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Pulmonary drug delivery. Part I: Physiological factors affecting therapeutic effectiveness of aerosolized medications

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As the end organ for the treatment of local diseases or as the route of administration for systemic therapies, the lung is a very attractive target for drug delivery. It provides direct access to disease in the treatment of respiratory diseases, while providing an enormous surface area and a relatively low enzymatic, controlled environment for systemic absorption of medications. As a major port of entry, the lung has evolved to prevent the invasion of unwanted airborne particles from entering into the body. Airway geometry, humidity, mucociliary clearance and alveolar macrophages play a vital role in maintaining the sterility of the lung and consequently are barriers to the therapeutic effectiveness of inhaled medications. In addition, a drug's efficacy may be affected by where in the respiratory tract it is deposited, its delivered dose and the disease it may be trying to treat.

Keywords: administration, aerosol, inhalation, lung, review

Introduction

Inhaled medications have been available for many years for the treatment of lung diseases and are widely accepted as being the optimal route of administration of first-line therapy for asthma and chronic obstructive pulmonary diseases. In recent years, the lung has been studied as a possible route of administration for the treatment of systemic diseases, such as diabetes mellitus. Behind this wave of novel inhaleable drugs is the recent development of new inhalation devices that make it possible to deliver larger drug doses (milligram compared with microgram dosing) to the airways and achieve greater deposition efficiency than the older devices (>50% lung deposition *vs.* ≤20% with older devices) [1]. For the lungs to be the target organ or a route of administration, the appropriate amount of drug must be deposited past the oropharyngeal region to achieve therapeutic effectiveness. The site of deposition, that is on central or peripheral airways, and whether the distribution of the inhaled drug is uniform or non-uniform may also play a role in an inhaled drug's effectiveness. Today, there are more than 65 different inhaled products of more than 20 active ingredients marketed to treat respiratory diseases [2]. Despite the widespread use of inhaled medications, our knowledge is limited with regard to the optimal lung deposition, site for local therapeutic response, the factors that determine the absorption, clearance, and the role the bronchial circulation plays in the redistribution of the inhaled agents.

In the foreseeable future, not only will we see more efficient and more efficacious inhaled therapies for respiratory diseases, but the introduction to market of inhaleables for gene therapy and the treatment of systemic diseases. With more emphasis on the lung as a route of administration, physicians, pharmacists and other health professionals will need to have a basic understanding of the science behind pulmonary drug delivery. Part I of this review on pulmonary drug delivery addresses the physiological factors affecting therapeutic effectiveness of inhaled drug therapy, including aerosol particle size, airway geometry, lung clearance mechanisms, and lung disease. In Part II, we consider the role the inhalant delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications.

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Optimal site of deposition for treatment of lung diseases

Inhalation of drugs for the treatment of local diseases such as asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, and chronic bronchitis, has been commonplace for many years. The advantages of inhaled over systemic delivery of these drugs are listed in Table 1 [3].

The therapeutic effect of aerosolized therapies is dependent upon the dose deposited and its distribution

Table 1 Advantages of pulmonary delivery of drugs to treat respiratory and systemic disease.

Treatment of respiratory diseases	Treatment of systemic diseases
Deliver high drug concentrations directly to the disease site	A noninvasive 'needle-free' delivery system.
Minimizes risk of systemic side-effects	Suitable for a wide range of substances from small molecules to very large proteins [20, 21].
Rapid clinical response	Enormous absorptive surface area (100 m^2) and a highly permeable membrane (0.2–0.7 μm thickness) in the alveolar region [22, 23].
Bypass the barriers to therapeutic efficacy, such as poor gastrointestinal absorption and first-pass metabolism in the liver	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 [72].
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 MDI	A less harsh, low enzymatic environment that is devoid of hepatic first-pass metabolism.
	Reproducible absorption kinetics. Pulmonary delivery is independent of dietary complications, extracellular enzymes and interpatient metabolic differences that affect gastrointestinal absorption [21].

within the lung. The influence of the latter on the effectiveness of inhaled therapies is less clear. Ruffin and colleagues [4] demonstrated that a small dose of histamine aerosol deposited predominantly in the large conducting (central) airways was as effective in increasing airway obstruction as an 11-fold greater dose of histamine aerosol deposited diffusely, suggesting that the receptors for histamine reside mainly in the large airways and that surface concentration of a drug affects response.

If a drug aerosol is delivered at a suboptimal dose or to a part of the lung devoid of the targeted disease or receptor, the effectiveness of therapy may be compromised. The receptors for the β_2 agonist, salbutamol and the muscarinic-3 (M3) antagonist, ipratropium bromide are not uniformly distributed throughout the lung. Autoradiographic studies have shown β_2 adrenergic receptors present in high density in the airway epithelium from the large bronchi to the terminal bronchioles. Airway smooth muscle has a lower β-receptor density, greater in the bronchioles than bronchi [5]. However, >90% of all β receptors are located in the alveolar wall, a region where no smooth muscle exists and whose functional significance is unknown. Another autoradiographic study has shown a high density of M3 receptors in submucosal glands and airway ganglia and a moderate density in smooth muscles throughout the airways, nerves in intrapulmonary bronchi and in alveolar walls [6]. The location of these receptors in the lung suggests that ipratropium bromide needs to be delivered to the conducting airways, while salbutamol requires a more peripheral delivery to the medium and small airways to produce a therapeutic effect. In contrast to bronchodilators, inhaled anti-inflammatory therapy is probably most beneficial when evenly distributed throughout the lung, since inflammatory cells, such as eosinophils, lymphocytes, macrophages and dendritic cells, are present throughout the airways and the alveolar tissue in asthma [7, 8].

Since particle size affects the lung deposition of an aerosol, it also can influence the clinical effectiveness of a drug. Johnson and colleagues showed that the bronchodilation response to cumulative doses of ipratropium bromide delivered either as a 3.3-μm or 7.7-μm aerosol was identical, whereas the response to salbutamol was significantly greater with the finer (3.3 μm) aerosol, suggesting targeting drug aerosol to the location of their receptors in the lung does influence its effectiveness (Figure 1) [9]. Rees *et al*. [10] reported the varying clinical effect of 250 μg of aerosolized terbutaline from a metered dose inhaler (MDI) given as three different particle sizes: <5 μm, 5–10 μm and 10–15 μm. In asthmatics, the greatest increase in forced expiratory volume in 1 s (FEV_1), specific airway conductance (sGaw) and flow at 50% of vital capacity (V_{50}) was found with the smallest particle size (<5 μm), suggesting that the smaller particle aerosol was considerably more effective than larger particle size aerosols in producing bronchodilation since it has the best penetration and retention in the lungs in the presence of airway narrowing. Using three monodisperse salbutamol aerosols [mass median aerodynamic diameter (MMAD) of 1.5 μm, 2.8 μm, 5 μm], Zanen and colleagues [11] demonstrated in patients with mild to moderate asthma that the 2.8 μm particle size aerosol produced a superior bronchodilation compared with the other two aerosols. In patients with severe airflow obstruction (FEV_1 <40%), Zanen *et al*. [12] demonstrated that the optimal particle size for β_2 agonist or anticholinergic aerosols is approximately 3 μm. They examined the effect on lung function of equal doses of three different sizes of monodisperse aerosols, 1.5 μm, 2.8 μm and 5 μm, of salbutamol and ipratropium bromide. Their findings suggest that small particles penetrate more deeply into the lung and thereby, more effectively dilate the small airways than larger particles, which are filtered out in the upper airways. The 1.5-μm aerosol induced

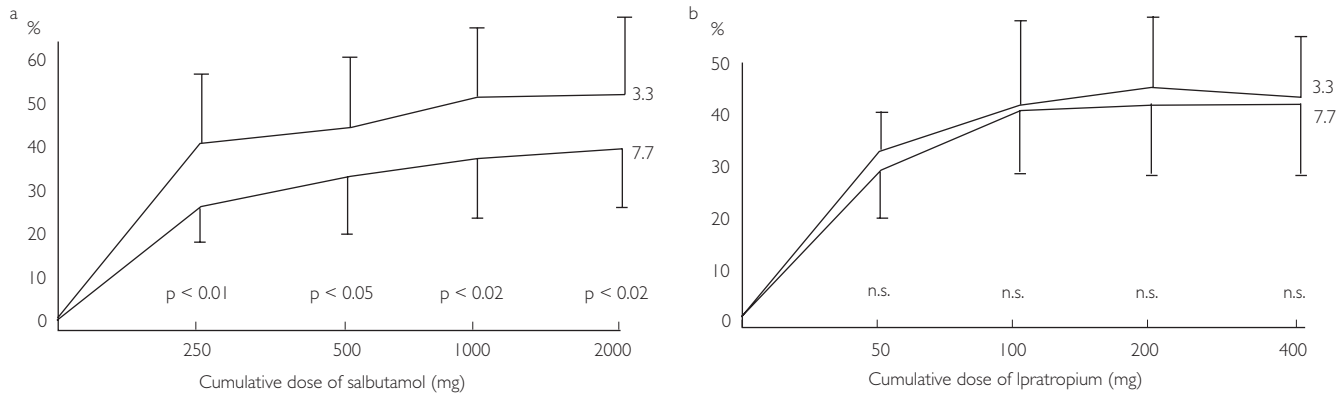


Figure 1 The effect of the drug aerosol's particle size on therapeutic efficacy. (a) Percent improvement in forced expiratory volume in 1 s (FEV_1) following inhalation of two different size aerosols of salbutamol, 3.3 μm and 7.7 μm. The dose–response curves show that, for the β-agonist, salbutamol, the small particle aerosol (3.3 μm) produced a greater bronchodilator response at all doses compared with the larger particle size aerosol. (b) Percent improvement in FEV_1 following inhalation of two different size aerosols of ipratropium bromide, 3.3 μm and 7.7 μm. For the muscarinic antagonist, ipratropium bromide, there were no significant differences in the dose–response curves between the two aerosols. (From Johnson MA *et al*. *Chest* 1989; 96: 1–10 [9].)

significantly less bronchodilation than the 2.8-μm aerosol, suggesting this fine aerosol may be deposited too peripherally to be effective since smooth muscle is not present in the alveolar region.

The optimal site of deposition in the respiratory tract for aerosolized antibiotics depends on the infection being treated. Many pneumonias represent a mixture of purulent tracheobronchitis and alveolar infection. Successful therapy would theoretically require the antibiotic to be evenly distributed throughout the lungs. However, those confined to the alveolar region would probably benefit from a greater peripheral deposition. *Pneumocystis carinii* pneumonia, the most common life-threatening infection among patients infected with HIV, is found predominately within the alveolar spaces with relapses occurring in the apical region of the lung after treatment with inhaled pentamidine given as a 1-μm MMAD aerosol [13]. The mechanism suggested for this atypical relapse is the poorer apical deposition of the aerosol. Regional changes in intrapleural pressure result in the lower lung regions receiving relatively more of the inspired volume than the upper lung when sitting in an upright position or standing. This influence on deposition has been shown to occur in an experimental lung model analysing sites of aerosol deposition in a normal lung. The experiment showed a 2 : 1 ratio in overall deposition for a 4 μm aerodynamic diameter aerosol between the lower and upper lobes when in the upright position [14]. Baskin and colleagues [13] demonstrated that this gradient could be reduced by administering aerosolized pentamidine to patients in the supine position. Thus, receiving aerosolized pentamidine in the supine position may reduce the risk of relapse in the apical lobes of the lung by increasing the amount of antibiotic deposited in the upper lung regions. This theory remains to be proven in a clinical trial.

Chronic lung infection with *Pseudomonas aeruginosa* in patients with cystic fibrosis (CF) or non-CF bronchiectasis resides in the airway lumen with limited invasion of the lung parenchyma [15, 16]. Infection starts in the smaller airways, the bronchioles, and moves into the larger airways. The optimal site of deposition for inhaled antimicrobial therapy would therefore be a uniform distribution on the conducting airways. Mucus plugs in the bronchi and bronchioles may prevent deposition of even small particle aerosols in regions distal to the airway obstruction, as shown in Figure 2, possibly the regions of highest infection, and thereby may limit the therapeutic effectiveness of the aerosolized antibiotic [17–19].

Optimal site of deposition for treatment of systemic diseases

Pulmonary drug delivery offers several advantages as a route of administration for the treatment of systemic diseases compared with intravenous, oral, buccal, transdermal, vaginal, nasal or ocular administration. The advantages of pulmonary administration are listed in Table 1 [20–23]. Until recently, aerosol drug delivery has been limited to topical therapy for the lung and nose. The major contributing factor to this restriction was the inefficiencies of available inhalation devices that deposit only 10–15% of the emitted dose in the lungs. While appropriate lung doses of steroids and bronchodilators can be achieved with these devices, for systemic therapies large amounts of the drug are necessary to achieve therapeutic drug levels, systemically. Recent advances in aerosol and formulation technologies have led to the

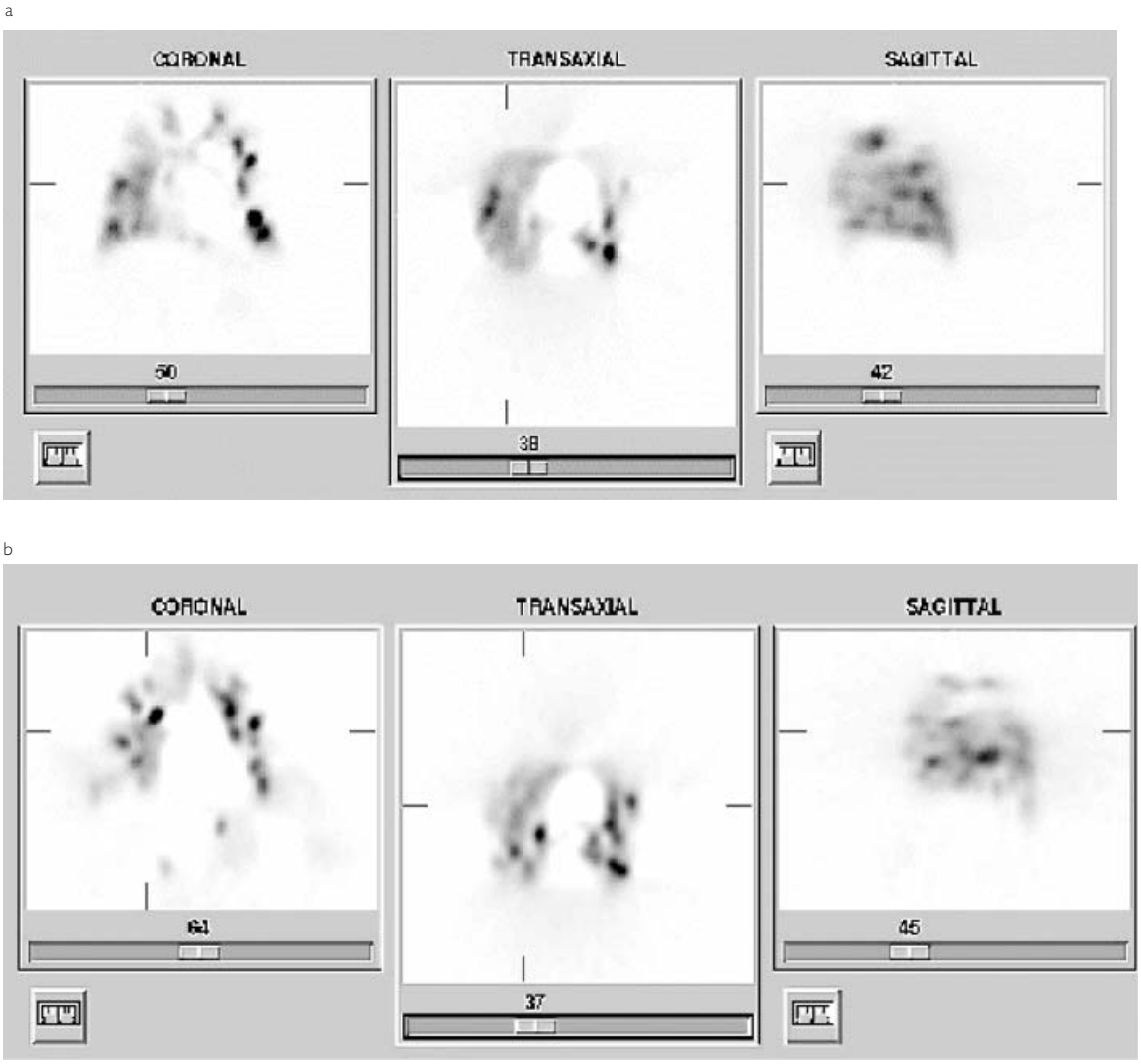


Figure 2 Positron emission tomography emission slices for all three planes following inhalation of ^{18}fluorodeoxyglucose (18FDG) of two different particle sizes in a cystic fibrosis patient [age 23; forced expiratory volume in 1 s (FEV_1) 57% of predicted]. (a) Ultravent nebulizer: mass median aerodynamic diameter (MMAD) 1.5 μm, fine particle fraction (FPF) of 95% (measured with Andersen Cascade Impactor at 28.3 Lpm). (b) Pari LC Star nebulizer: MMAD 4.5 μm, FPF for FDG aerosol of 65%. Although a difference in distribution is evident with the two sizes of aerosols, distribution of the small particle aerosol (1.5 μm) is non-uniform with the aerosol being centrally distributed. The darker areas (hotspots) on the scans are points of impaction, possibly at airway obstructions. (Reproduced with permission of the author [63].)

development of delivery systems that are more efficient and that produce small particle aerosols allowing higher drug doses to be deposited in the alveolar region of the lungs where they are available for systemic absorption.

Most macromolecules cannot be administered orally because proteins are digested before they are absorbed into the bloodstream. Also, their large size prevents them from naturally passing through the skin or nasal membrane, and therefore they cannot be administered intranasally or transdermally without the use of penetration enhancers. Thus, the easiest route of administration for proteins has been through intravenous or intramuscular/subcutaneous injection. It has been known for many years that proteins can be absorbed from the lung, as demonstrated with insulin in 1925 [20]. Macromolecules <40 kDa (<5–6 nm in diameter) rapidly appear in the blood following inhalation into the airways. Insulin which has a molecular weight (m wt) of 5.7 kDa and a diameter of 2.2 nm peaks in the blood 15–60 min after inhalation [24–29]. Macromolecules >40 kDa (>5–6 nm in diameter) are slowly absorbed over many hours; inhaled albumin (68 kDa) and α_1-antitrypsin (45–51 kDa) have a T_{max} of 20 h and between 12 and 48 h, respectively [21].

The lung is the only organ through which the entire cardiac output passes. Before the inhaled drug can be

absorbed into the blood from the lung periphery, it has several barriers to overcome: lung surfactant, surface lining fluid, epithelium, interstitium and basement membrane and the endothelium. Drug absorption is regulated by a thin alveolar–vascular permeable barrier. The number of alveoli ranges from 200 million to 600 million, resulting in an enormous epithelial surface area with epithelium consisting of a thin single cellular layer (0.2–0.7 μm thickness) [30]. While these properties promote efficient gas exchange through passive transport, they also provide a mechanism for efficient drug delivery to the bloodstream. Although the mechanism of absorption is unknown, it has been hypothesized that macromolecules either pass through the cells via absorptive transcytosis (adsorptive or receptor mediated), paracellular transport between bijunctions or trijunctions, or through large transitory pores in the epithelium caused by cell injury or apoptosis [23, 31]. Thus, the high bioavailability of macromolecules deposited in the lung (10–200 times greater than nasal and gastrointestinal values) may be due to its enormous surface area, very thin diffusion layer, slow surface clearance and antiprotease defence system [23].

Aerosol particle size

Aerosol particle size is one of the most important variables in defining the dose deposited and the distribution of drug aerosol in the lung (Figure 3) [32]. Fine aerosols are distributed on peripheral airways but deposit less drug per unit surface area than larger particle aerosols which deposit more drug per unit surface area, but on the larger, more central airways [4]. Most therapeutic aerosols are almost always heterodisperse, consisting of a wide range of particle sizes and described by the log-normal distribution with the log of the particle diameters plotted against particle number, surface area or volume (mass) on a linear or probability scale and expressed as absolute values or cumulative percentage. Since delivered dose is very important when studying medical aerosols, particle number may be misleading, as smaller particles contain less drug than larger ones, as seen in Figure 4. Particle size is defined from this distribution by several parameters. Mass median diameter of an aerosol refers to the particle diameter that has 50% of the aerosol mass residing above and 50% of its mass below it. The aerodynamic diameter relates the particle to the diameter of a sphere of unit density that has the same settling velocity as the particle of interest regardless of its shape or density. MMAD is read from the cumulative distribution curve at the 50% point (Figure 4). Geometric standard deviation (GSD) is a measure of the variability of the particle diameters within the aerosol and is calculated from the ratio of the particle diameter at the 84.1% point on the cumulative distribution curve to the MMAD. For a log-normal distribution, the GSD is the same for the number, surface area or mass distributions. A GSD of 1 indicates a monodisperse aerosol, while a GSD of >1.2 indicates a heterodisperse aerosol.

Particles can be deposited by inertial impaction, gravitational sedimentation or diffusion (Brownian motion) depending on their size. While deposition occurs throughout the airways, inertial impaction usually occurs in the first 10 generations of the lung, where air velocity is high and airflow is turbulent [33]. Most particles >10 μm are deposited in the oropharyngeal region with a large amount impacting on the larynx, particularly when the drug is inhaled from devices requiring a high inspiratory flow rate (DPIs) or when the drug is dispensed from a device at a high forward velocity (MDIs) [34, 35]. The large particles are subsequently swallowed and contribute minimally, if at all, to the therapeutic response. One example is fluticasone propionate, with its poor oral absorption demonstrated by similar plasma lev-

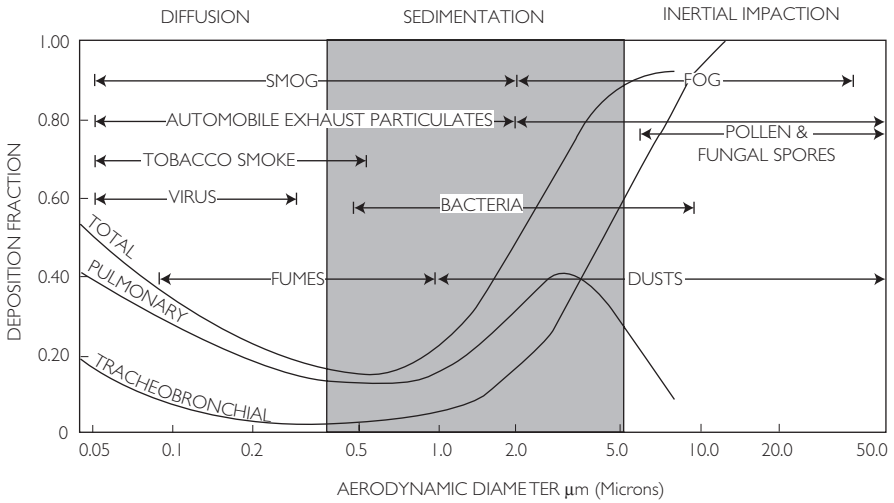


Figure 3 Relationship between particle size and lung deposition. (Reprinted with permission of the author [32].)

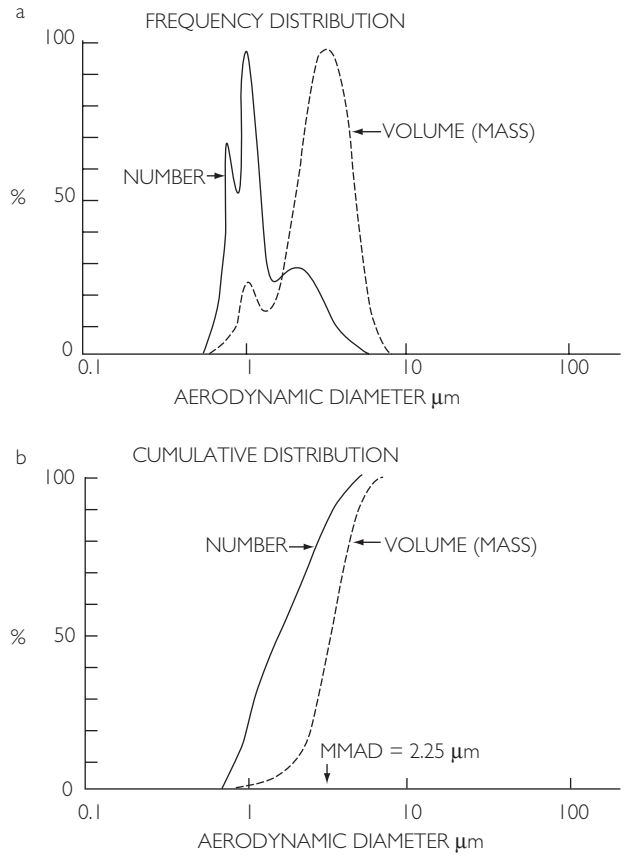


Figure 4 Frequency (a) and cumulative (b) distribution curves for Beclovent metered dose inhaler (MDI) used with an Aerochamber, in terms of number of particles and volume (mass) of particles *vs.* particle aerodynamic diameter. The volume distribution curves are displaced to the right of the number distribution curves. The smaller number of large particles within the aerosol carry the greater mass of the drug; this is reflected in the larger, second peak of the volume distribution curve, which corresponds to the smaller second peak of the number distribution curve. Mass median aerodynamic diameter (MMAD) is read from the cumulative distribution curve at the 50% point and if the distribution is log-normal, the geometric standard deviation (GSD) can be calculated as the ratio of the diameter at the 84.1% point to the MMAD. Particle distribution was measured using the Anderson Cascade Impactor. (Reprinted with permission of the author [72].)

els when inhaled from an MDI or an MDI + spacer. Hence the oral component of the inhaled dose provides no added therapeutic benefit. In contrast are drugs that can be absorbed orally including salbutamol and terbutaline, that when swallowed can produce a delayed therapeutic response. In the tracheobronchial region, inertial impaction also plays a significant role in the deposition of particles, particularly at bends and airway bifurcations. Deposition by gravitational sedimentation predominates in the last five to six generations of airways (smaller bronchi and bronchioles), where air velocity is low [33]. In the alveolar region, air velocity is negligible, and thus the contribution to deposition by inertial impaction is nil. Particles in this region have a longer residence time and are deposited by both sedimentation and diffusion. Particles not deposited during inhalation are exhaled. Deposition due to sedimentation affects particles down to 0.5 μm in diameter, whereas below 0.5 μm, the main mechanism for deposition is by diffusion.

Targeting the aerosol to conducting or peripheral airways can be accomplished by altering the particle size of the aerosol and/or the inspiratory flow rate. It is difficult to predict the actual site of deposition, since airway calibre and anatomy differ among people, but in general, aerosols with a MMAD of 5–10 μm are mainly deposited in the large conducting airways and oropharyngeal region [36]. Particles 1–5 μm in diameter are deposited in the small airways and alveoli with >50% of the 3 μm diameter particles being deposited in the alveolar region. In the case of pulmonary drug delivery for systemic absorption, aerosols with a small particle size would be required to ensure peripheral penetration of the drug [37]. Particles <3 μm have an approximately 80% chance of reaching the lower airways with 50–60% being deposited in the alveoli [23, 38]. Since this is a new area of scientific research, the most effective particle size for the treatment of systemic diseases has not been determined.

The clearance mechanisms of the lung

Like all major points of contact with the external environment, the lung has evolved to prevent the invasion of unwanted airborne particles from entering the body. Airway geometry, humidity and clearance mechanisms contribute to this filtration process. The challenge in developing therapeutic aerosols is to produce an aerosol that eludes the lung's various lines of defence.

Airway geometry and humidity

Progressive branching and narrowing of the airways encourage impaction of particles. The larger the particle size, the greater the velocity of incoming air, the greater the bend angle of bifurcations and the smaller the airway radius, the greater the probability of deposition by impaction [39]. The lung has a relative humidity of approximately 99.5%. The addition and removal of water can significantly affect the particle size of a hygroscopic aerosol and thus deposition [40]. Drug particles are known to be hygroscopic and grow or shrink in size in high humidity, such as in the lung, as demonstrated in Figure 5. A hygroscopic aerosol that is delivered at relatively low temperature and humidity into one of high humidity and temperature would be expected to increase in size when inhaled into the lung. The rate of growth is a function of the initial diameter of the particle, with

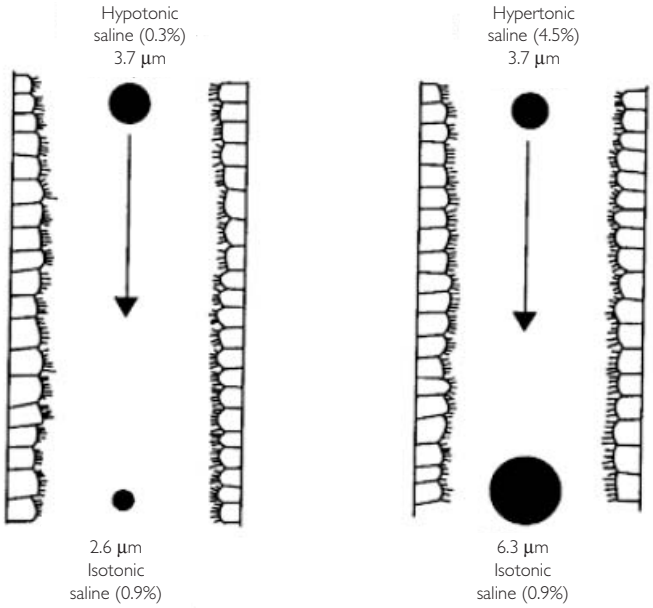


Figure 5 Illustration of hygroscopic growth and shrinkage of hypertonic and hypotonic droplets of the same initial size (3.7 μm) in the humid environment of the respiratory tract. (From Phipps PR *et al*. Regional deposition of saline aerosols of different tonicities in normal and asthmatic subjects. *Eur Respir J* 1994; 7: 1474–1482 [40].)

the potential for the diameter of fine particles <1 μm to increase five-fold compared with two-to-three-fold for particles >2 μm [41]. The increase in particle size above the initial size should affect the amount of drug deposited and particularly, the distribution of the aerosolized drug within the lung. Ferron and colleagues [42, 43] have predicted that for initial sizes between 0.7 μm and 10 μm, total deposition of hygroscopic aerosols increases by a factor of 2. However, Xu and Yu [44] demonstrated that for NaCl particles with an initial size of 0.1 μm, the distribution pattern in the airways was similar to that for nonhygroscopic particles of the same size with diffusion remaining the primary mechanism of deposition. Using 2D-imaging to detect deposition changes may be unsuccessful. A two-to-three-fold increase in diameter would not markedly alter the visible distribution pattern of these submicron gas-like aerosols. The total deposited dose may decrease but the resolution of current imaging techniques is not great enough to distinguish the shifts in generations in this peripheral lung region. For particles with an initial size of 1 μm, Xu and Yu were able to predict changes in the distribution pattern due to particle growth. The calculations showed a shift from deposition due to sedimentation to primarily impaction on more central airways [43].

Lung clearance mechanisms

Once deposited in the lungs, inhaled drugs are either cleared from the lungs, absorbed into the systemic circulation or degraded via drug metabolism. Drug particles deposited in the conducting airways are primarily removed through mucociliary clearance and, to a lesser extent, are absorbed through the airway epithelium into the blood or lymphatic system. Ciliated epithelium extends from the trachea to the terminal bronchioles. The airway epithelial goblet cells and submucosal glands secrete mucus forming a two-layer mucus blanket over the ciliated epithelium: a low-viscosity periciliary or sol layer covered by a high-viscosity gel layer. Insoluble particles are trapped in the gel layer and are moved toward the pharynx (and ultimately to the gastrointestinal tract) by the upward movement of mucus generated by the metachronous beating of cilia. In the normal lung, the rate of mucus movement varies with the airway region and is determined by the number of ciliated cells and their beat frequency. Movement is faster in the trachea than in the small airways and is affected by factors influencing ciliary functioning and the quantity and quality of mucus [35, 45]. For normal mucociliary clearance to occur, airway epithelial cells must be intact, ciliary structure and activity normal, the depth and chemical composition of the sol layer optimal and the rheology of the mucus within the physiological range. Mucociliary clearance is impaired in lung diseases such as immotile cilia syndrome, bronchiectasis, CF and asthma [46]. In immotile cilia syndrome and bronchiectasis, the ciliary function can be either impaired or non-existent. In CF, the ciliary structure and function are normal, but the copious amounts of thick, tenacious mucus present in the airways impairs their ability to clear the mucus effectively [47]. In these diseases, clearance of aerosolized drugs deposited

in the conducting airways generally is decreased and secretions are cleared from the lung by cough [48–50].

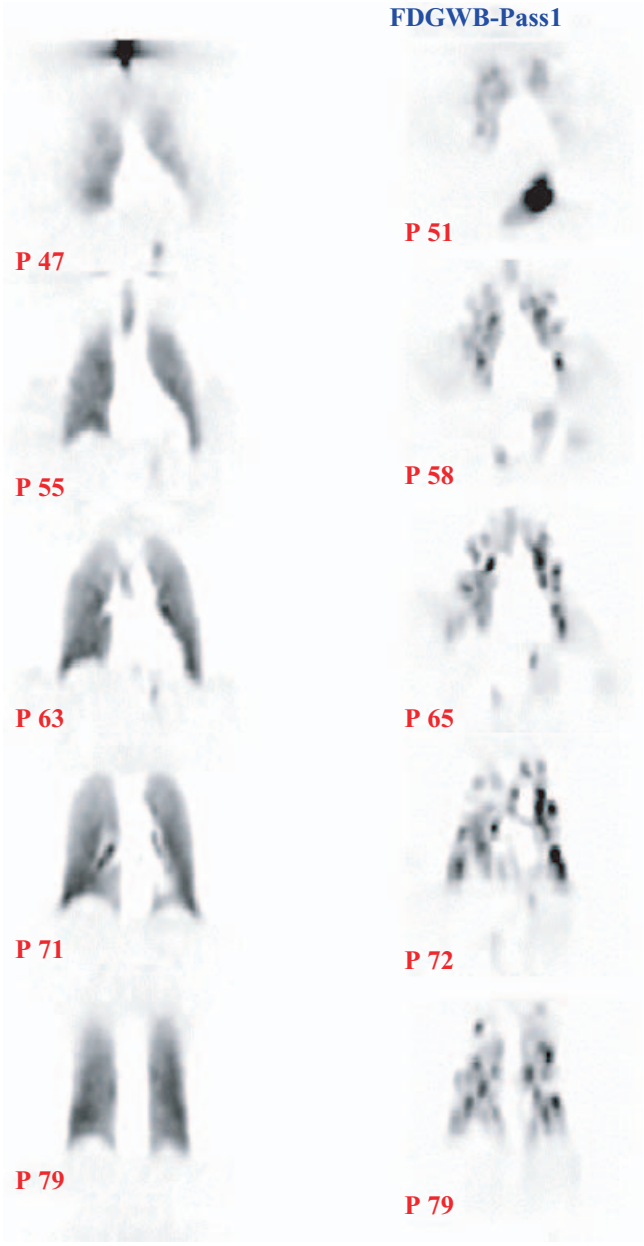
In addition to mucociliary clearance, soluble particles also can be removed by absorptive mechanisms in the conducting airways [51]. Lipophilic molecules pass easily through the airway epithelium via passive transport. Hydrophilic molecules cross via extracellular pathways, such as tight junctions, or by active transport via endocytosis and exocytosis [52]. From the submucosal region, particles are absorbed into either the systemic circulation, bronchial circulation or lymphatic system.

Drugs deposited in the alveolar region may be phagocytosed and cleared by alveolar macrophages or absorbed into the pulmonary circulation. Alveolar macrophages are the predominant phagocytic cell for the lung defence against inhaled microorganisms, particles and other toxic agents. There are approximately five to seven alveolar macrophages per alveolus in the lungs of healthy nonsmokers [53]. Macrophages phagocytose insoluble particles that are deposited in the alveolar region and are either cleared by the lymphatic system or moved into the ciliated airways along currents in alveolar fluid and then cleared via the mucociliary escalator [31]. This process can take weeks to months to complete [54]. Soluble drug particles deposited in the alveolar region can be absorbed into the systemic circulation, as discussed above. The pulmonary epithelium appears to be more resistant to soluble particle transport than the endothelium or the interstitium [37]. The rate of protein absorption from the alveoli is size dependent. Effros and Mason [37] demonstrated an inverse relationship between alveolar permeability and molecular weight. In rats, after intratracheal instillation of DDAVP (1-desamino-8-d-arginine vasopressin) (m wt 1.1 kDa), peak serum DDAVP levels occurred at 1 h compared with 16–24 h after intratracheal instillation of albumin (m wt 67 kDa) [38]. However, some proteins are cleared from the lung more rapidly than expected for their size. After intratracheal instillation or aerosolization of human growth hormone (m wt 22 kDa), peak serum levels were observed at 0.5–4 h, indicating a rapid, saturable clearance from the lung that is suggestive of receptor-mediated endocytosis [31].

Very little is known about how the drug-metabolizing activities of the lung affect the concentration and therapeutic efficacy of inhaled drugs. All metabolizing enzymes found in the liver are found to a lesser extent in the lung (CYP450 enzymes are 5–20 times lower than in liver) distributed throughout the conducting airways and alveoli [55–57]. Phase 1 cytochrome-450 (CYP450) enzymes, flavin-containing monooxygenases (FMO), monoamine oxidase (MAO), aldehyde dehyrogenase, NADPH-CYP450 reductase, for example, are all present in the lung. The monooxygenase system metabolizes fatty acids, steroids and lipophilic xenobiotics. Esterase present in high concentrations in alveolar macrophages, and to a lesser degree in alveolar type I and II cells, hydrolyses beclomethasone dipropionate to its monopropionate and beclomethasone. The human lung, however, appears to be a poor site for sulphation. Proteins and peptides are subject to hydrolysis by proteases, such as neutral endopeptidase and cathepsin H, present in the lung. The extent to which various proteins and peptides are metabolized is unclear. Vasoactive intestinal polypeptide (VIP) is believed to be completely degraded during the passage across the pulmonary epithelium and into the bloodstream [31, 58, 59]. Sources for the proteases are the alveolar macrophages and other inflammatory cells, such as neutrophils. Since these enzymes play a key role in the degradation of proteins and peptides, the effect of delivering aerosolized proteins and peptides to inflamed lungs where the level of proteases is higher, is unknown but may impair their efficacy [30]. Co-administration with protease inhibitors, such as bacitracin and sodium glycocholate, have been shown to reduce the metabolism of proteins and thereby improve pulmonary absorption [60, 61]. However, for most proteins degradation in the alveoli is not a major clearance mechanism, with >95% of proteins, including insulin, being absorbed intact from the lung periphery [31, 59].

Deposition in lung disease

Bronchoconstriction, inflammation and airway narrowing alter lung deposition. Respiratory diseases, such as CF and bronchiectasis, change the architecture of the lung through alterations in bifurcation angles and obstruction of the airways due to mucus accumulation, modifying the deposition and distribution patterns of aerosols. A decrease in the cross-sectional area of the lung caused by obstruction increases air velocities and turbulence in regions where the airflow is normally laminar. Airway obstruction diverts inspired air to unobstructed airways and, thus, very little drug is deposited in obstructed areas, often the areas that need to be reached in order to achieve the optimal therapeutic effect of the drug. In an obstructed lung, the aerosolized drug will be deposited more centrally in the lungs by inertial impaction compared with the uniform distribution achieved in the normal lung, as seen in Figure 6 [62, 63]. Pavia and colleagues [64] demonstrated that the depth of deposition was positively correlated with a patient's FEV_1. Patients with COPD have a significantly lower aerosol penetration than healthy volunteers (Figure 7) [65–67]. However, if their FEV_1 is increased through bronchodilation, an increase in peripheral penetration of drug particles can occur (Figure 8). Laube and colleagues studied the effect



(a) Normal **(b) Cystic Fibrosis**

Figure 6 A section of sequential coronal lung slices (from anterior to posterior) following inhalation of a 4.5-μm ^{18}fluorodeoxyglucose (^{18}FDG) aerosol in (A) normal volunteer with forced expiratory capacity in 1 s (FEV_1) of 98% predicted (images on left side) and (B) cystic fibrosis (CF) patient with FEV_1 of 57% predicted (images on right side). A uniform distribution of the aerosol is seen in the normal lung compared with the non-uniform, central distribution of the same aerosol in CF. (Reproduced with permission of the author [63].)

of bronchial obstruction on central airway deposition of a radioaerosol (MMAD 1.12 μm) [68]. They found that bronchial obstruction enhanced central airway deposition with clearance of the radioaerosol inversely correlated

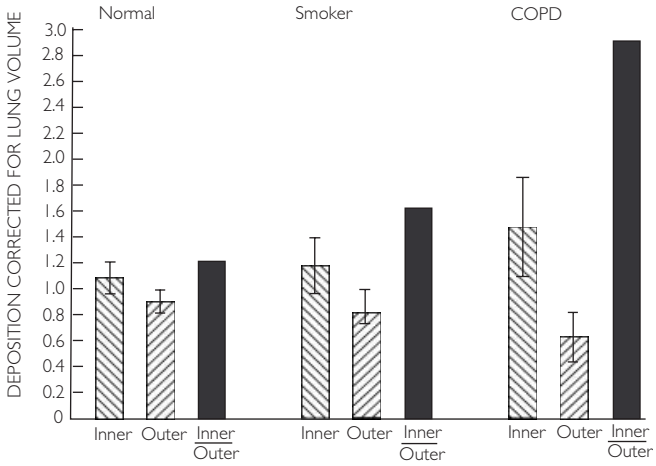


Figure 7 Differences in the lung distribution of the same radioactive aerosol among normals, smokers and chronic obstructive pulmonary disease (COPD) subjects. Inner zone represents centrally deposited aerosol and outer represents the aerosol deposited peripherally, both expressed as striped columns. The inner : outer ratio is expressed by solid column. Deposition in the periphery of the lung is greatly decreased in COPD and to a lesser extent in smokers compared with normals. The reverse is seen in the central airways, with more aerosol being deposited in this region for subjects with COPD and smokers. The inner : outer ratio illustrates the different pattern of deposition in the three groups. (Reprinted with permission of author [67].)

with FEV_1. Nearly 50% of the radioaerosol was cleared from the lung after 97 min in those patients with an FEV_1 of 30–40% compared with <10% when FEV_1 was >80%. In patients with low FEV_1 (severe obstruction), aerosol distribution was extremely uneven with predominately central airway deposition compared with the uniform distribution characteristic of patients with unobstructed airways. Ilowite *et al.* [18] also reported an inverse correlation between FEV_1 and central airway deposition in patients with CF. There was a wide variation in deposited aerosol with a coefficient of variation (CV) of 60.2% among patients. When breathing patterns were controlled, the variation in deposition decreased to a CV of 18.6%, highlighting the importance of breathing pattern on the deposition of aerosols.

Bronchial circulation

The lung receives the entire cardiac output and thus is the best perfused organ in the body. However, only the alveolar region and respiratory bronchioles are supplied by the pulmonary circulation. Blood flow to the larger airways (trachea to terminal bronchioles) is via the systemic circulation and these airways receive approximately 1% of the cardiac output [69]. The role of the bronchial

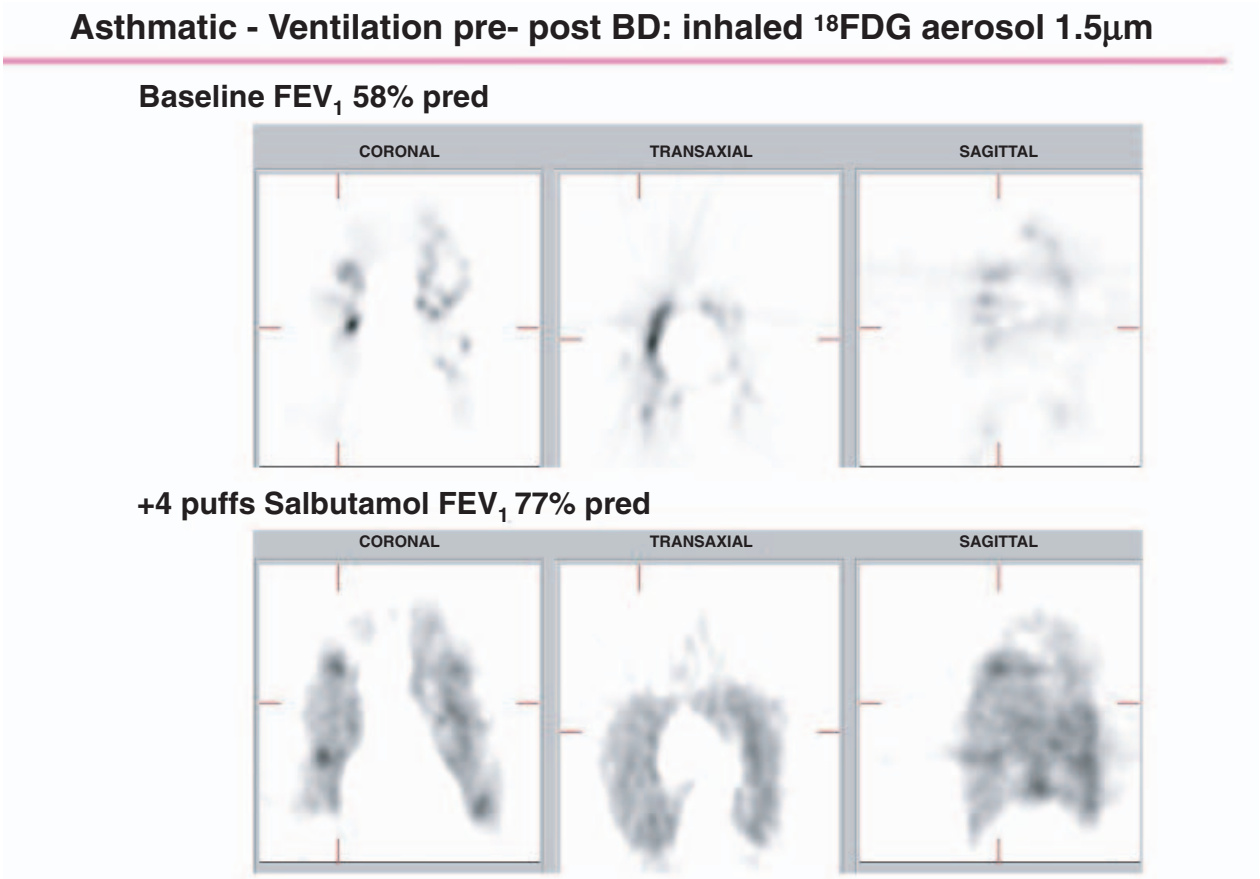


Figure 8 Positron emission tomography scans (one example per plane) showing marked improvement in ventilation post-bronchodilator in an asthmatic subject. Deposition of 18 fluorodeoxyglucose (18FDG) aerosol (1.5 μm MMD) was poor presalbutamol. (Reproduced with permission from author [63].)

circulation in distributing aerosolized drugs to regions distal from the original site of deposition or to nonventilated regions of the lung is unknown. The endobronchial circulation is recirculated to the peripheral airways and lung parenchyma via the bronchial veins and right atrium. Bronchial blood flow is augmented in diseases, such as bronchiectasis, from 1% to as much as 30% of cardiac output. In sheep, bronchial blood flow increased with antigen- and histamine-induced bronchoconstriction [70]. Theoretically, inhaled drugs that are absorbed into the circulation from the tracheobronchial regions can be redistributed downstream and peripheral to airway obstructions, into otherwise poorly accessible areas of the lung which may aid in the drug's efficacy [70, 71]. Thus far, no experimental work in humans has been done to investigate the role of bronchial circulation in lung distribution of inhaled medications or its influence on their efficacy.

Conclusions

As the end organ for the treatment of local diseases or as the route of administration for systemic therapies, the lung is a very attractive target for drug delivery. It provides direct access the site of disease for the treatment of respiratory diseases without the inefficiencies and unwanted effects of systemic drug delivery. It provides an enormous surface area and a relatively low enzymatic, controlled environment for systemic absorption of medications. But it is not without barriers. Airway geometry, humidity, clearance mechanisms and presence of lung disease influence the deposition of aerosols and therefore influence the therapeutic effectiveness of inhaled medications. A drug's efficacy may be affected by the site of deposition in the respiratory tract and the delivered dose to that site. To provide an efficient and effective inhalant therapy, these factors must be considered. Aerosol particle size characteristics can play an important role in avoiding the physiological barriers of the lung, as well as targeting the drug to the appropriate lung region. The type of inhalation devices and drug formulation are determinants of the drug aerosol's particle size. In Part II, the inhalational delivery devices' and drug formulations' effect on the therapeutic effectiveness of aerosolized drug therapy will be reviewed.

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