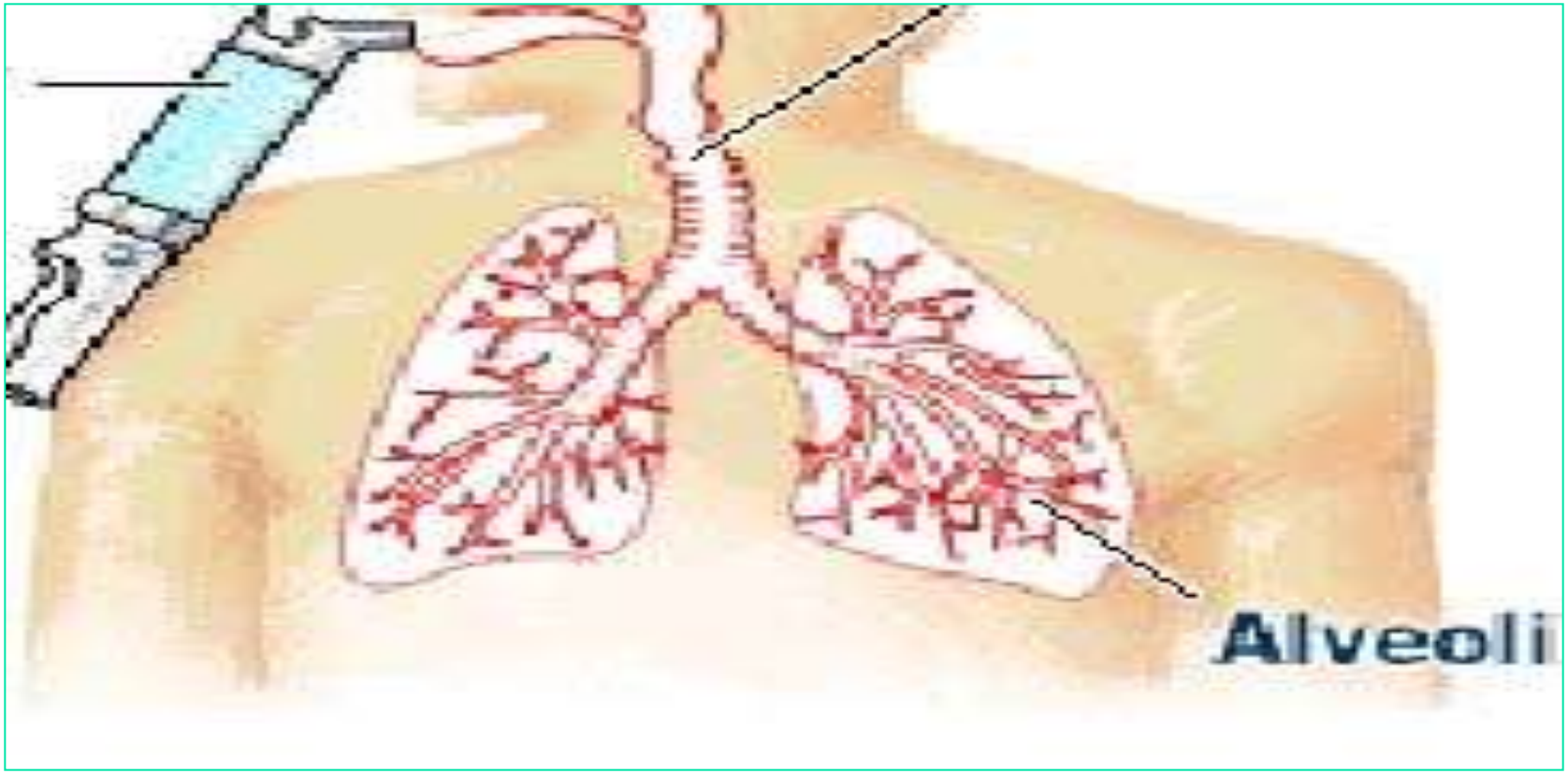
Pulmonary Drug Delivery



Outlines:

- Introduction
- Advantages and limitations
- Anatomy and physiology
- Mechanisms of drug absorption
- Biopharmaceutical considerations
- Pulmonary drug delivery systems

Introduction

- The administration of a drug at its site of action can result in a rapid onset of activity, which may be highly desirable in treating many respiratory diseases.
- Smaller doses can be administered locally compared to delivery by the oral or parenteral routes, thereby reducing the potential incidence of adverse systemic effects and reducing drug costs.

- The pulmonary route is also useful where a drug is poorly absorbed orally, e.g. sodium cromoglicate, or where it is rapidly metabolized orally, e.g. isoprenaline.
- The lung may also be used as a route for delivering drugs having systemic activity, because of its large surface area, the abundance of capillaries and the thinness of the air–blood barrier.
- The potential for delivering biopharmaceuticals,

such as insulin, vaccines and growth hormone via the airways is now well established.

What are the advantages and limitations of pulmonary DDS ??

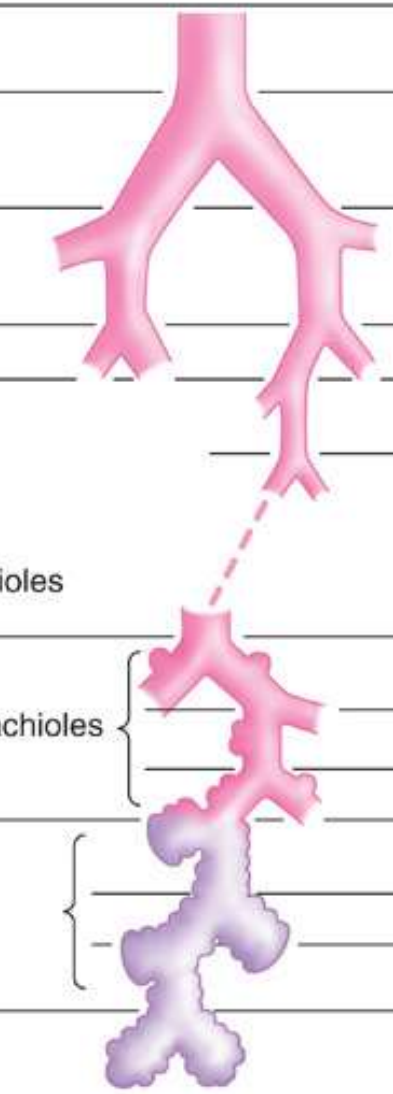
Anatomy and physiology

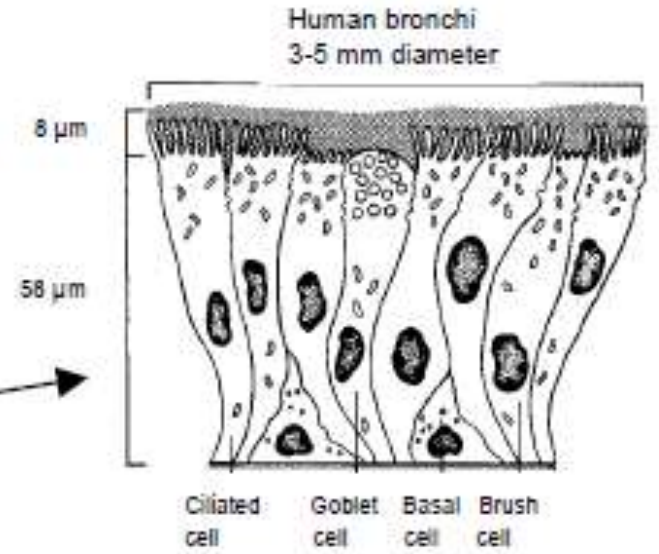
- The lung is the organ of external respiration, in which oxygen and carbon dioxide are exchanged between blood and inhaled air.
- The structure of the airways also efficiently prevents the entry, and promotes removal of airborne foreign particles, including microorganisms.
- They contain approximately $2–6 \times 10^8$ alveoli, producing a surface area of 100–140 m^2 in an adult male.

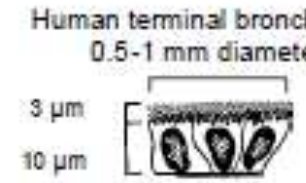
Pulmonary epithelium

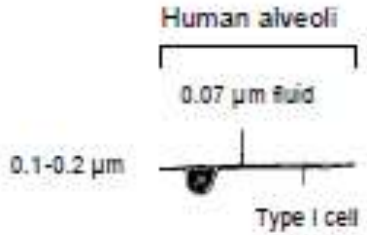
- Bronchi
  - Mainly ciliated and goblet cells, some serous and Clara cells
- Bronchioles
  - Mainly ciliated cuboidal cells, some serous and Clara cells
- Alveolar region
  - Type I pneumocytes
  - Type II pneumocytes
  - Alveolar macrophages

	Name of branches	Number of tubes in branch
Conducting zone	Trachea	1
	Bronchi	2
		4
		8
	Bronchioles	16
		32
	Terminal bronchioles	6×10^4
Respiratory zone	Respiratory bronchioles	5×10^5
	Alveolar ducts	
	Alveolar sacs	8×10^6









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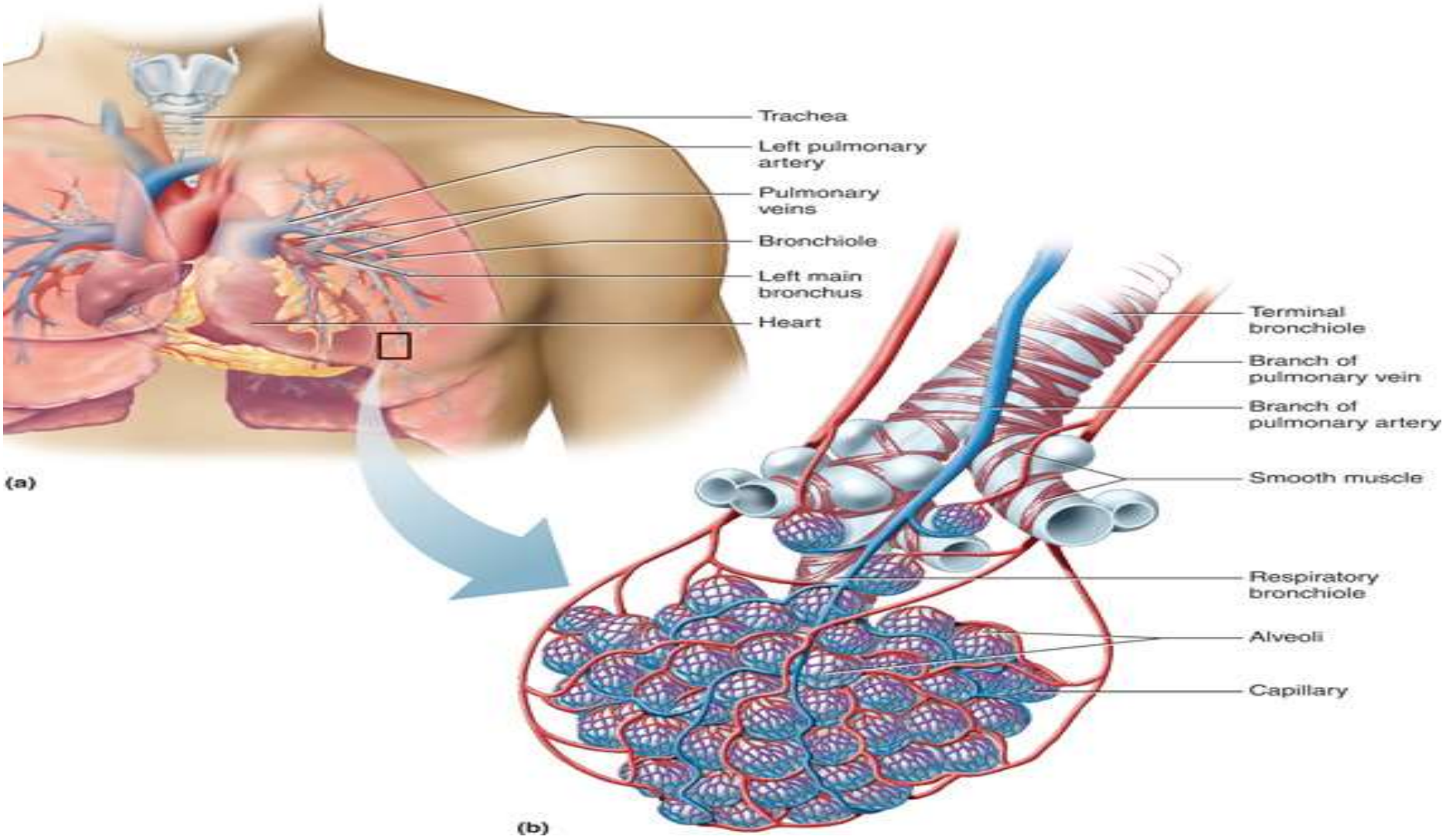
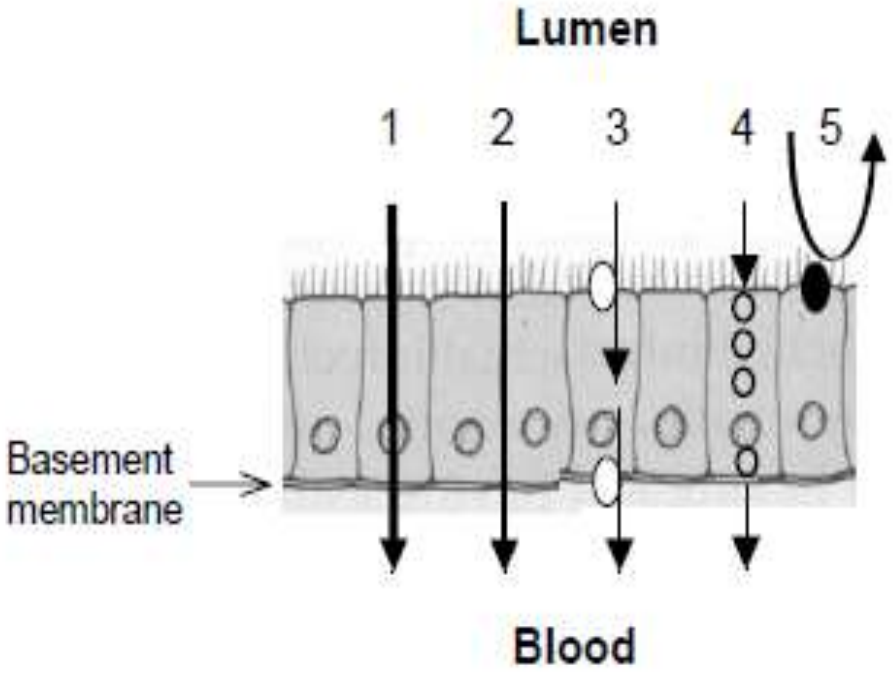


Abundance of pulmonary capillaries
Ventilated air is brought into close proximity to the "pulmonary" blood
Efficient and thorough gas exchange between the air and the blood.

- The conducting airways are lined with ciliated epithelial cells.
- Insoluble particles deposited on the airways walls in this region are trapped by the mucus, swept upwards from the lungs by the beating cilia to the throat, and are swallowed.

Mechanisms of drug absorption



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

Figure 4. Epithelial drug transport mechanisms.

- Passive diffusion
- Transporter-mediated absorption and efflux
- Vesicle-mediated endocytosis and transcytosis
- Particle transport

Passive diffusion

- The rate of absorption was increased with an increase in lipophilicity for compounds with partition coefficients (chloroform/buffer pH 7.4) ranging from –3 to 2.
- Hydrophilic solutes appear to be absorbed by passive diffusion through the intercellular junction pores.

- Most exogenous macromolecules with a molecular weight less than 40 kDa are thought to be absorbed from the air space through tight junctions by passive diffusion.
- The absorption rate of hydrophilic compounds is inversely related to the molecular weight (range 60- 75000 Da).

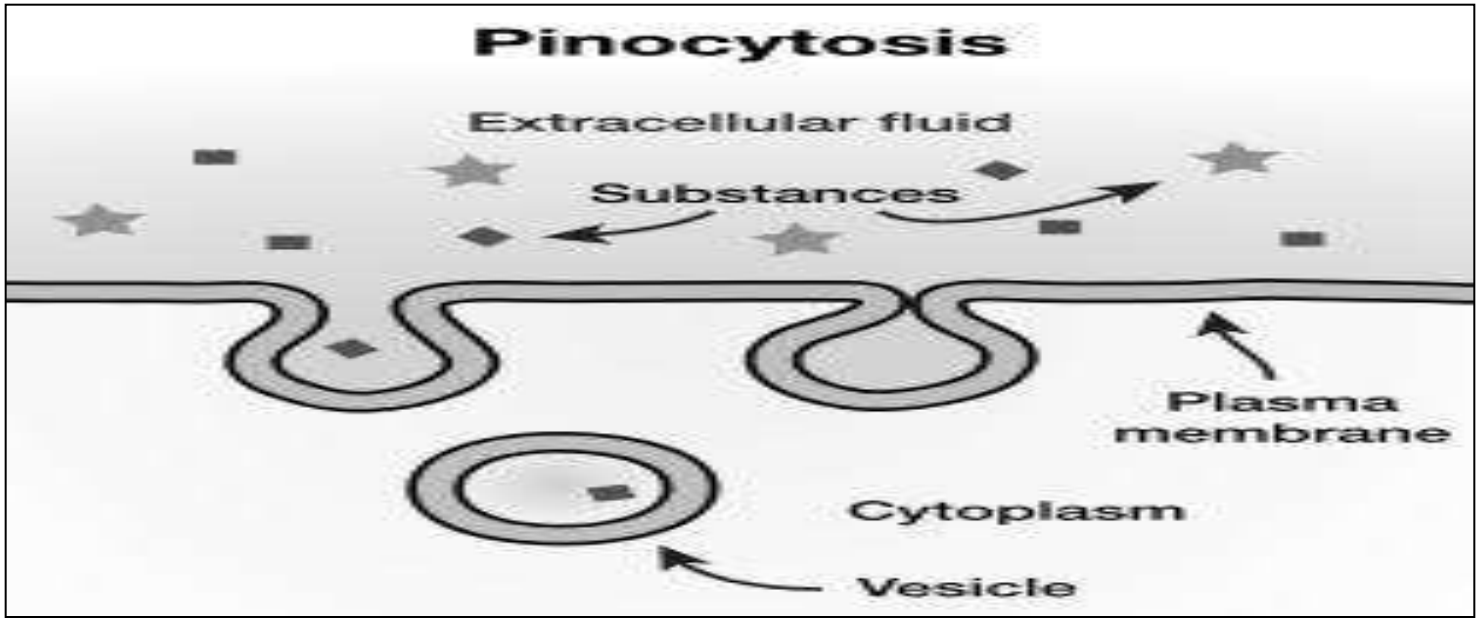
Transporter-mediated absorption and efflux

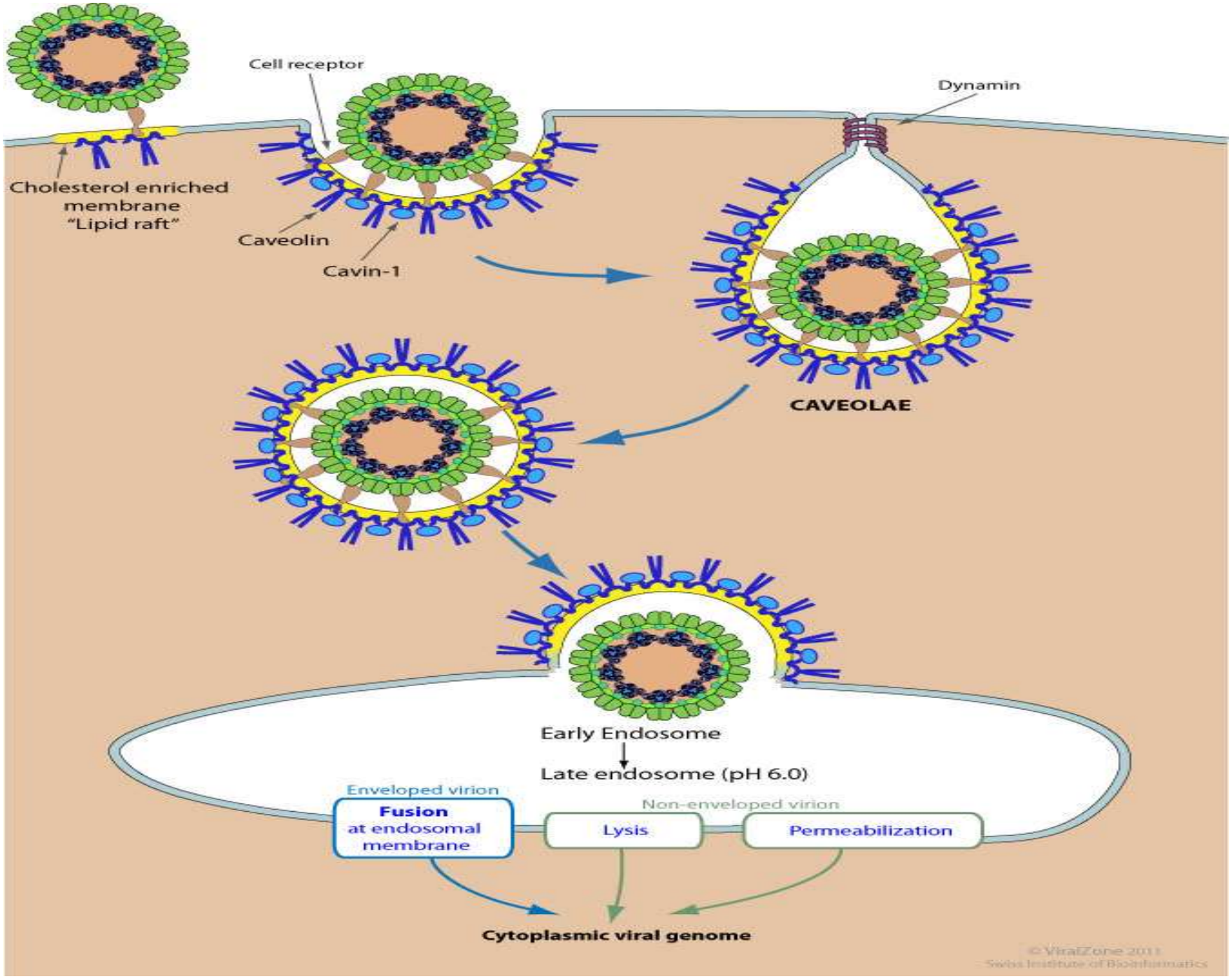
- Evidence of carrier-mediated transport through the pulmonary epithelial barrier is relatively limited.
- Efflux transporter proteins, first known to mediate multidrug resistance (MDR) in tumor cells, are thought to be involved in the protection of the lungs against inhaled toxic pollutants.

Vesicle-mediated endocytosis and transcytosis

- The existence of a high numerical density of membrane vesicles within the alveolar endothelial cells and epithelial type I cells has long been recognized.
- Most of the vesicles are non-coated or smooth-coated vesicle populations, morphologically recognized as caveolae.

- The number of caveolae-like structures in the alveolar type I epithelium is less numerous than in the endothelium.
- They may be involved in the transcytosis or vesicular movement of macromolecules across endothelial cells




Cell receptor
Dynamin
Cholesterol enriched membrane "Lipid raft"
Caveolin
Cavin-1
CAVEOLAE
Early Endosome
Late endosome (pH 6.0)
Enveloped virion
Fusion at endosomal membrane
Non-enveloped virion
Lysis
Permeabilization
Cytoplasmic viral genome
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Swiss Institute of Bioinformatics

Particle transport

- Ultrafine particles (diameter ≤100 nm) have been demonstrated to pass rapidly (within 5 min) from the lungs into the systemic circulation after intratracheal instillation into hamsters and aerosol inhalation in humans.

- After administration of aerosolized ultrafine particles into rats, the particles were found in the alveolar walls and in pulmonary lymph nodes which suggests that drainage into the lymph may contribute to the air-to-blood transport of the inhaled particles.

Biopharmaceutical considerations

The deposition of a drug/ aerosol in the airways is dependent on four factors:

- The physicochemical properties of the drug.
- The formulation.
- The delivery/ liberating device.
- The patient (breathing patterns and clinical status).

Why deliver drugs to the lung?

- Local administration
  - Target large and small bronchial airways
    - Bronchodilators, steroids, antibiotics
    - DNase (Pulmozyme) - macromolecule
    - Cyclosporine
- Systemic
  - Target alveolar region
    - Morphine, fentanyl – conventional molecules
    - Insulin - macromolecule

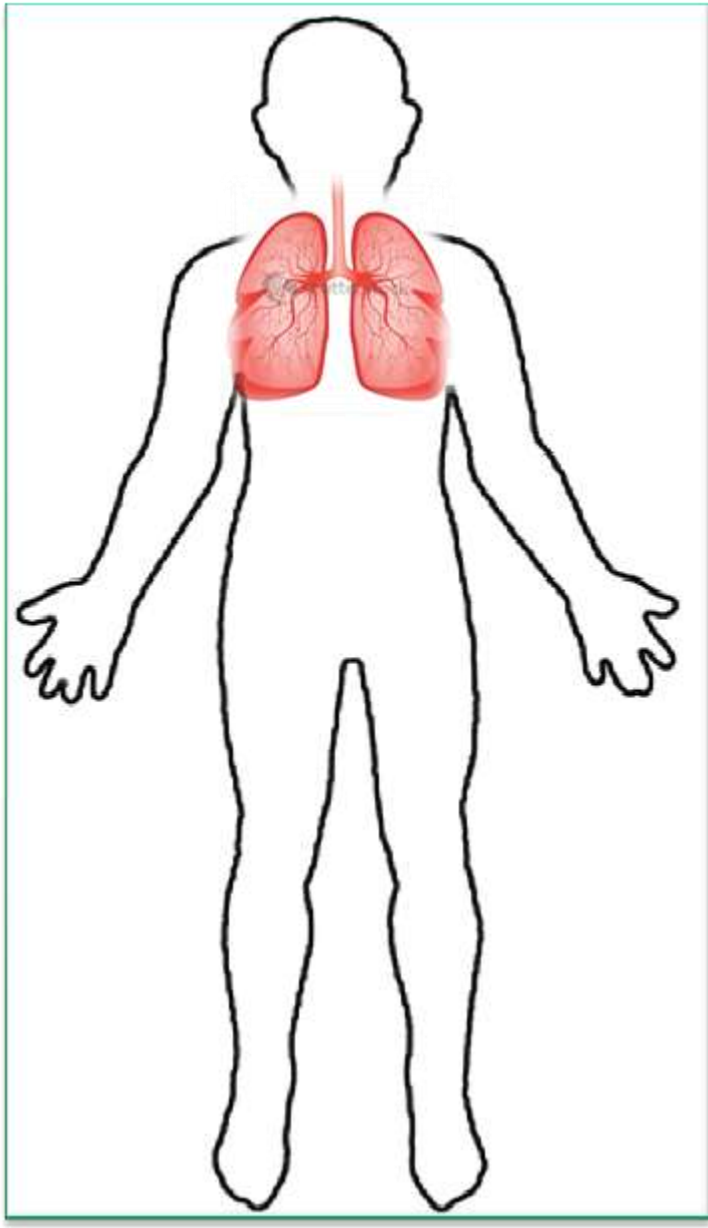


Table 2: Factors that may affect the pulmonary absorption rate and bioavailability

Device and formulation	Drug	Physiology
particle properties (size, density, shape, charge)	dissolution rate	breathing pattern
	solubility	blood flow
deposition pattern	lipophilicity	airway morphology
excipients	molecular weight	surface area
concentration	charge	mucociliary clearance
osmolarity	hydrogen bonding potential	lung surfactant
viscosity	aggregation/complex binding	alveolar macrophages
pH	conformation	epithelial permeability
dose size/volume	chemical stability	endothelial permeability
	enzymatic stability	transporter proteins
		enzymatic/metabolic activity
		disease
		tissue composition (drug sequestration)

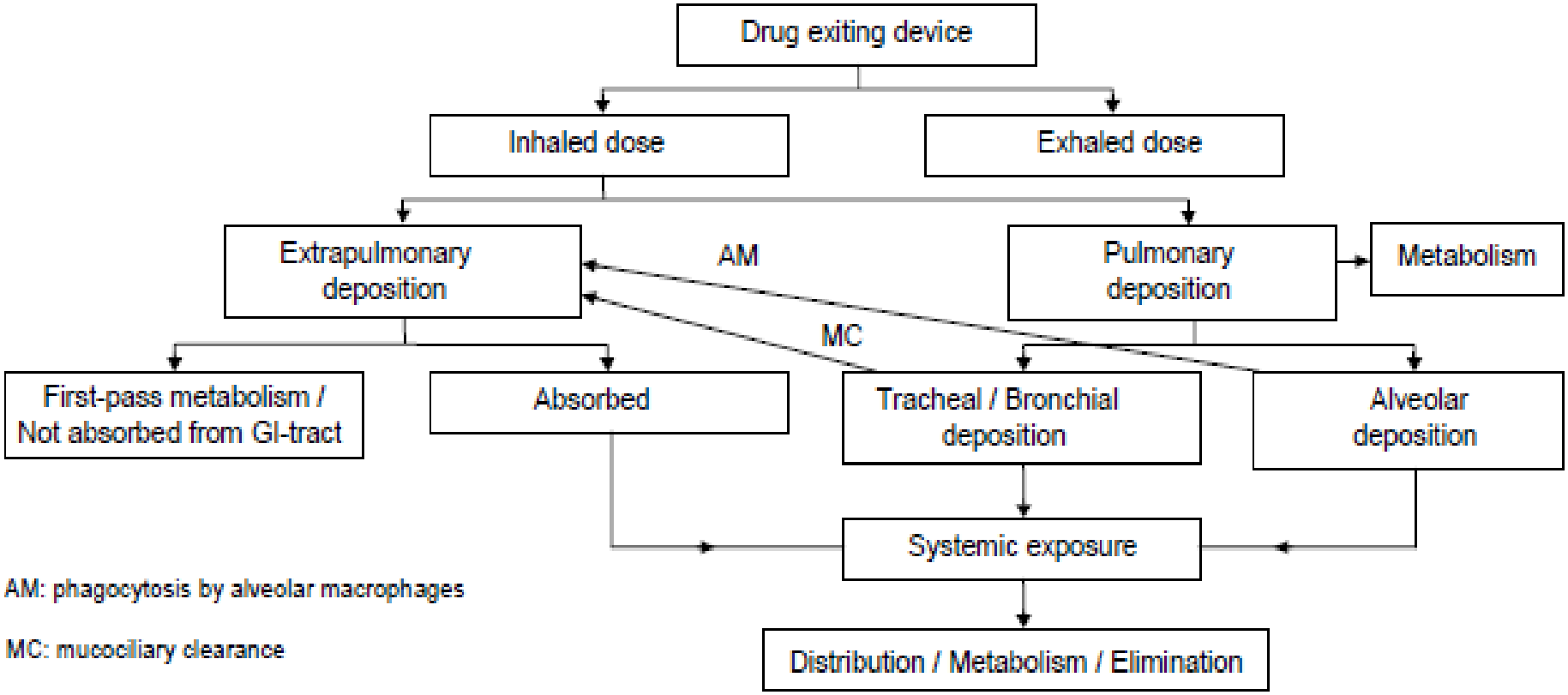


Figure 6. Schematic illustration of the fate of an inhaled drug.

The physicochemical properties of the drug

Particle size and density:

The most fundamentally important physical property of an aerosol for inhalation.

The particle size of an aerosol is usually standardized by calculation of its aerodynamic diameter, da, which is (the physical diameter of a unit density sphere which settles through air with a velocity equal to the particle in question).

For approximately spherical particles:

$$d_a = d_p(\rho/\rho_0)^{1/2} \qquad (37.1)$$

where d_p is physical diameter, ρ is particle density and ρ_0 is unit density, i.e. 1 g/cm^3.

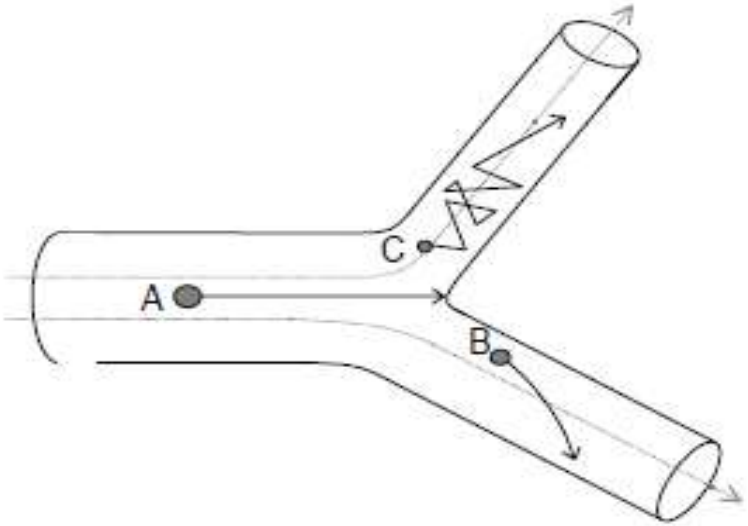
When d_p is the mass median diameter (MMD), d_a is termed the mass median aerodynamic diameter (MMAD).

- Large porous particles, with large physical diameters of the order of 20 μm are efficiently delivered to and deposited in the lungs.
- Their low density, due to the porous or hollow nature of their structure means such particles have a small aerodynamic diameter and are thus carried in the inspired air, deep into the lungs.

- As a particle enters the respiratory tract, the change from ambient to high relative humidity (approximately 99%) results in condensation of water on to the particle surface, which continues until the vapour pressure of the water equals that of the surrounding atmosphere.

- Hygroscopic growth will affect the deposition of particles, resulting in deposition higher in the respiratory tract than would have been predicted from measurements of their initial size.

- The most important mechanisms of particle deposition in the respiratory tract are inertial impaction, sedimentation, and diffusion



A Impaction

B Sedimentation

C Diffusion

Figure 5. Mechanisms of particle deposition in the airways.

- Inertial impaction occurs predominantly in the extrathoracic airways and in the tracheobronchial tree, where the airflow velocity is high and rapid changes in airflow direction occurs.
- Generally, particles with a diameter larger than 10 μm are most likely deposited in the extrathoracic region, whereas 2-10 μm particles are deposited in the tracheobronchial tree by inertial impaction.

- A long residence time of the inspired air favors particle deposition by sedimentation and diffusion.
- Sedimentation is of greatest importance in the small airways and alveoli and is most pronounced for particles with a diameter of 0.5-2 μm.
- Ultrafine particles (<0.5 μm in diameter) are deposited mainly by diffusional transport in the small airways and lung parenchyma where there is a maximal residence time of the inspired air.

H.w ??

- Find the mathematical relationship for each mechanism of deposition.
- What is the meaning of interception as deposition mechanism?

Breathing patterns

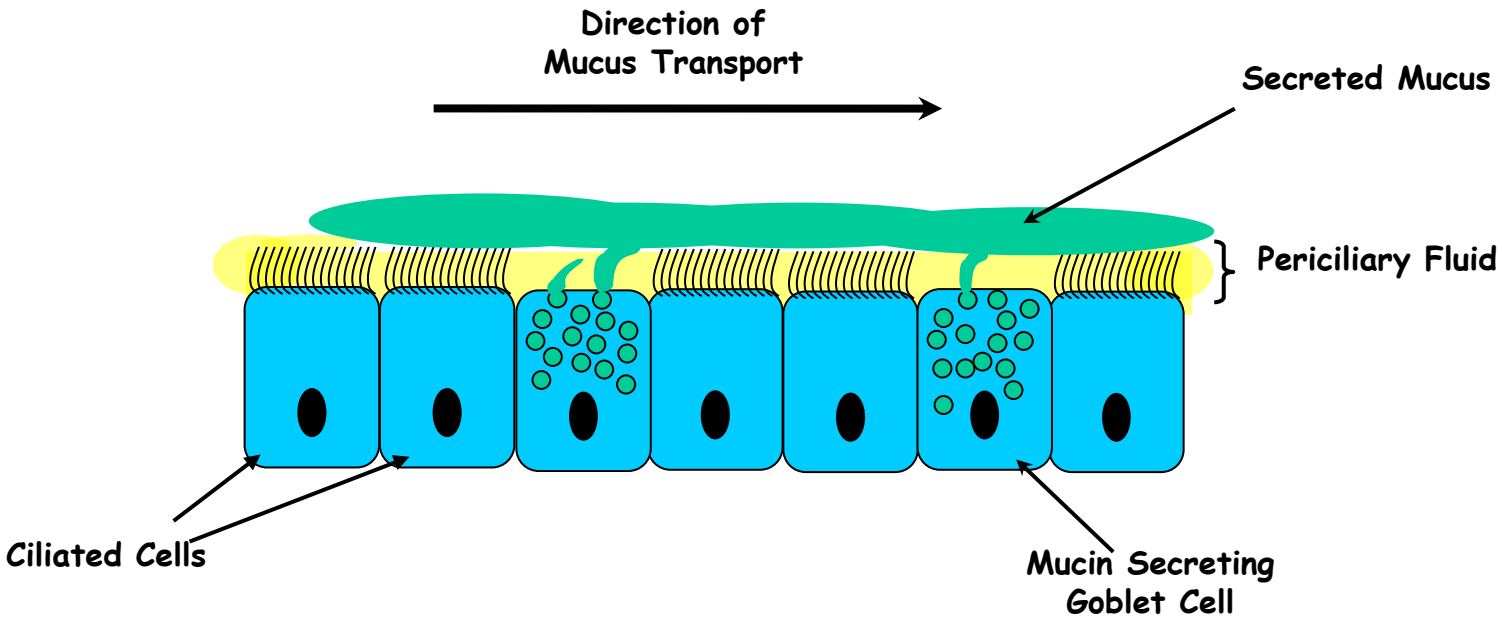
Patient-dependent factors, such as breathing patterns, lung physiology and the presence of pulmonary disease also affect particle deposition.

Optimal aerosol deposition occurs with slow, deep inhalations to total lung capacity, followed by breath-holding prior to exhalation.

Clearance of inhaled particles and drug absorption

- Particles deposited in the ciliated airways are cleared by mucociliary clearance within 24 hours and are ultimately swallowed.
- Insoluble particles penetrating to the alveolar regions, and which are not solubilized in situ, are removed more slowly.
- Alveolar macrophages engulf such particles and may be removed via the lymphatics.

Mucociliary clearance



- The rate of drug absorption, and consequently drug action, can be influenced by the formulation.
- Rapid drug action can generally be achieved using solutions or powders of aqueous soluble salts, whereas slower or prolonged absorption may be achieved using suspension formulations, powders of less soluble salts or novel drug delivery systems such as liposomes and microspheres.

Fate of particles in the airway

- Mucus barrier
  - Dissolution
  - Diffusion (thickness; micro-viscosity; size of drug; charge interactions)
- Mucociliary clearance
  - Ends at terminal bronchioles
- Alveolar clearance
  - Uptake by alveolar macrophages

Factors affecting the absorption and metabolism of drugs

- Area
- Thickness of absorption barrier
- Blood supply
- Deposition site
  - Area of alveolar region 10X larger than TB region
  - Airway to blood path length 10X larger in TB region
  - Blood flow 10X higher in alveolar region
  - Mucociliary clearance present in TB region
- Enzymatic activity
  - Cytochrome P-450; esterases, peptidases, monooxygenases, various transferases
- Membrane permeability

Pulmonary drug delivery systems

- **Pressurized metered-dose inhalers**

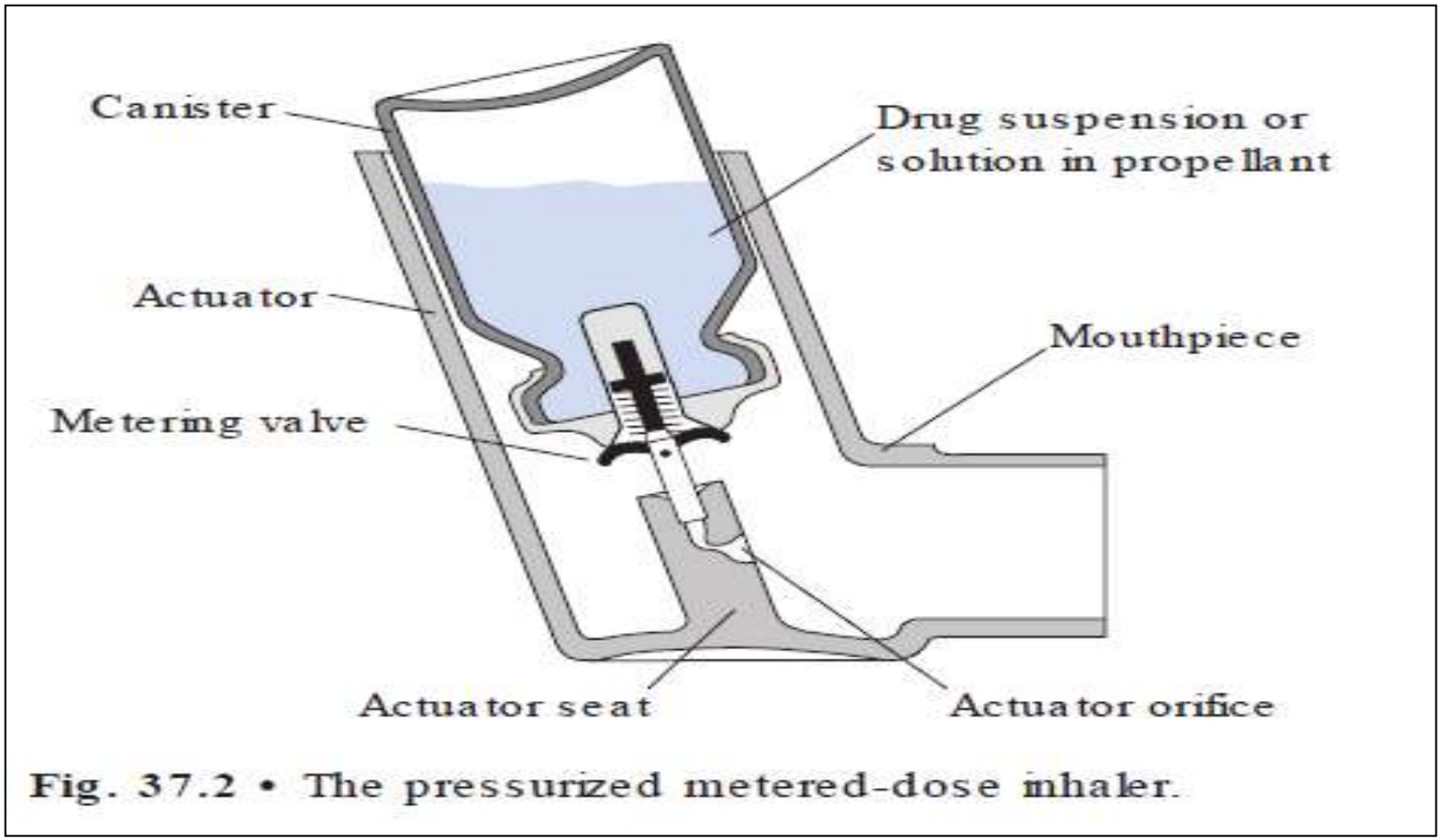
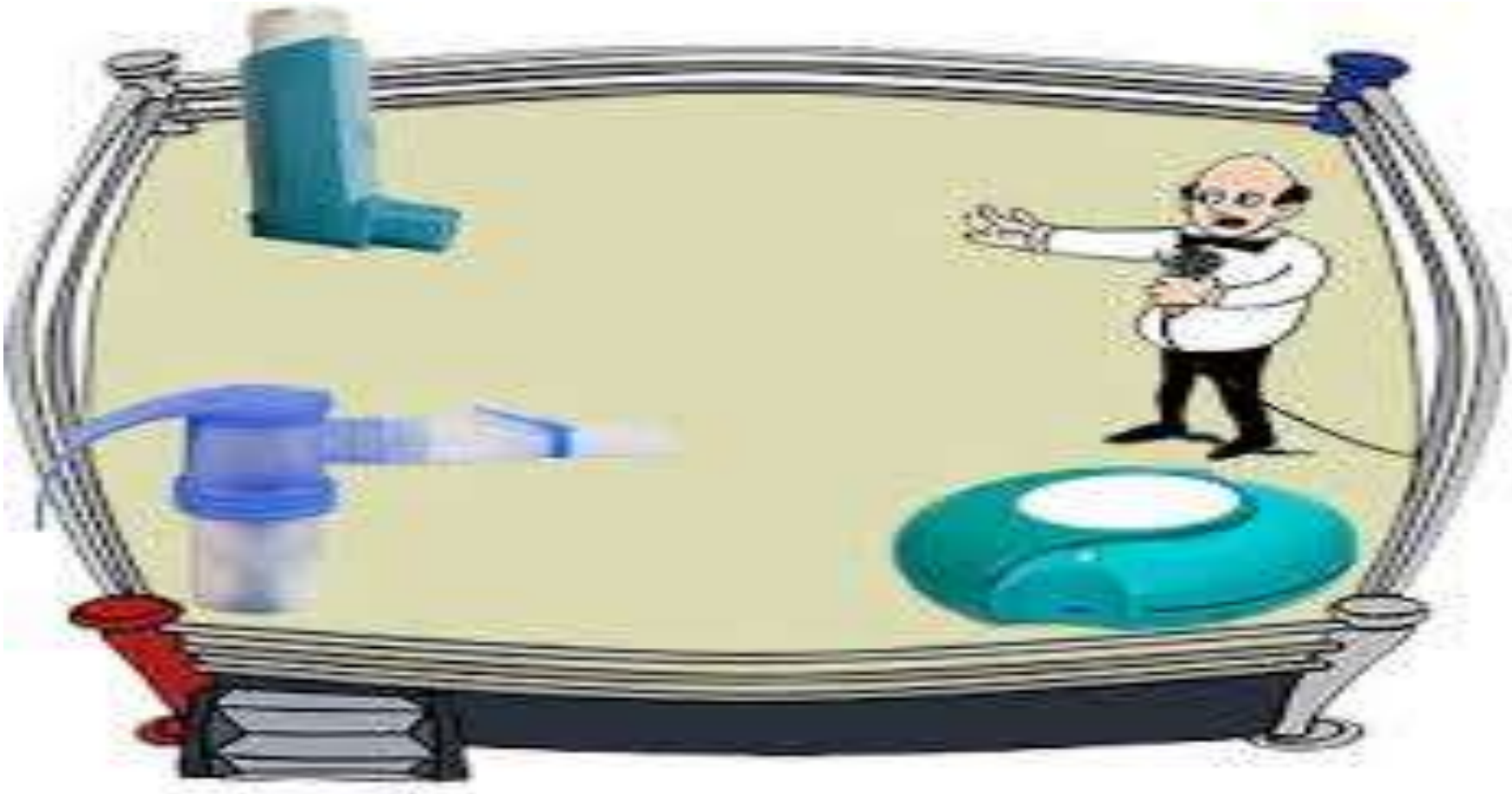


Fig. 37.2 • The pressurized metered-dose inhaler.



- **Dry powder inhalers**

- Unit dose devices with drug in HGC.
- Multidose devices with drug in foil blisters.
- Multidose devices with drug preloaded in inhaler.
- Breath-assisted devices

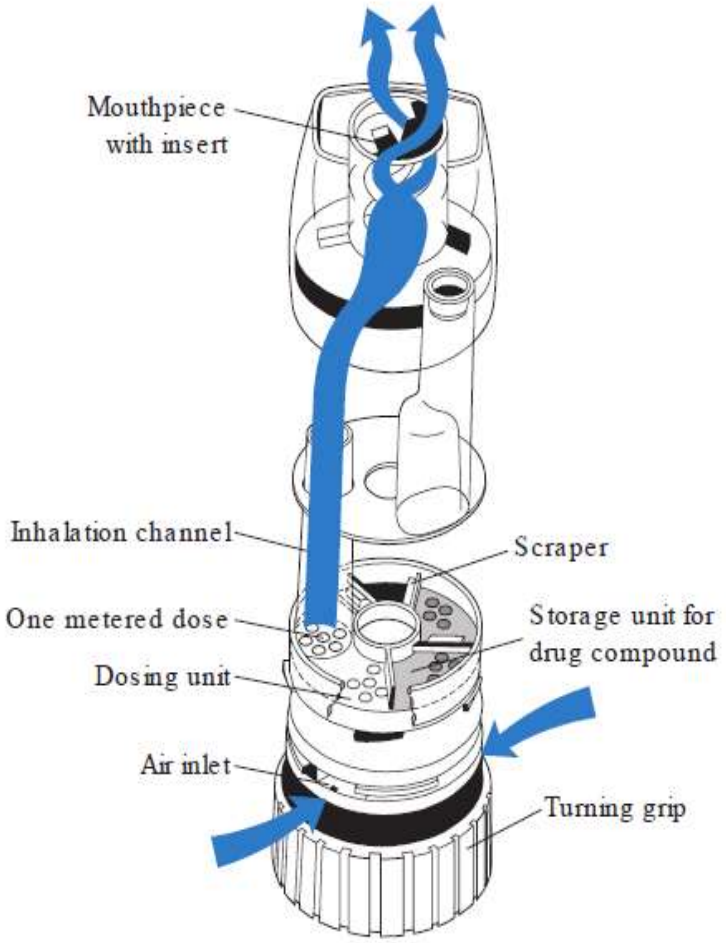


Fig. 37.8 • The Turbohaler®. (Courtesy of AstraZeneca.)

To view

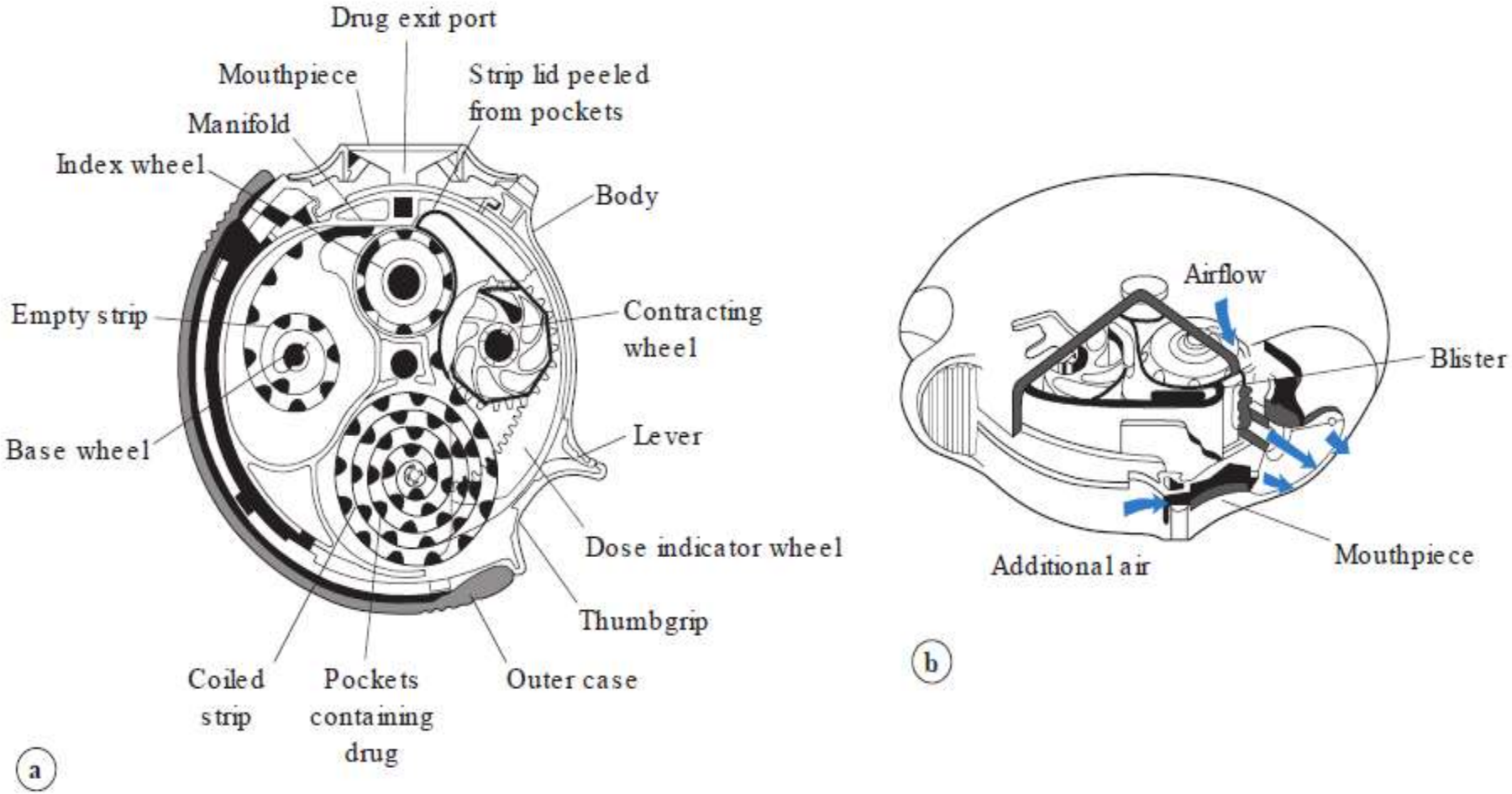


Fig. 37.7 • The Accuhaler/Diskus® dry powder inhaler, showing (a) a schematic diagram and (b) a cross-sectional representation of the device. (Courtesy of Prime et al, 1996, with permission.)

To view

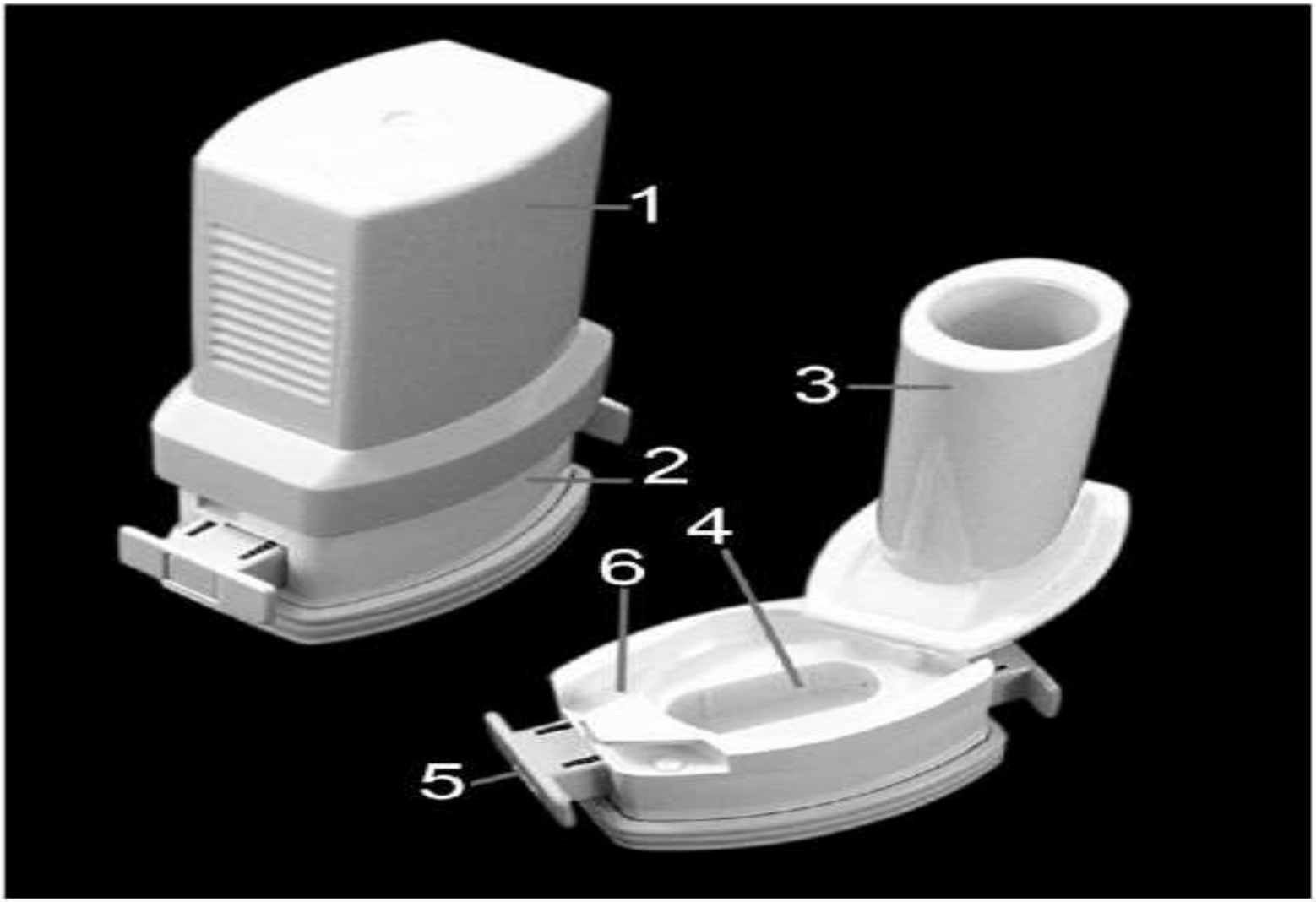


Fig. 37.5 • The Aerolizer/Cyclohaler® dry powder inhaler. Comprising: 1 cap; 2 base; 3 mouthpiece; 4 capsule chamber; 5 button attached to pins for piercing capsule; 6 air inlet channel

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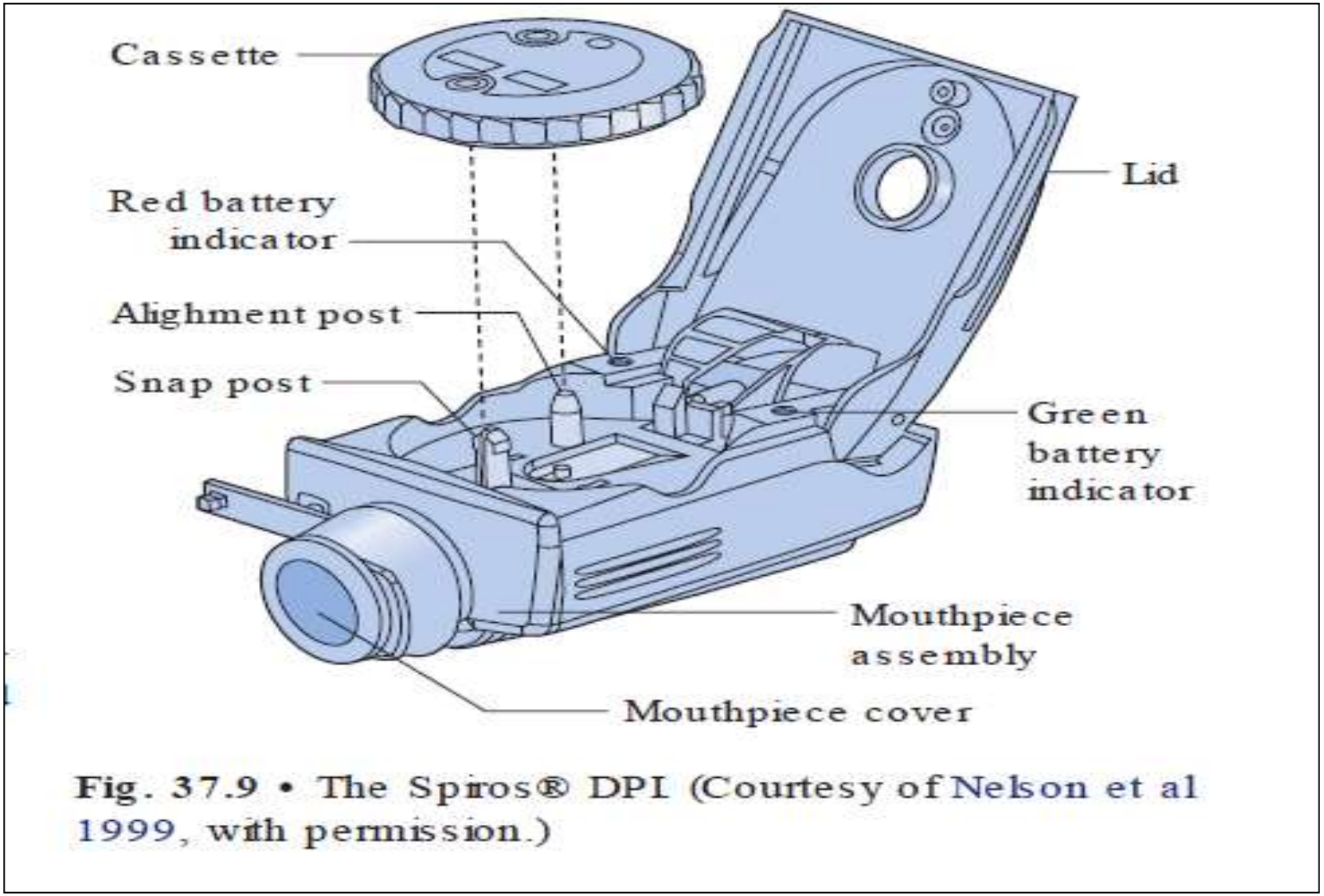

Fig. 37.9 • The Spiros® DPI (Courtesy of Nelson et al 1999, with permission.)

Breath-assisted device (To view)

Nebulizers

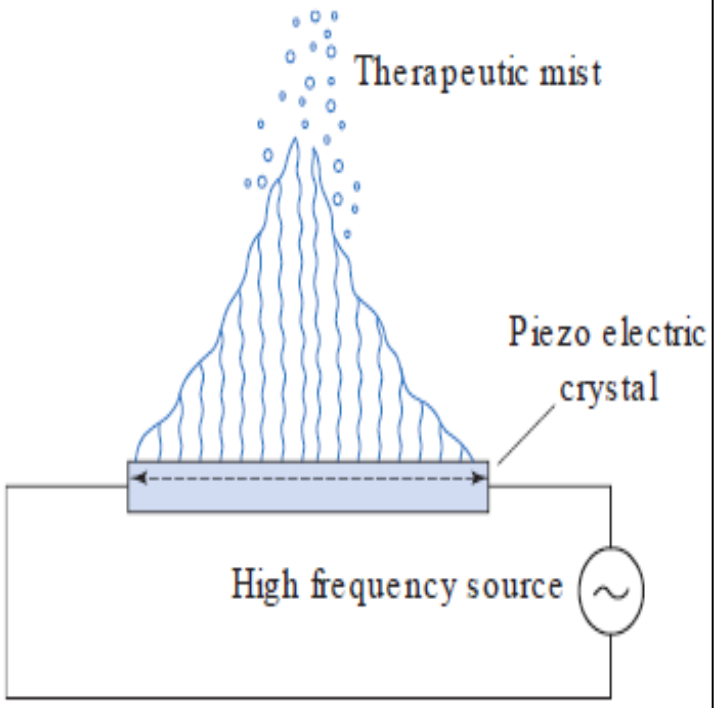

Fig. 37.11 • Schematic diagram of an ultrasonic nebulizer. (Courtesy of Atkins et al, 1992, with permission.)

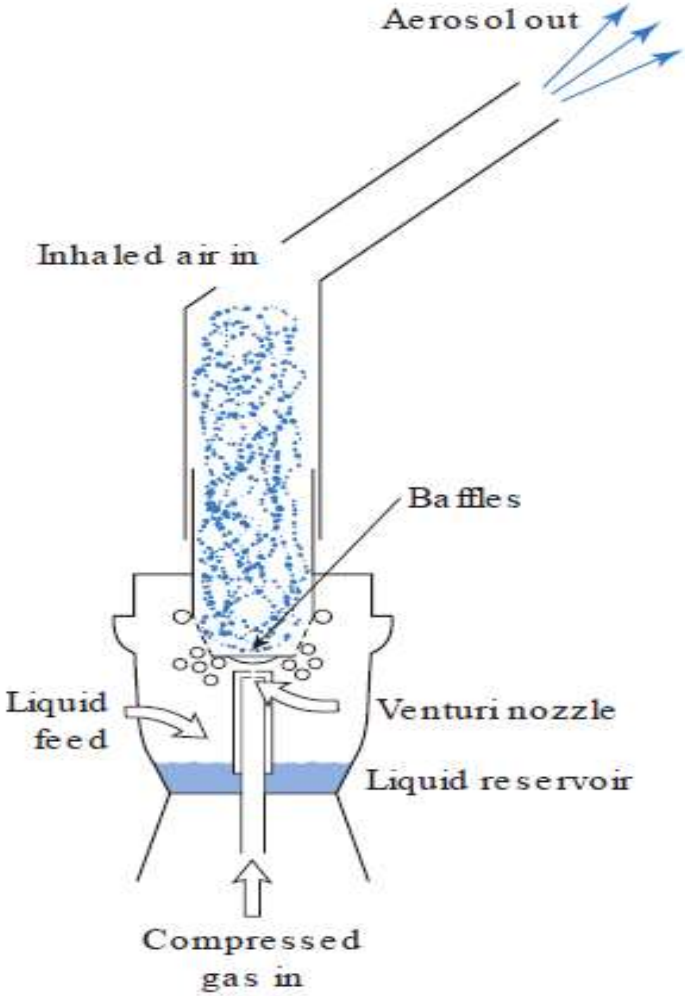

Fig. 37.10 • Schematic diagram of a jet nebulizer. Compressed gas passes through a Venturi nozzle, where an area of negative pressure is created. Liquid is drawn up a feed tube and is fragmented into droplets. Large droplets impact on baffles, and small droplets are carried away in the inhaled air stream.

To view