Drug Properties Affecting Aerosol Behavior

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Introduction

Localized delivery of drugs to the respiratory tract has become an increasingly important and effective therapeu-

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imizing adverse effects. On the other hand, the large surface area for absorption and the relatively low metabolic activity of the lungs make this organ system a potential route for the systemic delivery of drugs that cannot be delivered by other means. Many studies have shown that the lungs provide substantially greater bioavailability for macromolecules than any other port of entry to the systemic circulation.

The efficacy of a therapeutic aerosol is mainly determined by the amount of drug reaching the target site. The human lung has evolved to prevent the entry of atmospheric particulates. Therefore, unlike other routes of administration, delivering a known dose of drug to the site of action via inhalation requires a multidisciplinary scientific effort. Activities have focused on investigating both particle technology and drug delivery technology as means of increasing the fraction of drug that reaches the periphery of the respiratory tract. Many studies have demonstrated that drug distribution and deposition along the respiratory tract depends on several factors: (1) characteristics of the inhaled formulation (particle diameter, size distribution, shape, electrical charge, density, and hygroscopicity), (2) anatomy of the respiratory tract, and (3) breathing patterns, such as frequency, tidal volume, and flow. The ideal site of deposition along the airways for drugs intended for local delivery is not well understood. Because the location of autonomic receptors varies within the respiratory tract, successful therapy may depend on targeting specific receptor sites in the lung with different types of drugs.

The rate of absorption from the periphery of the lung has been shown to be twice as fast as that taking place from the central portions, owing to the variable thickness of bronchial epithelial cells versus alveolar epithelial cells. Therefore, to achieve maximum bioavailability of drugs aimed for systemic delivery, attention is required to deliver the drug to the periphery of the lungs. Drug residence time and, therefore, duration of effect at the site of action is a function of the rate of pulmonary clearance and pulmonary absorption, which in turn are determined by several factors, including the physicochemical properties of the drug, such as molecular weight, dissolution rate, partition coefficient, and charge. An ideal inhalation aerosol for local delivery may be that for which the rate of pulmonary absorption and clearance are relatively slow. It has been observed that by increasing lipophilicity and optimizing particle size (mass median aerodynamic diameter \(< 5 \mu m\)) and release rate, it is possible to increase the lung residence time of the drug. The therapeutic effect and the duration of this effect are determined not only by the drug dose and its pulmonary clearance, but also by drug-drug interactions. These interactions can take place at the level of drug-receptor binding (pharmacodynamic interaction) and/or during drug disposition (pharmacokinetic interactions: at the level of absorption, protein binding, and/or metabolism).

Numerous systems are available to deliver aerosols to the lungs. These include jet and ultrasonic nebulizers, propellant-driven metered-dose inhalers (pMDIs, pressurized canister), and dry powder inhalers (DPIs). The overall success of an aerosol delivery system is determined by its formulation components, the mechanism of dispersion, and patient compliance. In general, \(< 20\%\) of the total drug in the inhaler device is delivered to the lower airways. The challenges encountered with aerosol drug delivery include the control of particle size and distribution of the formulation and the reproducibility in dose uniformity. Several studies have demonstrated the need for spacers and auxiliary devices to optimize the aerosol delivery from pMDIs. However, adopting methods that increase the fraction deposited at the site of action might increase variability. It may be preferable to deliver smaller fractions of the dose reproducibly.

**Delivery Devices**

Inhaled therapeutic aerosols are generated by different devices (Fig. 1) that aim to deliver an aerosol to the lower airways. Inhalation devices can be classified into 3 categories: pMDIs, DPIs, and nebulizer inhalers. Aerosol generators are characterized using: (1) the output (mass of drug delivered per unit time), (2) the distribution of the agent in different aerodynamic size fractions, and (3) intra-device and inter-device reproducibility of operation.

**Propellant-Driven Metered-Dose Inhalers**

pMDIs are the most frequently prescribed aerosol delivery system because they are effective and convenient for a large proportion of patients. The fundamental components of pMDIs are an actuator, a metering valve, and a pressurized container that holds the micronized drug suspension or solution, propellant, and surfactant. The high vapor pressure propellant supplies the energy for dispersion in these delivery systems. The limitations of these devices are (1) poor coordination between actuation and inhalation by some patients, and (2) the release of aerosol particles as large particles at a very high velocity (100 km/h). This results in a high oropharyngeal impaction of particles, with approximately 80% of the dose depositing in the oropharynx and only 10% in the pulmonary airways.

To overcome the necessity for patient coordination usually required with these devices, breath-actuated pMDIs have been designed. These are essentially similar to conventional pMDIs, with the exception that the dose delivery is triggered by the patient’s inspiratory flow. The need of spacer and auxiliary devices for optimizing drug delivery...
from pMDIs has been reported.\textsuperscript{28,35} Attaching a spacer to the pMDI mouthpiece ensures that the emitted droplets become smaller and have reduced velocity before they are inhaled. The spacer acts as a holding chamber in which the large particles are filtered off, resulting in a reduction of the dose to the patient and impaction losses on the posterior wall of the oropharynx. Consequently, the dose deposited in the oropharynx by such devices is smaller, but the dose delivered to the pulmonary region is the same as or higher than that of a pMDI without a spacer.\textsuperscript{36}

**Dry Powder Inhalers**

DPIs are the most recent development in respiratory therapy. The majority of these devices are breath-activated inhalers that rely on the patient’s inspiratory flow to deaggregate and deliver the drug for inhalation, thereby eliminating the requirement of inhalation coordination inherent in pMDI use. However, with DPIs there is the need to generate at least moderate inspiratory flow in order to accomplish effective drug delivery. The drug in a DPI is in the form of a finely milled powder in large aggregates, either alone or in combination with some carrier substance, commonly lactose.\textsuperscript{37} Most of the particles are initially too large to be carried into the lower airways, but the turbulent air stream created in the inhaler during inhalation causes the aggregates to break up into primary particles sufficiently small to be carried into the lower airways. Therefore, the deposition pattern depends on the inspiratory flow generated by the patient. A very low inspiratory flow is likely to move the dose from the inhaler into the patient’s mouth, with very low deposition in the pulmonary airways. Shear, turbulence, and mechanical intervention may be used to aid in the dispersion of aerosols from dry powders.\textsuperscript{38} Dry powder generation is often hindered by aggregation of the small particles,\textsuperscript{39} which is in turn exacerbated by the hygroscopic nature of the drug\textsuperscript{40} and its electrostatic charge. The reduction of powder hygroscopicity and electronic charge may enhance the future prospects of aerosol powder formulation.

**Nebulizers**

Nebulization is of increasing interest because it offers opportunities for novel techniques as well as providing a potential means of administration for aqueous formulations of biomolecules.\textsuperscript{10} The most frequently used methods of nebulization are the air jet and ultrasonic devices.\textsuperscript{41} The air jet nebulizer produces a stream of high air velocity that causes liquid to spray as a mist. Ultrasonic nebulizers utilize high frequencies to convert liquid into a fine mist.\textsuperscript{34} A wide range of droplet size distributions are produced by both types of generators, depending on the brand, the operating conditions, and the composition of the liquid being nebulized.\textsuperscript{31–43} Nebulizers produce smaller droplets than do pMDIs, and these smaller droplets penetrate more easily to the small airways.\textsuperscript{34}

**Mechanisms of Drug Deposition**

Drugs for inhalation therapy are administered in aerosol form. An aerosol is defined as a suspension of liquid or solid in the form of fine particles dispersed in a gas. The ability of the aerosolized drug to reach the peripheral airways is a prerequisite for efficacy. Herein lies the fundamental problem of inhalation therapy, as the anatomy and physiology of the respiratory tract have evolved to prevent the entry of particulate matter. The regional pattern of deposition efficiency determines the specific pathways and rate at which deposited particles are ultimately cleared and
Factors Controlling Respiratory Drug Deposition

The factors that control drug deposition are (1) characteristics of the inhaled particles, such as size, distribution, shape, electrical charge, density, and hygroscopicity, (2) anatomy of the respiratory tract, and (3) breathing patterns, such as frequency, tidal volume, and flow. Of these factors, aerosol particle size and size distribution are the most influential on aerosol deposition.

Particle Characteristics

The size of the particles is a critical factor affecting the site of their deposition, since it determines operating mechanisms and extent of penetration into the lungs. Aerosol size is often expressed in terms of aerodynamic diameter ($D_{ac}$). The aerodynamic diameter is defined as the equivalent diameter of a spherical particle of unit density having the same settling velocity from an air stream as the particle in question. Thus, particles that have higher than unit density will have actual diameters smaller than their $D_{ac}$. Conversely, particles with smaller than unit density will have geometric diameters larger than their $D_{ac}$. Aerosol size distributions may be characterized as practically monodisperse (uniform sizes, geometric standard deviation of $<1.2$) or polydisperse (nonuniform sizes, geometric standard deviation $\geq 1.2$).

In mammals, respiratory anatomy has evolved in such a way as to actively prevent inhalation of airborne particulates. The upper airways (nose, mouth, larynx, and pharynx) and the branching anatomy of the tracheobronchial tree act as a series of filters for inhaled particles. Thus, aerosol particles $>100\ \mu m$ generally do not enter the respiratory tract and are trapped in the naso/oropharynx. Particles $>10\ \mu m$ will not penetrate the tracheobronchial tree. Particles must generally be $<5\ \mu m$ in order to reach the alveolar space. On the other hand, particles $<0.5\ \mu m$ in diameter penetrate the lung deeply, but have a high tendency to be exhaled without deposition. However, some studies have found that breath-holding can minimize expiration of small particles.

Respiratory Tract Anatomy

Airway geometry affects particle deposition in various ways. For example, the diameter sets the necessary displacement by the particle before it contacts an airway surface, cross-section determines the air velocity for a given flow, and variations in diameter and branching patterns affect mixing between tidal and reserve air. In contrast to many species of laboratory animal, humans have large lungs, a more symmetrical upper bronchial airway pattern, and are not obligate nose breathers. These anatomical differences produce greater amounts of upper bronchial par-
particle deposition in humans. In fact, large interspecies differences in the lung clearance of inhaled particles have been reported. The interspecies variability in lung clearance may limit the applicability of animal models for particle-related diseases of the human bronchial upper airways. Thus, since the respiratory systems of animals and humans differ anatomically, differences in deposition patterns are also expected.

Respiratory Patterns

The pattern of respiration during aerosol exposure influences regional deposition, since breathing volume and frequency determine the mean flow rates in each region of the respiratory tract, which, in turn, influence the effectiveness of each deposition mechanism. Turbulence tends to enhance particle deposition, the degree of potential depending on the particle size. Rapid breathing is often associated with increased deposition of larger particles in the upper respiratory tract, while slow, steady inhalation increases the number of particles that penetrate to the peripheral parts of the lungs. Byron proposed a mathematical model that identified the effect of particle size and breathing pattern on drug deposition. Slow breathing, with or without breath-holding, showed a broad maximum deposition in the ciliated airways (tracheobronchial region). The pulmonary maximum occurred between 1.5 μm and 2.5 μm with breath-holding and between 2.5 μm and 4 μm without breath-holding. Rapid inhalation showed similar trends: the tracheobronchial region maximum falls and shifts to between 3 μm and 6 μm. Pulmonary deposition sharpens and occurs between 1.5 μm and 2 μm with breath-holding, and between 2 μm and 3 μm without breath-holding.

When the above considerations are taken into account, the ideal scenario for aerosol would be: (1) aerosol Dₐₑ < 5 μm, to minimize oropharyngeal deposition, (2) slow, steady inhalation, and (3) a period of breath-holding on completion of inhalation.

Structure and Function of the Respiratory Tract

Assuming that an inhaled aerosol is successfully formulated and delivered in a reproducible dose to the lungs, attention should be given to the impact of respiratory structure and function on drug delivery. The following review briefly describes the important anatomical and histological features of the airways related to clearance of particulates.

The respiratory tract can be divided into upper and lower airways, with the line of division being the junction of the larynx and trachea. The upper airways or nasopharyngeal region consists of the nose, mouth, larynx, and pharynx. Below the contours of the nasopharyngeal region, the lower airways resemble a series of tubes undergoing regular dichotomous branching. Successive branching from the trachea to the alveoli reduces the diameter of the tubes, but markedly increases the surface area of the airways, which allows gas exchange (Table 1). The lower airways can be divided into 3 physiologic zones: conducting, transitional, and respiratory zones. The conducting zone consists of the larger tubes responsible for the bulk movement of air and blood. In the central airways, air flow is rapid and turbulent and no gas exchange occurs. The transitional zone plays a limited role in gas exchange. The characteristic “D” shape of the trachea is maintained by cartilage supported by smooth muscle fibers. The epithelial layer of the trachea and main bronchi is made up of several cell types, including ciliated, basal, and goblet. A large number of mucus-producing and serum-producing glands are located in the submucosa.

The human lung consists of 5 lobules and 10 bronchopulmonary segments. Arranged adjacent to each segment are lung lobules composed of 3–5 terminal bronchioles. Each bronchiolo supplies the smallest structural unit of the lung, the acinus, which consists of alveolar ducts, alveolar sacs, and alveoli. At the level of small bronchi and bronchioles, the amount and organization of cartilage diminishes as the number of bronchial bifurcations increases. The acinus represents a marked change in morphology. The primary cells of the epithelium are the type I pneumocyte, which cover 90% of the entire alveolar surface. Type II pneumocytes are more numerous, but have a smaller total volume, and are responsible for the storage and secretion of lung surfactant. Less prevalent cell types include type III pneumocytes and alveolar macrophages. The alveolar blood barrier in its simplest form consists of a single epithelial cell, a basement membrane, and a single endothelial cell. While this morphologic arrangement readily facilitates the exchange, it can still represent a major barrier to large molecules. Before entering the systemic circulation, solutes must traverse a thin layer of fluid, the epithelial lining fluid. This layer tends to collect at the corners of the alveoli and is covered by an attenuated layer of surfactant. Unlike the larger airways, the alveolar region is lined with a surface active layer consisting of phospholipids (mainly phosphatidylcholine and phosphatidylglycerol) and several key apoproteins, of which four have been identified (A, B, C, and D). Apoprotein A is known to have a role in antibody recognition, as well as on the enhancement of phagocytosis of particulates by alveolar macrophages. The surfactant lining fluid plays an important role in maintaining alveolar fluid homeostasis and permeability, and participates in various defense mechanisms. Recent studies suggest that the surfactant may slow down diffusion out of the alveoli.

The respiratory airways, from the upper airways to the terminal bronchioles, are lined with a viscoelastic, gel-like mucus layer 0.5–5.0 μm thick. The secretion lining con-
sists of two layers: a fluid layer of low viscosity, which surrounds the cilia (periciliary fluid layer), and a more viscous layer on top, the mucus. The mucus is a protective layer that consists of a complex mixture of glycoproteins released primarily by the goblet cells and local glands. The mucus blanket removes inhaled particles from the airways by entrapment and mucociliary transport at a rate that depends on viscosity and elasticity. There is evidence of neural control on the release of mucus and, therefore, on the rate of mucus transport. The lung tissue is highly vascularized, which makes pulmonary targeting difficult because of fast absorption of most drugs (especially lipophilic and low-molecular-weight drugs).

### Pulmonary Clearance

The primary function of the pulmonary defensive response to inhaled particles is to keep the respiratory surfaces of the alveoli clean and available for respiration. The elimination of particles deposited in the lower respiratory tract serves an important defense mechanism to prevent potentially adverse interactions of aerosols with lung cells. Insoluble particulates are cleared by several pathways, which are only partially understood. These pathways are known to be impaired in certain diseases and are thought to depend on the nature of the administered material. Swallowing, expectoration, and coughing constitute the first sequence of clearance mechanisms operating in the naso/oropharynx and tracheobronchial tree. However, it has been suggested that the effect of cough may extend down to the level of the respiratory bronchioli, under conditions of excess mucus production.

A major clearance mechanism for inhaled particulate matter deposited in the conducting airways is the mucociliary escalator, whereas uptake by alveolar macrophages predominates in the alveolar region. In addition to these pathways, soluble particles can also be cleared by dissolution with subsequent absorption from the lower airways. The rate of particle clearance from these regions differs significantly and its prolongation can have serious consequences, causing lung diseases from the toxic effects of inhaled compounds. It is now well recognized that the lungs are a site for the uptake, accumulation, and/or metabolism of numerous endogenous or exogenous compounds. A number of reviews have covered several features of the metabolic functions of this organ. Most of these studies focused on the role of pulmonary cytochrome P-450 isozymes. All metabolizing enzymes found in the liver are also found in the lung, although in smaller amounts. These include phase I reactive pulmonary cytochrome P-450 isozymes, flavin-containing mono-oxygenases, monooamine oxidase, aldehyde dehydrogenase, nicotinamide adenine dinucleotide phosphate (NADPH), cytochrome P-450 reductase, esterases, and epoxide hydrolase, and phase II conjugating enzymes such as N-acetyltransferase and sulfotransferase.

The rate at which a drug is cleared and absorbed from the respiratory tract (Fig. 2) depends on the dynamic interaction of several factors, predominantly: (1) the muco-
ciliary clearance rate, (2) site of deposition along the airways, (3) biopharmaceutical factors (particulates vs drug in solution), (4) drug release rate, and (5) the physicochemical properties of the drug, such as molecular weight, partition coefficient, and charge.

Mucociliary Clearance

Mucociliary clearance is a physiologic function of the respiratory tract to clear locally produced debris, excessive secretions, or unwanted inhaled particles. It consists of ciliated epithelial cells reaching from the naso/oropharynx and the upper tracheobronchial region down to the most peripheral terminal bronchioles. Beating of the cilia, together with mucus secreted by the goblet cells, contributes to an efficient clearance mechanism. The ciliary beat frequency is in the range of 1,000–1,200 beats/min.\(^{11}\) Particles are transported at 5 mm/min if the effective stroke of a cilia is 5 \(\mu \text{m}\) and it beats at 1,000 beats/min. The normal mucociliary transport rates in humans are 5.5 mm/min in the trachea and 2.4 mm/min in the major bronchi.\(^{81}\) The basal rate of Evans blue transport in healthy guinea pigs is 4.4 \(\pm\) 0.02 mm/min.\(^{82}\)

Mucociliary clearance kinetics are difficult to quantify. Studies of clearance kinetics usually involve administration of 3 \(\mu \text{m}\) (\(D_{ae}\)) insoluble iron oxide aerosols to normal humans. Byron\(^ {12}\) used a mathematical model to analyze the clearance data resulting from the administration of iron oxide. He and other investigators\(^ {83-85}\) have observed that 48.9% of the deposited material remained 24 hours after administration. However, recent studies using 6 \(\mu \text{m}\) insoluble particles administered to humans at an extremely low inhalation flow of 0.05 L/s (to ensure deposition in the small ciliated airways), showed that a large proportion of these particles were retained after 24 hours (20% cleared, with a clearance half-time of 2 d).\(^ {86}\)

For normal mucociliary clearance to occur it is necessary that the epithelial cells are intact, the ciliary activity and the rheology of mucus is normal, and that the depth and chemical composition of the periciliary fluid layer is optimal. Thus, the mucociliary escalator can be impaired by altering the volume of mucus secretion, the mucus viscosity and elasticity, or the ciliary beat frequency. Adrenergic agonists drugs such as salbutamol (albuterol)\(^ {82,87}\) have been reported to enhance clearance, whereas beclomethasone has no effect on mucociliary function.\(^ {88}\) Mucociliary clearance is known to be impaired in smokers,\(^ {89}\) in patients with chronic bronchitis,\(^ {76}\) and in acute asthmatics.\(^ {90}\) Certain diseases have the opposite effect—that of enhancing clearance rates.\(^ {91}\)

Pulmonary Endocytosis

Alveolar macrophages are considered the most important lung phagocytes. Macrophages are normal motile residents of the airways, interstitial matrix, and alveolar regions of the lungs.\(^ {92}\) They are plentiful in the lung, with a ratio of 1:8 with respect to Type I cells,\(^ {93}\) and their numbers and activity can increase substantially during inflammation or infection. Particles deposited in the alveolar region are taken up rapidly by macrophages. Phagocytic times of a few minutes\(^ {94}\) up to an hour\(^ {95}\) have been reported. The contribution of pulmonary endocytosis to the overall lung clearance is determined by the particle size and particle shape,\(^ {96}\) solubility, particle burden,\(^ {97,98}\) and the chemical nature of the inhaled aerosol. Alveolar macrophage-mediated clearance is a much slower process than mucociliary clearance, with retention half-times in the range of 50–80 days in rats and about 10 times longer in humans.\(^ {99}\) Particle phagocytosis by alveolar macrophages can be: (1) fast and efficient (eg, titanium dioxide, diameter > 0.2 \(\mu \text{m}\)), (2) not efficient (eg, ultrafine particles), (3) incomplete (eg, long fibers cannot be completely phagocytized by a spherical cell with a diameter of approximately 12 \(\mu \text{m}\)), or (4) overloaded (ie, when particles occupy a large fraction of the volume of individual alveolar macrophages).\(^ {100}\) The long retention time of insoluble particles in the lungs can have serious consequences for pulmonary disease.

Alveolar macrophages can clear particles from the alveolar region in 4 ways: (1) transport along the alveolar surface to the mucociliary escalator, (2) internal enzymatic degradation, (3) translocation to the tracheobronchial lymph, and/or (4) combination of the interstitial lymphatic route and mucociliary transport (Fig. 3). It is believed that translocation of particle-laden macrophages to the mucociliary region is responsible for the initial rapid clearance of insoluble particles in the first 24 hours after deposition.\(^ {101}\) However, transport of particles to the larynx by macrophages is relevant only in rodents.
and is negligible in humans.\textsuperscript{102} The initial transport rate of particles deposited in the lung periphery has been reported as 0.001–0.005 L/d, with exponential decline and a half-time of about 150 days.

Translocation of particles by alveolar macrophages to the lymph is known to contribute little to the overall clearance and to be determined by particle sizes higher than 3\,\mu m\textsuperscript{103} and particle burden.\textsuperscript{104} A greater proportion (1.7\%) of a dose of 3\,\mu m particles were translocated to the lymph during a 128-day study, compared to 7\,\mu m particles (0.2\%), while no translocation was observed for 13\,\mu m particles.\textsuperscript{105} Ultrafine particles (20\,nm) were translocated into the interstitium to a greater extent than larger particles.\textsuperscript{106} Particles and particle-laden macrophages may be cleared from the alveolar region by translocation to the interstitium, with subsequent transport back to the airway epithelium surface (by an interconnecting pathway, namely, bronchus-associated lymphatic tissue), where they are cleared by the mucociliary escalator.\textsuperscript{107} This interconnecting pathway has not become generally accepted because of a lack of satisfactory evidence.

The enzymatic activity following phagocytosis by alveolar macrophages is well known\textsuperscript{108,109} and its contribution to the overall pulmonary clearance requires consideration for enzyme-sensitive compounds such as biomolecules. Lung surfactant may cause large molecules to aggregate, which could enhance ingestion and digestion by alveolar macrophages.\textsuperscript{110}

**Pulmonary Absorption**

The main objectives of aerosol inhalation therapy have been to deliver the drug directly to the site of action and treat conditions within the tracheobronchial tree. However, the enormous absorptive surface area (approximately 100 m\textsuperscript{2}) of the alveolar epithelium and thin distal absorption surface (100–200 nm) make the lungs an attractive route for systemic delivery of drugs. Increasing interest in the lung as a route of delivery for systemic therapy has triggered detailed investigations of the mechanisms of drug absorption through the airways.

The mechanisms of absorption through the airways and the factors affecting this process have been investigated in detail.\textsuperscript{110,111} However, the translocation of molecules from the apical to the basal side of the epithelium is a subject of controversy and speculation. Absorption through membranes may be classified in general as paracellular and transcellular. Several routes of absorption have been proposed: (1) transport via membrane pores, (2) vesicular transport (through type I and/or type II lung cells), and (3) transport via the intercellular tight junctions.

In general, small molecules can cross the membrane by diffusion\textsuperscript{112} or by carrier-mediated transport.\textsuperscript{113} A nonselective transport process like bulk flow through large pores or pinocytosis has also been postulated for the transport of small lipid-insoluble molecules.\textsuperscript{114} In the case of macromolecules, it has been postulated that small peptides with molecular weight < 40 kilodaltons (kDa) may be absorbed by paracellular transport, while for large molecules (molecular weight > 40 kDa) transcytosis may be more important. There is evidence for receptor-mediated transport of some macromolecules, such as albumin.\textsuperscript{115}

**Transport Via Membrane Pores**

Populations of mathematical “equivalent pores” have been derived in order to account for the different absorption characteristics of molecules throughout the pulmonary epithelium:\textsuperscript{19,116} (1) small pores, which may represent the tight junctions or transcellular pores, have an estimated diameter of 1–5 nm;\textsuperscript{117} (2) large pores, which may represent junctions between cells, vesicular transport, trijunctional complexes, or cellular defects, and may be responsible for the transport of molecules with diameters > 5 nm; and (3) lipid pores for the absorption of highly lipid-soluble compounds.\textsuperscript{112} The existence of an ultra-large pore has also been proposed.\textsuperscript{110}

**Vesicular Transport (Transcytosis)**

The mechanism that cells use to transport molecules across the membrane without disrupting the barrier function of the cell membrane or its electrochemical potential
is known as transcytosis. The presence of vesicles within various epithelia has been demonstrated. Absorptive transcytosis may be receptor-mediated (membrane receptors) or non-receptor-mediated. The latter can be classified as: (a) fluid phase (fluid phase non-receptor-mediated transcytosis), characterized by the presence of noncoated vesicles called caveolae, or (b) absorptive transcytosis. Although there has been extensive research to elucidate fluid phase transcytosis, there is not enough evidence to support the role of this pathway in the transport of molecules across the pulmonary epithelium.

The transcytosis of some antibodies is mediated by receptors on the plasma membrane, receptor-ligand complexes are localized into clathrin-coated pits, and the complex is internalized and moved across the cell or delivered to lysosomes. Investigators have presented evidence for the existence of the albumin receptor on the alveolar epithelium. Some proteins, such as caveolin, albindin (a 22 kDa integral membrane protein), albumin receptor, molecular chaperones, and an insoluble triphosphate receptor are known to be transported into noncoated vesicles with opening diameters of approximately 40 nm. Whether receptor-mediated or not, transcytosis seems to be relatively slow. It takes hours to days to be completed for molecules with molecular weight > 40 kDa.

### Transport Via Tight Junctions

Tight junctions between the epithelial cells regulate the movement of small solutes, fluid, and ions. The importance of tight junctions in the transport of proteins is controversial. Tight junctions are known to be complex structures of multiple proteins, which serve as intricate and dynamic fasteners of cells to each other. The coupling zones enable adjacent cells to communicate metabolically and electronically and may endow mechanical support. The tightness or leakiness of the tight junctions may correlate with the number and continuity of rows or strands in the junctional web. The endothelial tight junctions’ structure and integrity differ from that of the epithelial tight junctions. The endothelium is known to be more permeable to macromolecules than the epithelium, and may not limit the protein absorption from the airways. Some investigators have reported that increasing intravascular pressure results in horseradish peroxidase moving through the junctions of the endothelial cells, but movement into the alveoli is blocked by the interepithelial junctions. The tightest endothelial junctions are seen in the arterioles and consist of 3–6 interconnected rows of particles and only rare discontinuities. The most tenuous junctions are seen in the venular endothelial cells, which are known to line the walls of the leakiest portion of the vascular system. Polypeptides of at least 12 kDa (3–4 nm in diameter) may pass into the interstitium via the endothelial tight junc-

### Factors Affecting Absorption Kinetics

The effects of molecular weight, partition coefficient, pH, release rate, interspecies variability, and osmolarity on absorption kinetics have been studied in detail. Investigators examined the absorption of saccharides and urea of various molecular weights, and found that the first-order rate constant (k) decreased with increasing molecular weight. Because of the low solubility of these hydrophilic compounds, these investigators proposed that absorption occurred through aqueous channels of intercellular spaces in the lipid membrane. In another study it was found that those compounds with molecular weight < 1,000 Da were absorbed at faster rates (half-time = 90 min) than the larger molecules (half-time = 3–27 h). Solutes with molecular weights in the range of 100–1,000 Da are absorbed with half-times of 8–40 minutes.

Once droplets containing drugs enter the fluid within the air spaces, they rapidly diffuse into the surrounding medium. The rate of clearance from the fluid lining the air spaces can be predicted using the following equation:

\[
\frac{dQ}{dt} = -PS\Delta c
\]

where Q is the quantity of drug in the air space, t is time, P is the permeability of the blood-gas barrier, S is the surface area of the barrier, and \(\Delta c\) is the concentration gradient across the barrier. Some studies have reported that solutes penetrate the alveolar wall at rates that increase with the lipid solubility of the compound. Those compounds having partition coefficients > 108 are absorbed rapidly. However, there appears to be no continuity for others with partition coefficients < 106. Lipid-soluble compounds are absorbed more rapidly than lipid-insoluble compounds, which cross the membranes at rates inversely proportional to their molecular weights. If the partition coefficients and molecular weights of the compounds are considered simultaneously, it may be possible to estimate which compound will be absorbed more quickly. Absorption half-times of one minute or less have been reported for highly lipid-soluble compounds, whereas for lipid-insoluble compounds (molecular weight 15–200 kDa), half-times of 1 hour have been estimated. The time it takes for peptides
and proteins to peak in the blood system (which depends on the rate of absorption) following lung delivery is molecular-weight-dependent. Small soluble peptides peak 10–30 minutes after administration, while large proteins peak in hours to days.\textsuperscript{134}

Most therapeutic agents are weak acids or bases and are present in solution as both the ionized and nonionized species. The nonionized entities are usually lipid-soluble and can diffuse across the cell membrane, whereas ionized molecules are usually unable to penetrate the lipid membrane because of their low lipid solubility. Therefore, the transport through membranes for a weak electrolyte is determined by its pK\textsubscript{a} (ie, the negative logarithm of its dissociation constant) and the pH gradient across the membrane. Since the membrane is more permeable to the nonionized form of any drug, it would be expected that weak acids would be absorbed more rapidly at low pH values, while weak bases would be absorbed more quickly at higher pH. The pH of the alveolar epithelial fluid is normally about 6.9.\textsuperscript{135} Thus, the extent and rate of pulmonary absorption of weak bases may be more pronounced than that for weak acids. In studies of labeled \textsuperscript{14}CO\textsubscript{2} and H\textsuperscript{14}CO\textsubscript{3}\textsuperscript{−}, the H\textsuperscript{14}CO\textsubscript{3}− diffused across the pulmonary epithelium at a rate at least 600 times slower than that of the \textsuperscript{14}CO\textsubscript{2}.\textsuperscript{136} The loss of certain molecules such as CO\textsubscript{2}, alcohols, and acetone from the lungs is limited by the rate of perfusion rather than the permeability of the alveolar-capillary barrier.\textsuperscript{136,137} Acidic solutions (pH 3) of insulin have a higher extent of pulmonary absorption than those of pH 7.\textsuperscript{138}

The absorption rate following intratracheal administration of various compounds has been calculated in several animals species.\textsuperscript{139} Lipid-insoluble drugs were absorbed approximately 5 times faster in mice than in rats, and roughly 2.5 times more slowly in rabbits than in rats. Lipophilic drugs were absorbed at similar rates in all the tested species.

The effect of osmotic pressure on cell membrane integrity and pulmonary absorption has been studied in detail. Water without solutes was extracted from the tissues when hypertonic solutions were injected into the pulmonary arterial inflow.\textsuperscript{140} The water that was removed from the air spaces was essentially devoid of solutes when isolated lungs were filled with isotonic solutions and perfused with hypertonic solutions.\textsuperscript{141} This indicates that hydrophilic solutes were not dragged along with the water. The osmolarity of inhaled aerosols could have a variety of effects on the absorption of solutes contained in the inhaled droplets. Hypotonic droplets would be expected to lose water to the relatively hypertonic bronchial walls and therefore shrink before reaching the alveolar surfaces. On the other hand, hypertonic droplets would tend to swell,\textsuperscript{130} altering the size of the droplet and therefore, the pattern of deposition along the airways. The administration of a hypotonic solu-

The relationship between dissolution, drug release rate, and absorption rate, and their effect on the extent of undesired and desired systemic effects has been demonstrated by the pulmonary delivery of slow-release preparations. A drug with a rapid release rate dissolves quickly after pulmonary deposition and is absorbed into the circulation at a rate determined by its chemical structure, as mentioned earlier. Pulmonary administration of a drug incorporated in a slow-release preparation, such as a liposome\textsuperscript{143} or microsphere,\textsuperscript{144} results in lower pulmonary absorption rate than that of free drug. The rate of absorption of sodium cromoglycate was slower when inhaled as a liposome preparation (dissociation constant [K\textsubscript{a}] = 0.027/h) than when inhaled as free drug (K\textsubscript{a} = 0.43/h).\textsuperscript{145} Triamcinolone acetonide phosphate encapsulated in liposomes is absorbed more slowly (K\textsubscript{a} = 0.5/h) than the free drug following intratracheal instillation in rats (K\textsubscript{a} = 2/h).\textsuperscript{143}

The physicochemical properties of a drug formulation, such as particle size,\textsuperscript{21,146} lipophilicity,\textsuperscript{22} and crystal form,\textsuperscript{21} play a central role in the dissolution rate and, consequently, the absorption rate. Lipophilic drugs with relatively large particle sizes dissolve more slowly than small hydrophilic particles. A drug with a fast dissolution rate dissolves immediately after pulmonary deposition and is absorbed into the systemic circulation at a rate determined by its partition coefficient and molecular weight. A powder formulation of fluticasone propionate, one of the most lipophilic inhaled glucocorticoids, was absorbed more slowly from the airways (mean absorption time = 4.9 h) than less lipophilic glucocorticoids such as flunisolide and budesonide of the same particle sizes (mean absorption time = 0.04 h and 0.2 h, respectively).\textsuperscript{147} Formulations with slow dissolution rates may be more appropriate for the local activity of drugs, since the biological activity is directly related to drug concentration at the site of action. However, slowing down the release of inhaled drugs for systemic therapy may be very detrimental, especially for biomolecules.

**Drug-Drug Interactions**

Multiple drug therapy may be essential in the treatment of several diseases, such as heart failure, cancer, and asthma, and infectious diseases such as tuberculosis and human immunodeficiency virus. The term “drug-drug interaction” refers to the possibility that one drug may alter the intensity of pharmacologic effect of another drug given concurrently. These interactions may be pharmacokinetic, pharmacodynamic (eg, interaction between agonist and antagonist at the level of the receptors), and/or chemical-chemical interactions (Fig. 4).
Chemical-Chemical Interactions

Chemical-chemical interactions have mostly been studied in the toxicology of air pollutants, where it was shown that the unwanted effects of certain oxidants may be enhanced in the presence of other aerosols. A study using a guinea pig model found that the irritant effects of SO₂ (the second most abundant air pollutant) are greatly enhanced in the presence of aqueous aerosols of various water-soluble salts. Physical and chemical interactions of aerosolized drugs with the surface active layers and the mucus layer in the respiratory tract are important determinants of the stability and activity of inhaled therapeutic agents. Particulate matter depositing on the alveolar surface can be coated with surfactant and is shown to form liposomes, which may enhance the uptake by macrophages.

Pharmacokinetic Interactions

Although pharmacokinetic interactions can lead to changes in absorption, protein binding, and urinary excretion, the effect on metabolism is generally more pronounced. Drug interactions based on metabolism are mainly associated with phase I metabolism through the cytochrome P-450 system. Thus, if the affected pathway represents the major route of elimination of the drug under consideration, increased or decreased drug plasma/tissue level may prolong or decrease the pharmacologic effect.

The handling of some endogenous and exogenous substances by the pulmonary endothelium involves several processes: uptake and biotransformation (serotonin, prostaglandin E and F), metabolism at the endothelium surface without uptake (angiotensin, adenosine nucleotides, bradykinin), and uptake with gradual release unchanged (propranolol, lidocaine, imipramine). The detoxification of serum vasoconstrictor substance (5-HT) on passage through the heart-lung preparation provides the first demonstration of the metabolic function in the lung. The lung selectively removes endogenous norepinephrine, 5-HT, and β-phenylethylamine from the blood and converts angiotensin I to angiotensin II. This implies that drugs with properties similar to these endogenous compounds may also be candidates for metabolism and sequestration by the lung. Treatment of the lung with selective inhibitors of mitochondrial monoamine oxidase markedly reduces the uptake of β-phenylethylamine. Thus, the lung uptake of exogenous compounds similar to β-phenylethylamine may also be reduced by monoamine oxidase inhibitors.

Pre-exposure to one concentration of oxygen mitigates later exposure to 100% oxygen by modifying cellular and enzymatic composition of the lungs. Damage of the alveolar zone by the antioxidant butylated hydroxytoluene can be enhanced by subsequent exposure to oxygen concentration that otherwise would have little if any demonstrable effect. This synergistic interaction between butylated hydroxytoluene and oxygen may result in pulmonary fibrosis.

Inhaled glucocorticoids, the first line of drugs for treating asthma, are metabolized mainly by the liver cytochrome P-450 IIIA enzyme family. These enzymes are both inducible and inhibitive (Table 2). Phenytoin, phenobarbital, rifampicin, promidone, ephedrine, phenylbutazone, and tyrosine are examples of compounds that alter glucocorticoid disposition by inducing liver metabolic capacity.

Table 2. Selected Inhibitors and Inducers of Cytochrome P-450 IIIA

<table>
<thead>
<tr>
<th>Inhibitors of P-450 IIIA</th>
<th>Inducers of P-450 IIIA</th>
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<tr>
<td>17α-Estradiol</td>
<td>Dexamethasone</td>
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<tr>
<td>17α-Ethynylestradiol</td>
<td>Rifampicin</td>
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<tr>
<td>Testosterone</td>
<td>Phenobarbital</td>
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<td>Cyclosporine</td>
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<td>Terfenadine</td>
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<td>Ketokonazole</td>
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<td>Troleandomycin</td>
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<td>Cimetidine</td>
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<td>Erythromycin</td>
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Esterases are present in high levels in alveolar macrophages and, to a lesser extent, in type I and type II alveolar cells.\textsuperscript{156} Beclomethasone dipropionate, an inhaled glucocorticoid used for treating asthma, is converted to a more potent compound, beclomethasone monopropionate, by lung esterases.\textsuperscript{157} Thus, the coadministration of drugs that are metabolized by esterases with this drug may alter its pharmacologic effect.

**Pharmacodynamic Interactions**

Pharmacodynamic interactions may occur at a common receptor site or at different sites in an organ, resulting in an addition or inhibitory effect. There is strong evidence to suggest a dynamic interaction between glucocorticoids and \(\beta\) agonists, two classes of drugs used in the treatment of asthma.\textsuperscript{158} Glucocorticoids increase the expression of \(\beta\) adrenoceptors, probably by increasing gene transcription.\textsuperscript{159} In addition, \(\beta\) agonists reduce the binding of glucocorticoid receptor to glucocorticoid-response elements within the nucleus by activating a transcription factor that interacts with the glucocorticoid receptor.\textsuperscript{160} Interactions at the receptor site have been also found in isolated perfused lung experiments.

**Summary**

The widespread use of aerosol therapy in the treatment of pulmonary diseases is based on optimizing drug properties and aerodynamic behavior of airborne particulates. In order to understand drug properties and aerodynamic behavior, it is important to recognize that each category of inhaler delivers a product with different physicochemical characteristics, and that these properties determine the site of deposition and the mechanism of clearance from the lungs. The complex interplay of these properties and the physiology and anatomy of the lungs must be considered to fully understand the implications for drug delivery. The aerodynamic behavior of aerosols under various inspiratory flow conditions influences the site of deposition. Once the particle comes to rest in the lungs, mechanisms of clearance are invoked, including dissolution and absorption, or, for more insoluble materials, mucociliary transport or cell-mediated transport. Finally the pharmacokinetics of drug disposition dictate the pharmacodynamic effects of the drugs responsible for efficacy.

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DRUG PROPERTIES AFFECTING AEROSOL BEHAVIOR


