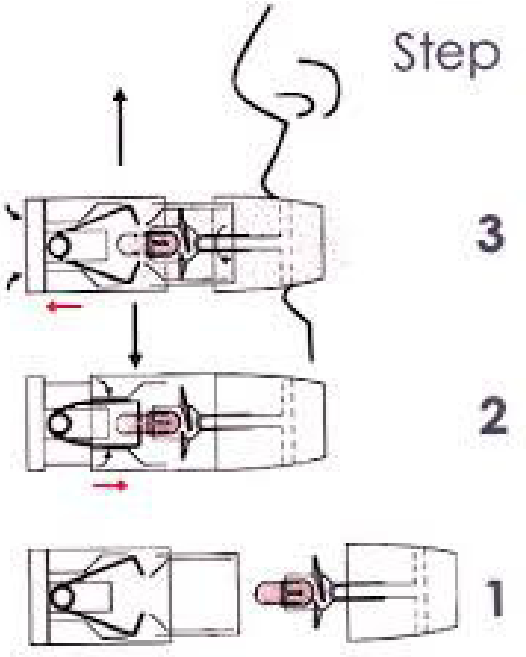
Single-dose devices

- While are reusable, they are inconvenient because an individual dose has to be loaded into the device each time it is used.
- **The Spinhalers (Aventis)** was developed to deliver sodium cromoglycate in individual gelatin capsules. The patient inserts a capsule onto a propeller seated inside the inhalation channel, and the capsule is pierced by two needles that are actuated by a sliding cam arrangement.
- When the patient inhales strongly through the mouthpiece, the propeller turns and vibrates, dispensing the drug as an aerosol.



① Hard gelatin capsule
② Dispersion apparatus
③ Mouthpiece

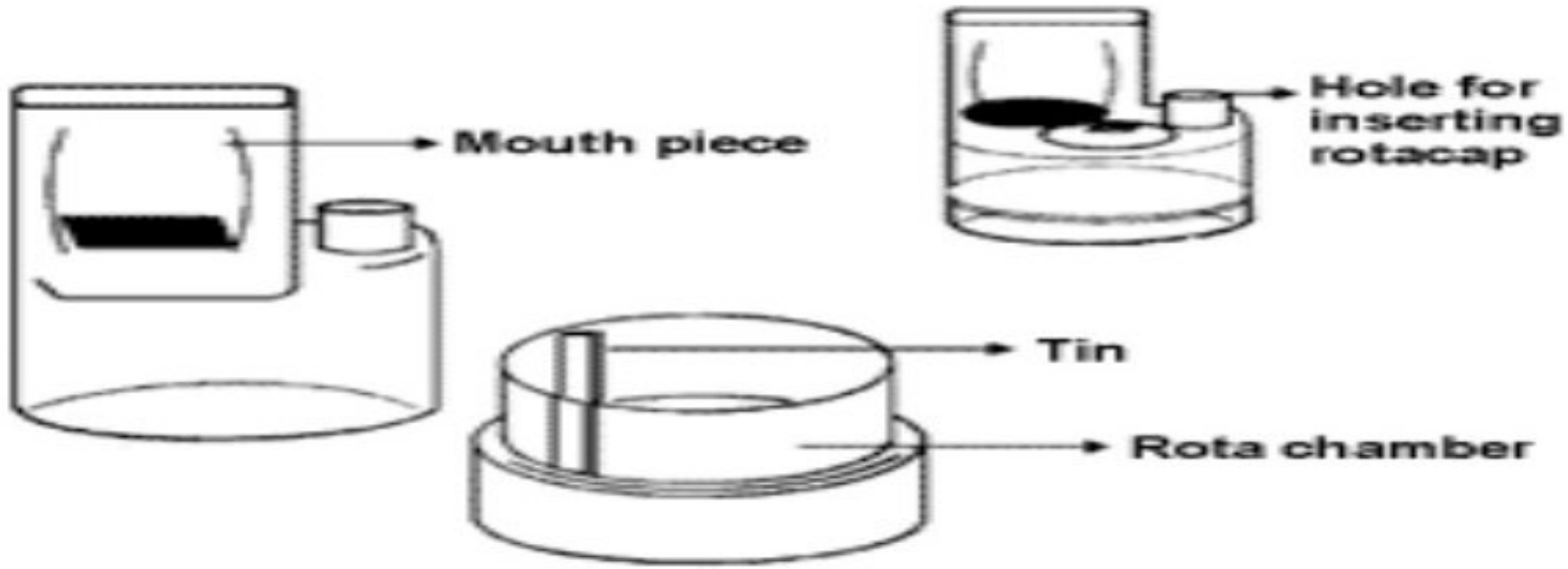
The Spinhalers (Aventis)



ROTAHALER

ROTAHALER

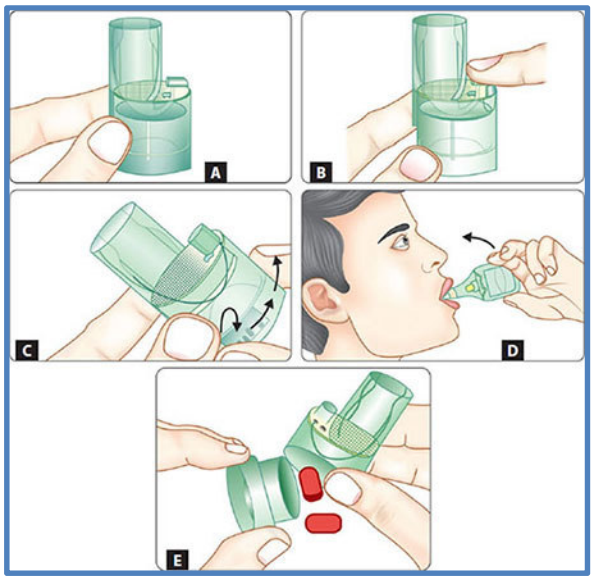
The Rotahaler is just one of many devices that are available. It uses special capsules, called Rotacaps, that contain the medication in a very fine powder form that is effectively delivered into the lungs when you inhale through the Rotahaler.



ROTAHALERS

- Rotahalers (GlaxoSmithKline) has been used to deliver salbutamol and beclomethasone dipropionate.
- With this inhaler, a capsule is loaded and a twist motion causes the two halves of the capsule to separate and release the powder.
- When the patient inhales, the drug is drawn through a grid and exits the inhaler.

Steps for Rotahaler Working



A.

- Hold Rota haler vertically and put capsule (Clear end first) into square hole. Make sure top of rotacap is level with top of hole. (If there is a rotacap already in the device this will be pushed into shell).

B & C

- Hold rotahaler horizontally, twist bottle sharply forwards and backwards. This splits capsule into two parts.

D

- Breathe out gently. Keep rotahaler level and put mouthpiece between lips and teeth and breathe in powder quickly and deeply.

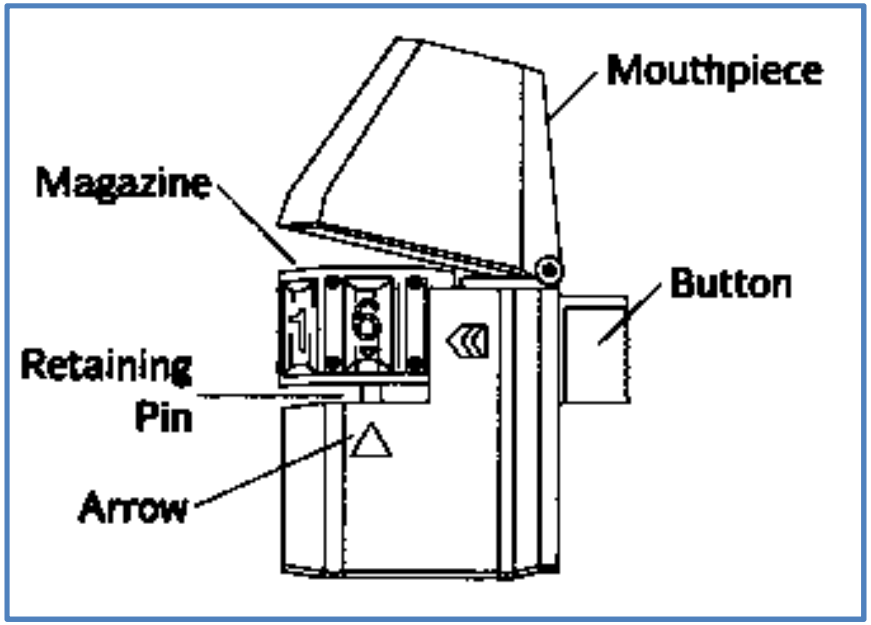
E

- Remove rotahaler from mouth and hold breath for 10 sec.
- If any powder is left repeat steps 3 and 4. Open the Rota haler and discard the empty capsule.

Multiple unit dose devices

- The Aerohalers (Boehringer Ingelheim) was the first DPI to hold more than one capsule; a six-capsule inhaler is currently available.
- This inhaler has been used to deliver fenoterol and ipratropium bromide.
- The magazine of capsules is loaded into position, allowing two needles to pierce a capsule.
- The patient's inspiration pulls air through the holes, vibrating the capsule and delivering the formulation into the airstream.

Aerohalers (Boehringer Ingelheim)



Diskhalers (GlaxoSmithKline)

- It was the first inhaler to use drug formulations prepackaged into single dose blisters in a multidose package.
- This inhaler has been used to deliver a range of products, including salbutamol, salmeterol xinafoate, beclomethasone dipropionate, and futicasone propionate.
- The inhaler uses refill disks, each of which contains four or eight blisters. When the lid of the Diskhaler is opened and closed, the disk rotates and a new blister is available to be pierced.
- When the patient inhales through the mouthpiece, the drug formulation is drawn from the blister and is dispersed as an aerosol into the respiratory tract

Parts of the DISKHALER:

COVER
keeps the DISKHALER clean and free of foreign matter; replace cover when not in use

WHITE MOUTHPIECE
where the medicine is inhaled by mouth

DARK BROWN WHEEL
rotates to the next blister of medicine

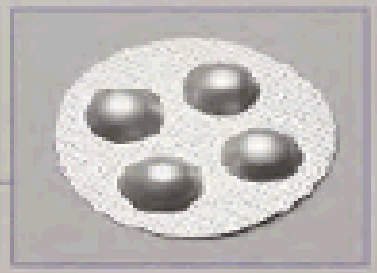
WHITE TRAY
pulls in and out of DISKHALER body

RAISED RIDGES
help you pull out the tray for loading

NEEDLE
punctures the blister to release medicine

DISKHALER BODY

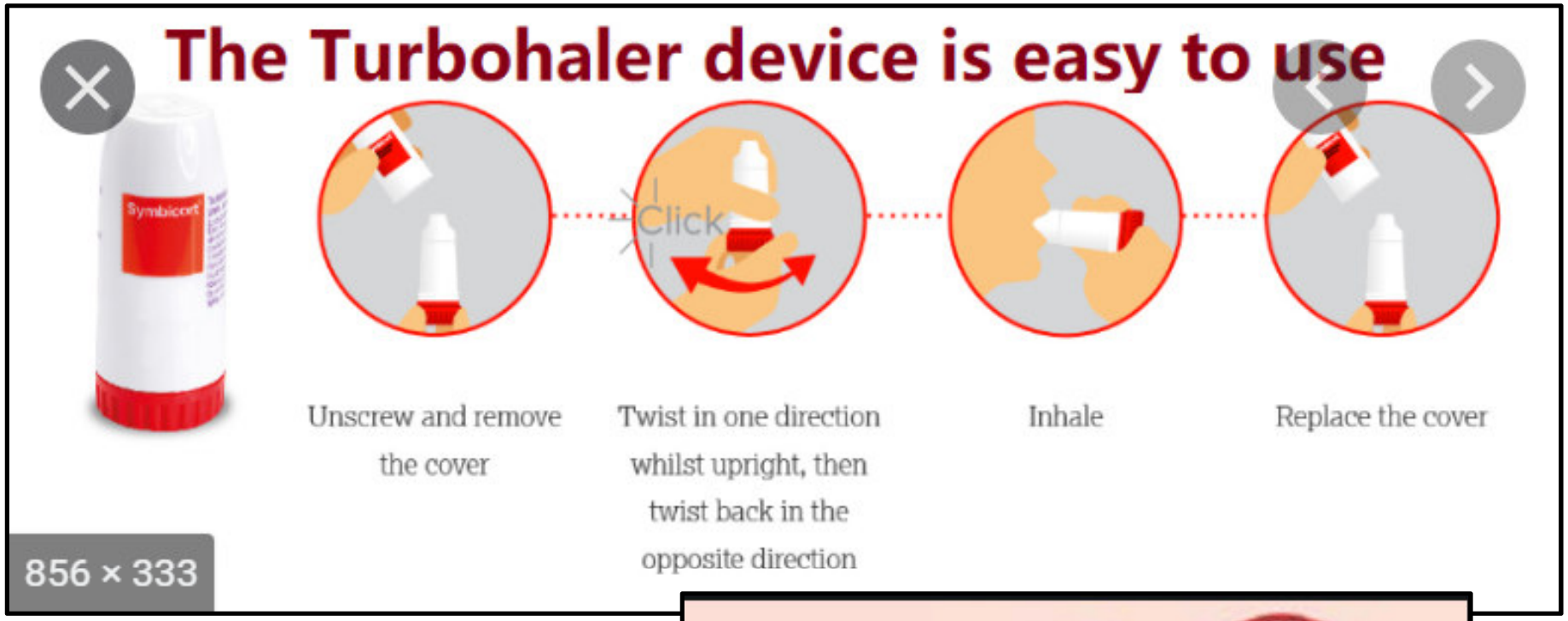
HALF-CIRCLE FLAP
lifts up and down to operate plastic needle



SILVER MEDICINE DISK
contains 4 blisters of medicine; the disk fits into the dark brown wheel inside the DISKHALER

Multi dose devices

- The Turbuhalers was the first DPI to dispense doses metered from a reservoir inside the inhaler.
- When the patient activates the inhaler by twisting the base prior to inhalation, the Turbuhalers reservoir system deposits a single dose of the drug into a series of holes in a dosing disk.
- The turbulence generated in spiral-formed channels in the mouthpiece during inhalation breaks up the agglomerates into fine particles, which are then inhaled into the lungs.


The Turbohaler device is easy to use
Symbicort
Click
Unscrew and remove the cover
Twist in one direction whilst upright, then twist back in the opposite direction
Inhale
Replace the cover
856 × 333

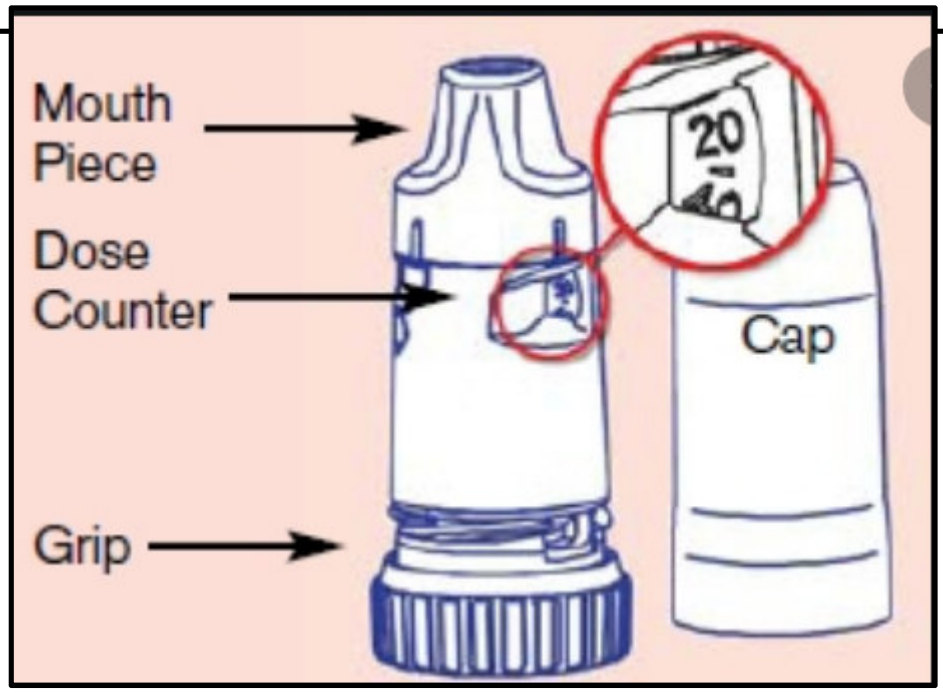

Mouth Piece
Dose Counter
Grip
20
Cap

TABLE I. Current and future "passive" (breath-actuated) dry powder inhalers (table modified from Parry-Billings (37) and Ashurst *et al.* (38))

	Single dose	Multiple unit dose	Multidose
Marketed	Spinhaler® (Aventis)[a] Rotahaler® (GSK) Aeroliser™ (Novartis)[c] Inhalator® (Boehringer) Eclipse (Aventis)	Diskhaler® (GSK) Diskus® (GSK)[b] Aerohaler® (Boehringer)[d]	Turbuhaler® (AstraZeneca) Easyhaler® (Orion) Novolizer® (ASTA Medica) Clickhaler® (IB) Pulvinal® (Chiesi)
In development	Turbospin (PH and T) AIR™ Inhaler (Alkermes)	Flowcaps® (Hovione) MicroDose DPI (MicroDose) Delsys DPI (Delsys) Technohaler® (IB)	Ultrahaler® (Aventis) Taifun® (Focus Inhalation) MAGhaler (Mundipharma) Cyclovent (Pharmachemie) Twisthaler® (Schering-Plough) Airmax (Yamanouchi) Dispohaler (AC Pharma) Jago DPI (Skyepharma)

[a] Formerly Fisons.
[b] Known as Accuhaler in UK.
[c] Also known as Cyclohaler (Pharmachemie) and Monohaler (Miat).
[d] Also known as Inhalator-M.
GSK: GlaxoSmithKline; IB: Innovata Biomed.

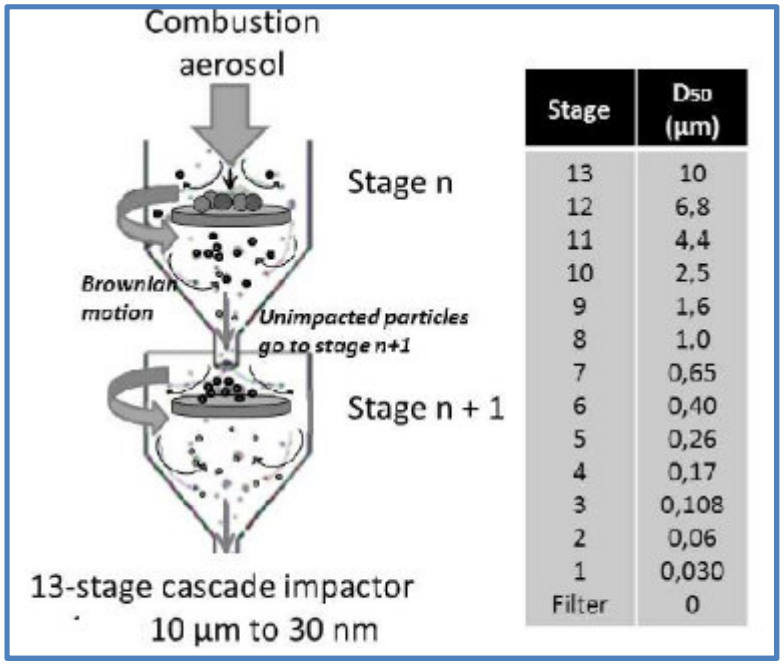
EVALUATION OF PULMONARY DRUG DELIVERY DEVICES

- Cascade impactors
- In- vitro
- In-vivo
- Continuous cell cultures
- Primary cell cultures
- Air-interface Cultures
- Passive Inhalation
- Whole Body Exposure System
- Head only or Nose only exposure systems
- Direct Intratracheal Administration
- Intranasal Administration

Cascade impactors

- Cascade impactors operate on the principle of inertial impaction.
- Each stage of the impactor comprises a series of nozzles or jets through which the sample laden air is drawn, directing any airborne towards the surface of the collection plate for that particular stage. **Whether a particular particle impacts on that stage is dependent on its aerodynamic diameter.**
- Particles having sufficient inertia will impact on that particular stage collection plate, whilst smaller particles will remain entrained in the air stream and pass to the next stage where the process is repeated.
- The stages are normally assembled in a stack or row in order of decreasing particle size.
- As the jets get smaller, the air velocity increases such that smaller particles are collected.

Cascade Impactor



Stage	D50 (µm)
13	10
12	6,8
11	4,4
10	2,5
9	1,6
8	1,0
7	0,65
6	0,40
5	0,26
4	0,17
3	0,108
2	0,06
1	0,030
Filter	0

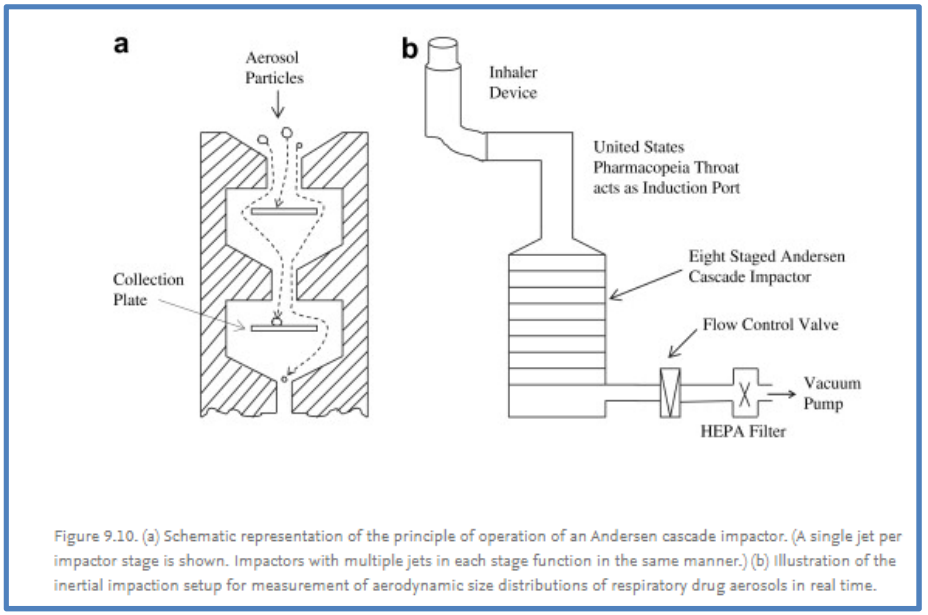
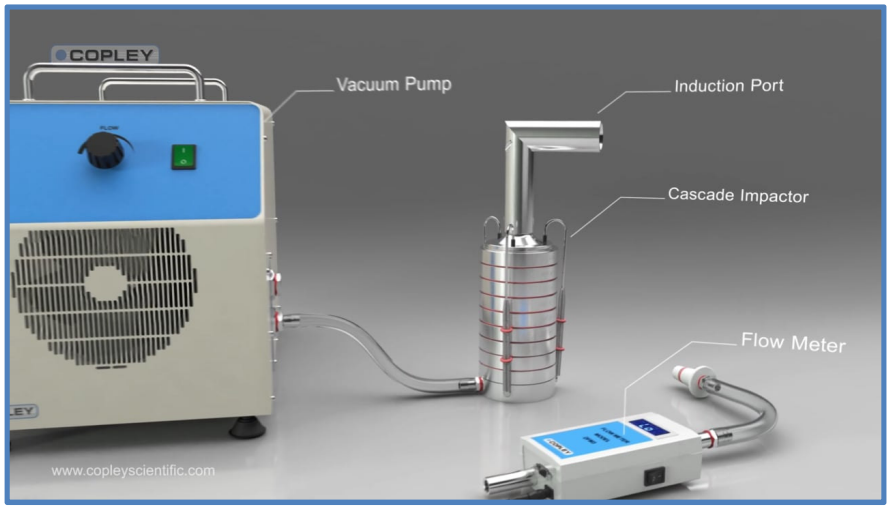


Figure 9.10. (a) Schematic representation of the principle of operation of an Andersen cascade impactor. (A single jet per impactor stage is shown. Impactors with multiple jets in each stage function in the same manner.) (b) Illustration of the inertial impaction setup for measurement of aerodynamic size distributions of respiratory drug aerosols in real time.



Cascade impactor

- At the end of the test, the particle mass relating to each stage is recovered using a suitable solvent and then analysed usually using HPLC to determine the amount of drug actually present.
- The Andersen Cascade Impactor (ACI) is most commonly used impactor within the pharma industry for the testing of inhaled products.
- The ACI is an 8-stage cascade impactor suitable for measuring the aerodynamic particle size distribution (APSD) of both MDIs and DPIs.
- This is also used to measure parameters like Fine Particle Fraction(FPF) and mass median aerodynamic diameter(MMAD).
- **Limitation**
  - Measurements in cascade impactors are done at room temperature and at low relative humidity which is not representative of human airways ambient conditions.

In-vitro

- In vitro model is used in this method .
- It is important that epithelial cells form a tight monolayer in order to represent the natural epithelial barrier.
- Monolayer tightness and integrity are classically assessed by measuring **Trans Epithelial Electrical Resistance(TEER)** and potential difference across monolayer .
- Monolayer of lung epithelial cell allow characterization of drug transport, assessment of potential drug and formulation toxicity.

In-Vivo

- Animal study is carried out to get information on drug deposition, metabolism, absorption and kinetic profile as well as drug and formulation tolerability.
- Non-human primates are used in advanced research. By contrast, small rodent (mice, rats and guinea pigs) are common models for initial studies on pulmonary drug delivery.
- Human branching is symmetric , in contrast monopodial branching of non human primates mammals.
- Different mucocilliary clearance
- Large mammal have longer airways than small rodents.

Continuous cell cultures

- Continuous cell culture is more reproducible and easier to use than primary cell culture but often don't have differentiated morphology and biochemical characteristics of original tissue.
- There are few cell line derived from alveolar epithelial cells.
- A549 is type II alveolar epithelial cell line that originates from human lung adenocarcinoma. It is used to study metabolic and toxicological studies.

Air- Interface culture

- **Air interface culture are models** that allow aerosol particle to deposit directly onto semi dry apical cell surface.
- Drug deposition and dissolution occur in a small volume of cell lining fluid, a situation that mimics more closely the deposition on the lung surface in vivo.
- The AIC showed greater similarity to airways epithelial morphology, with greater glycoprotein secretion, more pronounced microvilli.

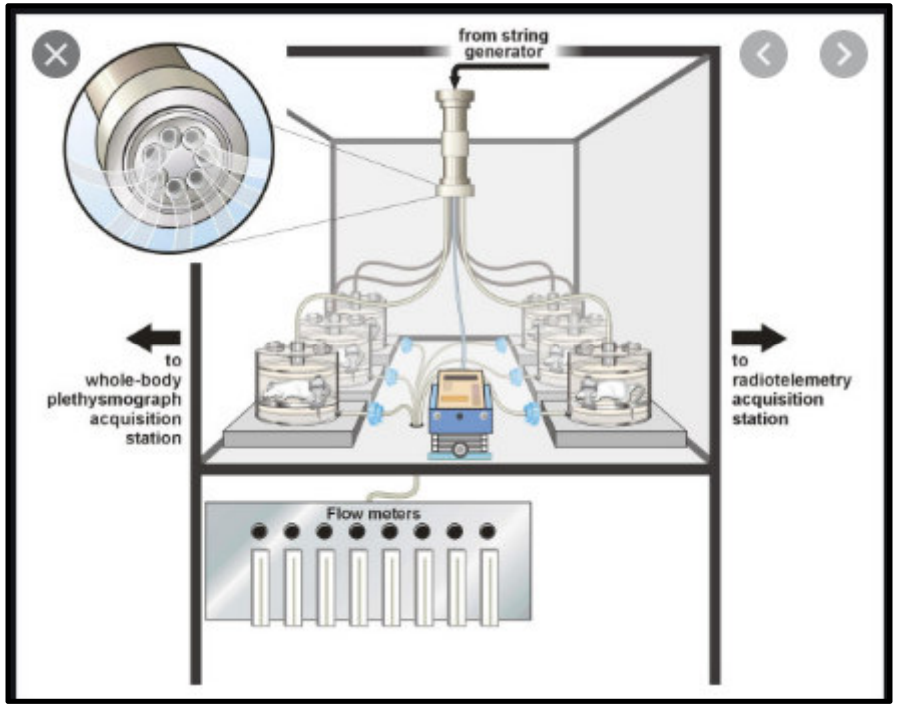
Passive Inhalation

- During passive inhalation of aerosolized drug, animal are kept awake and allowed to breathe normally. Device most frequently used are nebulizers
- Passive inhalation is principally used in the mouse and less frequently in larger animals(rat, dog, guinea pig)
- Drug concentration in the aerosol is determined by sampling.

Whole Body Exposure System

- In whole body exposure system, animal are placed in a sealed plastic box that is connected to nebulizer or generator dry powder aerosol.
- There is potential drug absorption across the skin after deposition on animal fur, from the nasal mucosa and from GIT.

Whole Body Exposure System

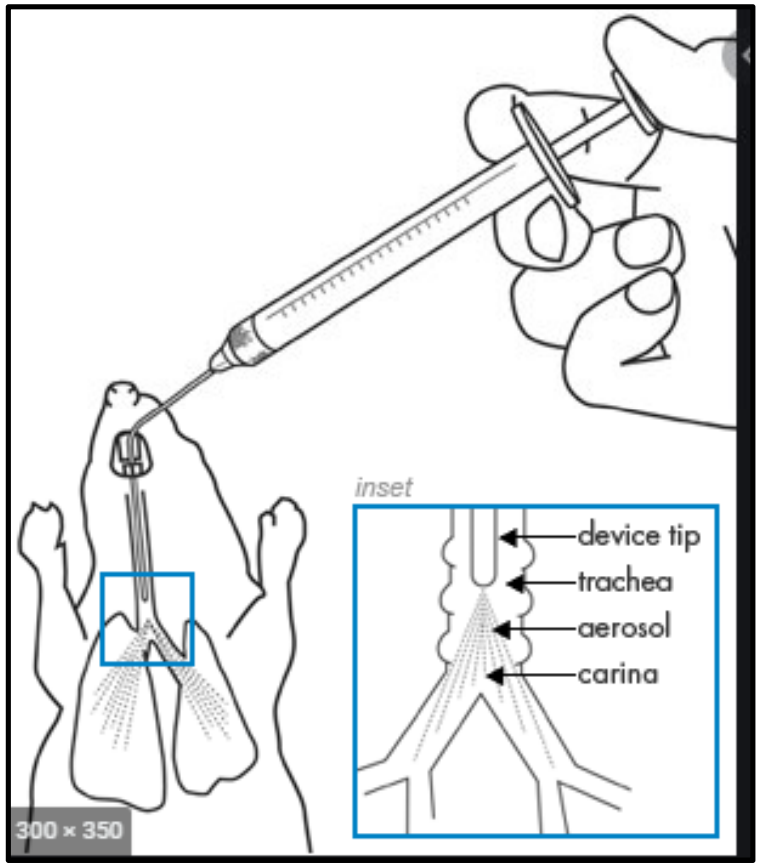


Head only or Nose only exposure system

- In Head only or Nose only exposure systems, the animal is attached to the exposure chamber and only the head or nose is in contact with aerosol.
- The system can be designed for delivering drugs to one or several animal.
- Compared to whole body exposure system, this method offer several advantages.

Direct intra-tracheal administration

- Dry powders can be delivered intratracheally using a powder insufflator or by generating a powder aerosol.
- It is done to measure drug deposition and systemic drug absorption.
- Advantages of intratracheal administration of drugs include the perfect control of the drug dose delivered , absence of drug losses in instrumentation, bypassing of nasal passages .



Intranasal administration

- Intranasal administration is mostly known for local drug delivery to the nasal mucosa but it can be used for intrapulmonary drug administration in mice.
- Intranasal administration is performed on the anaesthetized mouse kept in a vertical position.
- With the help of micropipette, the drug solution is deposited on nostril and simply aspired in respiratory airways during breathing.


Thank you!
grammarly