Targeting Inhaled Therapy beyond the Lungs

Ninell P. Mortensen^a Anthony J. Hickey^b

^aSystems and Translational Sciences, and ^bTechnology for Industry and the Environment, Discovery Sciences Technologies Group, RTI International, Research Triangle Park, N.C., USA

Key Words

Aerosolization · Drug delivery · Drug release · Dissolution rate · Inhaled therapy · Systemic delivery

Abstract

Pulmonary disease has been the primary target of inhaled therapeutics for over 50 years. During that period, increasing interest has arisen in the use of this route of administration to gain access to the systemic circulation for the treatment of a number of diseases beyond the airways. In order to effectively employ this route, the barriers to transport from the lungs following deposition of aerosols must be considered, including the nature of the disease (whether proximal, as in pulmonary hypertension, or distal, as in diabetes). Delivery to the systemic circulation begins with the efficiency of aerosol generation and subsequent deposition in the airways and proceeds to the influence of mechanisms of clearance, including absorption, metabolism, and mucociliary and cell-mediated transport, on the residence time of the drugs in the lungs. The nature of the drug (small or large molecules/low or high molecular weight), susceptibility to degradation and general physicochemical properties play a role in the chemistry of its formulation, physics of aerosol delivery and biology of disposition.

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Introduction

The recent US Food and Drug Administration approval of Afrezza [1] will increase the interest in the lung as a route for systemic administration of drugs. Moreover, it should resurrect the enthusiasm for protein and peptide delivery that fueled decades of scientific inquiry and led to many novel technologies but waned upon the withdrawal of Exubera (inhaled insulin, Pfizer) in 2007. A number of diseases with symptoms that manifest beyond the airways, including pulmonary hypertension (proximally) and migraine headaches (distally), have been the subject of recent developments [2].

In this context, a review of the considerations regarding the systemic delivery of drugs is timely. There are a number of reasons for selecting the pulmonary route of administration for systemically acting agents. These may be divided into pharmaceutical, metabolic and physiolog-

Previous articles in this series: 1. Usmani OS: New developments in inhaled drugs: within and beyond the lungs. *Respiration* 2014;88:1–2. 2. Lavorini F, Fontana GA, Usmani OS: New inhaler devices – the good, the bad and the ugly. *Respiration* 2014;88:3–15. 3. Rubin BK, Williams RW: Aerosolized antibiotics for non-cystic fibrosis bronchiectasis. *Respiration* 2014;88:177–184.

Fig. 1. Chemical, physical and biological considerations that define the sequence of events from product development through optimal pharmaceutical aerosol product performance to achieve the desired bioavailability and therapeutic effect.

ical. Many drugs are not orally bioavailable due to intrinsic physiochemical properties or chemical instability in the extreme pH conditions of the gastrointestinal tract. Others are subject to metabolism prior to or following absorption to inactive or toxic metabolites. The disease itself may present physiological advantages to pulmonary delivery due to the proximity of the systemic target: a notable example being pulmonary hypertension.

In general, inhaled products require the combination of a drug formulation in an inhaler device that accurately meters the drug on the inspiratory flow of the patients resulting in lung deposition and disposition, as shown schematically in figure 1. Product development considerations focus on the formulation development, which depends on the physicochemical properties of the drug and the design of the device. The combined elements of the formulation, device and metering system allow for the product to dispense an accurate dose in appropriate particle/droplet sizes for deposition in the airways. Upon deposition, there are three major mechanisms of disposition absorption: mucociliary and macrophage uptake, and cell-mediated transport [3]. Each of these mechanisms may be influenced by a variety of biophysical and biochemical phenomena that will inhibit or enhance the bioavailability of the drug and are discussed in greater detail in the following sections.

Lung Physiology

Pulmonary drug delivery for remote targeting has received less attention than local delivery to treat lung conditions such as asthma and chronic obstructive pulmonary disease. Success for examples such as inhaled administration of human growth hormone [4–6] and insulin [7–13] is a strong motivator for exploring this route of drug administration. Inhaled drug delivery can be the answer to increase bioavailability of poorly soluble drugs that have poor absorption and bioavailability in the gastrointestinal tract when orally administered or are highly metabolized by the liver. Pulmonary drug delivery bypasses the first metabolism and has the potential for reduced drug metabolism and high bioavailability. However, pulmonary drug delivery presents the challenge of reaching sufficiently high circulating drug concentrations to achieve therapeutic levels. The biology of the lungs must be taken into consideration when designing inhaled therapies, in conjunction with the physicochemical properties of the aerosolized drug particles, their disposition in the lungs and drug bioavailability. The design and technical details of the different inhalers available for pulmonary drug delivery are beyond the scope of this review, but have been extensively described elsewhere [14–18].

Fig. 2. Schematic (a) and histopathological section (b) through the airway depicting ciliated epithelial cells [modified from 75].

Aerosol drug delivery to the lungs generally facilitates uptake to the systemic circulation. The optimal region to target for systemic delivery is the periphery (respiratory bronchioles and alveoli) due to the large surface area, the thin epithelial barrier and close proximity to the blood and lymphatic fluid.

The human lungs divide into two functional regions, the conducting airways and the respiratory region. The conducting airways include the nasal cavity and associated sinuses, the pharynx, larynx, trachea, bronchi and bronchioles. The respiratory region is comprised of the respiratory bronchioles, the alveolar ducts and the alveolar sacs. Together the conducting airways and respiratory regions account for an estimate 23–32 branchings or generations [15, 16, 19], and all compartments are maintained at high relative humidity, which affects the drug particle physicochemical properties as the drug particle travels through the lung. The role of humidity will be discussed later. The trachea, bronchi and bronchioles are collectively called the airways and branch off into the alveoli. In an adult, the surface area of these airways is only a few square meters in contrast to the alveolar surface area of more than 100 m².

Airways and Cells

The drug particle traveling to the alveolar space will encounter many different cell types (epithelial, ciliated, goblet, secretory and basal cells), which are adapted to serve the specialized functions of each compartment (table 1) [16].

The major cell type of the airways is the epithelial cell, which in the bronchi of the upper airways has a columnar morphology with a height of 58 µm, gradually thinning in deeper portions of the lungs to a height of 0.1–0.2 µm

Table 1. Pulmonary cells and their function

Cell	Putative function
Ciliated columnar	Mucus movement
Mucus (goblet)	Mucus secretion
Serous	Periciliary fluid
Clara (nonciliated epithelial)	Surfactant production, metabolism
Brush	Transitional form of ciliated epithelial cells
Basal	Progenitor for ciliated epithelial and goblet cells
Dendritic cells	Antigen-presenting cells
Neuroendocrine	Chemoreceptor, paracrine function
Alveolar type I	Alveolar gas exchange
Alveolar type II	Surfactant secretion, differentiation to type I cells
Alveolar macrophages	Pulmonary defense
Mast	Immunoregulation

forming a cellular monolayer in the alveoli (fig. 2) [16]. Two important cell types overall in the lungs are mucus-producing goblet cells and ciliated cells, which together form the mucociliary escalator, the ‘housekeeping’ system of the upper airways. If the drug particle deposits in the airway before reaching the alveolar space, it is likely to be carried to the trachea by the mucus escalator before its drug content is released. The protected viscous mucus layer lining epithelial cells is 8 µm thick in the bronchus transition through the airways into a 0.07-µm-thick surfactant layer in the alveoli. The mucus layer is comprised of inorganic salts, proteins, glycoproteins (mucins), lipids and water, whereas the surfactant layer contains phospholipids, cholesterol and proteins [19]. The presence and composition of this protective lining of the lungs is likely to affect both drug solubility and diffusion towards

Fig. 3. Disposition of intracellular infectious microorganisms (*Mycobacterium tuberculosis* and *Toxoplasma gondii*) in alveolar macrophages

the epithelium, and the interaction between drugs and cell surfaces and receptors. Inhaled particles deposited on ciliated epithelial regions of the lungs will embed in the mucus layer, where they are transported by the ciliated cells into the esophagus, and the material is expectorated and/or swallowed. The kinetics of particle deposition, as a function of their interaction with these features of the lungs, are an important consideration for bioavailability. Mucociliary clearance rates in the absence of unique cell binding phenomena are considered to be in the 12- to 24-hour range [20].

Uptake by alveolar macrophages in the periphery of the lungs is also a challenge to retaining drug particles in the lungs for sufficient time to release their contents unimpeded. Approximately 90% of alveolar macrophages are located at or near the spatial junctions between alveolar epithelial cells [21], and the air interface of each of the approximately 500 million alveoli is patrolled by 12–14 alveolar macrophages, which phagocytose any insoluble particle that deposits in this location [22]. Delivery of drugs to the lungs can either be designed to avoid phagocytic cells or to take advantage of the phagocytic nature of the macrophages. The benefits that accrue from each of these strategies are important to the action of the drug. Avoiding macrophage uptake is important for drugs which may be subject to degradation by the enzymes in these cells, which are designed to eliminate both endogenous and exogenous substances of biological origin [23]. Conversely, it may be desirable to target macrophages as

a target or a depot. Macrophages are frequently the host cells for infectious microorganisms and co-opting their phagocytic nature to deliver antibiotics allows for lower dose and more potent therapy [24, 25]. Figure 3 illustrates the sequence of events that allows two exemplary intracellular infectious microorganisms to enter the macrophage and then turn off the lysosomal antimicrobial processes and ultimately disconnect the vesicle from normal intracellular trafficking.

Pulmonary blood and lymphatic circulation are also essential features of the lungs and require consideration in respiratory drug delivery. In a normal healthy person, it is estimated that the pulmonary blood volume is approximately 10% of the total blood volume of the body, with 20–25% being arterial blood volume [26–28]. This presents the opportunity for rapidly achieving a high drug concentration in the bloodstream, but also the challenge of avoiding unintended metabolism and clearance of a drug. The entire cardiovascular output passes through the lungs, resulting in a high pulmonary blood flow, and the metabolic capacity of the lung should not be ignored [29].

Transport and Metabolism

Other biological obstacles in the fate of inhaled drug particles when they have reached the alveolar space are drug metabolism, efflux transporters (such as P-glycoprotein prominent in type I cells), protein binding and cellular permeability [19]. All metabolic enzymes found in the liver are also present in the lung, but at a lower level. For example cytochrome P₄₅₀ is 5–20 times lower in the lung compared to the liver [30–34]. General metabolic enzyme and transporter pathways are illustrated in figure 4.

Transporters

Other protein transporters such as breast cancer resistance protein, multidrug resistance-associated protein and lung resistance protein are found in the lungs and are responsible for the efflux transport of many drugs, which leads to lower absorption and bioavailability than expected [19]. All the listed biological functions are likely to differ between the various compartments of the lungs and need to be considered when designing inhaled therapies. Many aspects of pulmonary drug metabolism are not well understood at present. Also, as a combined entity, all the above biological functions will influence the rate and extent of drug absorption and retention in the lungs, which determine the bioavailability of the drug. Where under-

Fig. 4. General metabolic pathways and the role of efflux transporters. Courtesy of Matt Redinbo, University of North Carolina at Chapel Hill.

Table 2. Phase I metabolic enzymes and their appearance in the lungs [abstracted from 76]

Enzymes phase I CYPs	mRNA	Protein	Location
1A1	+++ (smokers)	+++ (smokers)	Bronchial epithelial cells, capillary endothelium, alveolar epithelium
1A2	+/-	+/-	Peripheral tissue
1B1	++	+/-	Alveolar macrophage epithelial cells, bronchial epithelial cells
2A6	++	+/-	Bronchial mucosa, epithelial cells
2A13	+	?	Bronchial mucosa, alveolar epithelium
2B6/7	+++	+++	Clara cells, bronchial and peripheral tissue, epithelial cells
2C8/18	+	+/-	Serous cells of bronchial glands, bronchial and peripheral tissue
2D6	+/-	+/-	Bronchial mucosa
2E1	+++	+++	Bronchial, bronchiolar and alveolar epithelium, endothelial cells
2F1	+++	?	Alveolar macrophage epithelial cells, endothelial cells
2J2	+	++	Bronchial and vascular smooth muscle cell, vascular endothelium, alveolar macrophages
2S1	+	+	Epithelial cells
3A4/5	+++	++	Bronchial, bronchiolar and alveolar epithelium, alveolar endothelium, alveolar macrophages
3A43	+	?	?
4B1	+	?	Bronchoalveolar macrophages
EHs	++	++	Bronchial epithelial cells
FMOs	++	+	?

standing the pulmonary drug metabolism comes in, is that the feasible amount of material delivered to the lungs is about 100–150 mg per dose [35], which is in contrast to the gastrointestinal tract, where several grams can be easily administered. Thus, in the presence of a lower level of metabolic enzymes, efflux transporters can still have a significant impact on pulmonary drug delivery compared to the gastrointestinal tract.

Metabolism

Lung metabolism for small natural peptides can be very significant unless they are chemically engineered to inhibit peptidases. Besides the phase I enzymes discussed above, phase II enzymes such as uridine glucuronosyl-transferase, sulfotransferase, glutathione S-transferase and peptidase activity have also been reported [36–40]. Somers et al. [34] compared the catalytic activity of both

Table 3. Phase II metabolic enzymes and their appearance in the lungs [abstracted from 76]

Enzymes phase II	mRNA	Protein	Location
UGT	+/-	+/-	Lung tissue
GST			
A1	++	+	Bronchial and bronchiolar epithelium
A2	++	+	Bronchial and bronchiolar epithelium
M1	++	+	Lung tissue
M2	++	+	Epithelium of the terminal airways
M3	++	+	Ciliated airway epithelium and smooth muscle
P1	++	+	Bronchial and bronchiolar epithelium
NAT	+	+	Bronchial epithelial cells, alveolar lining cells
SULT			
1A1	+	+	Bronchial epithelial cells
2B1b	+	+	Bronchial epithelial cells

UGT = Uridine glucuronosyltransferase; GST = glutathione S-transferase; NAT = N-acetyltransferase; SULT = sulfotransferase.

phase I and II enzymes in isolated human lung parenchymal and hepatocyte cells using liquid chromatography-tandem mass spectrometry and found that some evidence for substantial sulfation and deesterification capacity in lung parenchymal cells. Transcript profiling of xenobiotic-metabolizing enzymes encoding genes of nontumoral and tumoral lung tissue from patients with non-small lung cancer also showed the activity of several phase I and II enzymes, and, furthermore, stressed the differences in pulmonary metabolism caused by disease [40]. Tables 2 and 3 illustrate the metabolic enzymes which may be found in the lungs.

The location of enzymes within the airways and in subcellular organelles may also play a role in disposition since the route that the drug takes from the lungs will have both a spatial and temporal probability of passing through regions of high metabolic activity. Certain cells are known to be highly metabolic, such as Clara cells in the airways. Type II alveolar epithelial cells express enzymes required for metabolism, such as cytochrome P₄₅₀, but type I cells are thought to have little capacity for metabolism. Enzymes are distributed in many subcellular compartments but not uniformly, as shown in table 4.

General biochemical principles apply to the transport of molecules through or between cells, as illustrated in figure 5. Molecular and peptide absorbance kinetics in the pulmonary space can also be significantly influenced by naturally occurring glycosylation [7]. A study of α_1 -antitrypsin showed a fourfold lower $t_{\max}$ if the molecule was naturally glycosylated compared to nonglycosylated molecules [7].

Physical and Biological Barriers

Physical properties of a particle, such as particle size, aerodynamic particle size distribution, mass median aerodynamic diameter (d_a), mass distribution, shape and electrostatic charge, play an important role where the drug particles deposit in the lung. Also, the pharmacokinetic properties of drug release, which are influenced by solubility and dissolution rate, from particles and drug half-life are important factors to take into consideration for achieving a therapeutic concentration.

Pulmonary delivery of nanomedicine has to be designed to deliver the aerosolized drug particle to the intended area of the lung; the deposition is primarily based on particle size. Particle deposition occurs by inertial impaction, sedimentation, diffusion, interception and by electrostatic precipitation [15, 16, 41]. When the particle has sufficient momentum to follow its initial trajectory despite changes in the airstream, inertial impaction occurs, and the particle collides with the airway wall, often at or near a bifurcation in the lungs. Gravity also influences the particle route in the airways and in a time-dependent manner causes sedimentation. Particles small enough to be subject to random motions are subject to diffusion. Impaction and sedimentation are the dominant mechanisms of deposition of therapeutic aerosols.

The equivalent aerodynamic (d_a) and volume diameters of a particle are the most appropriate descriptors for aerosolized drug particles. The former is particularly important as lung deposition relates to particle aerodynamic behavior. For inhalation therapy, the optimal d_a for a particle is approximately 1–5 μm [42]. Particles larger

Table 4. Distribution of enzymes in subcellular compartments and their function [modified from 76]

Localization	Phase	Enzyme	Reaction
Cytosol	I	Esterase	Hydrolysis
	I	Epoxide hydrolase	Hydrolysis
	I	Azo and nitro reduction	Hydrolysis
	I	Carbonyl reduction	Hydrolysis
	I	Disulfide reduction	Reduction
	I	Sulfoxide reduction	Reduction
	I	Quinone reduction	Reduction
	I	Alcohol dehydrogenase	Reduction
	I	Aldehyde oxidase	Reduction
	I	Diamine oxidase	Oxidation
	II	Sulfate conjugation	
	II	Glutathione conjugation	
	II	Acylation	
	II	Methylation	
Microsomes	I	Esterase	Hydrolysis
	I	Epoxide hydrolase	Hydrolysis
	I	Azo and nitro reduction	Hydrolysis
	I	Carbonyl reduction	Hydrolysis
	I	Quinone reduction	Reduction
	I	Reductive dehalogenation	Reduction
	I	Prostaglandin H synthase	Reduction
	I	Flavin-monooxygenases	Reduction
	I	Cytochrome P ₄₅₀	Reduction
	II	Glucuronide conjugation	
	II	Glutathione conjugation	
	II	Amino acid conjugation	
	II	Methylation	
Lysosomes	I	Esterase	Hydrolysis
	I	Peptidase	Hydrolysis
Mitochondria	I	Alcohol dehydrogenase	Reduction
	I	Xanthine oxidase	Reduction
	II	Amino acid conjugation	
	II	Acylation	
Blood	I	Esterase	Hydrolysis
	I	Peptidase	Hydrolysis
	I	Carbonyl reduction	Hydrolysis
	II	Methylation	
Microflora	I	Azo and nitro reduction	Hydrolysis

than 5 μm usually experience inertial impaction early in the airways and are deposited in the oral cavity and pharynx. Particles that are smaller than 0.5 μm are subject to Brownian motion and settle very slowly, and they are often exhaled before settling occurs. Also influencing the aerodynamic behavior of drug particles is the shape factor, which is dependent on particle shape, surface roughness and surface area. The shape factor is defined by the

ratio of the drag force of the particle to that of a sphere of equivalent volume. Consequently, the drag force will be greater on a nonspherical particle with high surface roughness when compared to a spherical particle, and, as a result, d_a is smaller than anticipated. Creating porous particles that have a similar mass of a drug in a larger volume also increases the drag with respect to a solid particle of the same d_a [43]. Therefore, particle shape and density can be used to manipulate the aerodynamic properties of aerosols.

The d_a of a drug particle can be altered when entering the high relative humidity environment in the airways, and thereby drug deposition can also be altered [30]. Rarely does removal of water occur, more frequently the cause is particle acquisition, which is a function of the initial diameter, so a particle <1 μm may increase fivefold in contrast to the two- to threefold increase for a particle >2 μm [44].

The physicochemical properties of the molecule intended for delivery also play a critical role in the formulation of inhalation therapy. Crossing the airway epithelial barrier is naturally essential for the drug to enter the blood stream, and parameters such as molecular weight, lipophilicity (log P), solubility, pKa, protein binding, polar surface area and charge plays into that [19]. In general, lipophilic molecules cross the airway epithelium by passive transport and hydrophilic molecules via extracellular pathways. However, molecules are delivered as particles, and particles with low dissolution rate that reach the alveolar space, past the mucociliary escalator, encounter the many alveolar macrophages and are phagocytized or absorbed into the pulmonary circulation [30]. Particle surface properties, however, are of greater interest than dissolution rate in respect to disposition. Other physicochemical properties to take into account are van der Waals forces, hydrostatic interaction, mechanical interlocking, and electrostatic and capillary forces, which are important contributors to particle interactions in the lung, which influence aggregation, and particle-particle and particle-cell interactions. In pulmonary drug delivery, achieving the intended d_a and avoiding aggregation are essential for successful therapeutic results.

As mentioned above, the human airway is coated with a protecting surfactant layer, the protein content and composition of which varies between lung compartments. As soon as they interact with protein-rich environment, particles acquire a surface protein coating or corona. The corona is dynamic following the Vroman effect, which describes how the more abundant proteins will initially form a looser associated corona, to be re-

Fig. 5. Mechanisms of drug transport across the pulmonary epithelium.

placed with less abundant proteins with higher binding affinity to the surface [45, 46]. The protein corona composition and dynamics have been reported to be influenced by particle size, surface chemistry and charge [47–50]. The protein composition might play an important role in both macrophage uptake and transport across the epithelial barrier.

Fate of Microparticles and Nanoparticles

It is important to note that lung deposition occurs most effectively for microparticles usually in the 1- to 5- μm size range [51, 52]. The recent interest in nanoparticle delivery poses some important questions considering aerosol properties. Aerosol particles or droplets are delivered as dry powders alone (via dry powder inhalers), or aqueous (nebulizers or soft mist inhalers) or nonaqueous (pressurized metered dose inhalers) suspensions or

solutions [53]. Regardless of the primary particle size of the formulation (micro- or nano-sized), the particles delivered in these states from these devices are necessarily in micron sizes due to their intrinsic physicochemical properties and underlying forces of interaction. Thus, micron-sized aerosolized droplets may contain many nanoparticles that dry to form aggregates, and dry powders are dispersed as micro-agglomerated nanoparticles. Thus, conventional aerosol deposition phenomena occur, which for the size range of interest, 1–5 μm , for lung delivery is dominated by inertial impaction and sedimentation, as discussed earlier. It is of interest, from both safety and efficacy standpoints, to consider the extent and rate of deaggregation of nanoparticle agglomerates since this will influence a variety of elements of disposition from dissolution rate to route of elimination or access to the target site for therapy or off-target site for toxicity [54]. A micro-agglomerated nanoparticle construct may exhibit low density, in which case it may have two poten-

tially desirable properties: the first being its small aerodynamic particle size in relation to its geometric size, which is predicted by Stokes' law [55]. In principle, the longer nanoparticles which remain aggregated are more likely to behave as microparticles with respect to clearance mechanisms. However, their low density may mean that their geometric size is too large for macrophage uptake [43]. In addition, their large surface area may increase the dissolution rate for soluble particles [55]. In turn, this will have an effect on the pharmacokinetics of drug appearance in the systemic circulation. Due to lower solubility or for other reasons, such as the presence of a hydrophobic additive, particles exhibit retarded dissolution and will retain their primary particle structure for a defined time. Assuming that deagglomeration occurs within the time frame of mucociliary clearance, intact nanoparticles will interact differently with mucus and may be retained longer than microparticles by penetrating the mucus matrix to the epithelial surface [56]. Those particles that deposit in the periphery of the lungs will not be constrained by mucociliary clearance rates. Depending on deagglomeration rates and the intermediate size of fragments of the original particles, uptake by both alveolar and airway macrophages and dendritic cells is possible, resulting in the first contact with the primary elements of the immune system in the lungs [57]. The immune response to this exposure may dictate the safety of the proposed therapy. Certain nanoparticles may also pass directly through the epithelium, which has both safety and efficacy implications for systemic exposure depending on the time the particles take to disperse into the molecular state [58, 59].

The most prominent nanoparticles delivered have been macromolecules which are either proteins or nucleic acids. Since their hydrodynamic radius is of nanometer size, these are definitively in the category of nanoparticles. The importance of the molecular weight of these molecules has received considerable attention [60]. In general, clearance rates from the lung decrease with increasing molecular weight. It has been suggested that for all practical purposes with some exceptions for functionalized proteins, which may utilize active clearance pathways, the molecular weight range suitable for systemic delivery through the lungs is 5–20 kDa [7]. Delivery of proteins and peptides may be hindered by the instability of the drug in the presence of lung lining fluid, containing peptidases and other macromolecules (glycoprotein, glycolipid), by which they are degraded or to which they bind, respectively.

Historically, the influence of molecular weight on the transport of macromolecules was studied using fluores-

Fig. 6. Clearance as a function of molecular weight for fluorescent dextrans. The solid line depicts the mean and the dotted lines the range for data derived from a number of species including man [modified from 65, 77, 78]. The data points represent data points for which permeability across small airway epithelial cells in culture demonstrated equivalence to in vivo data.

cent-labeled dextrans [61, 62] or other polymers [63]. Clearance has been shown to be linearly and reciprocally related to molecular weight regardless of the species [64, 65]. Figure 6 illustrates the phenomenon as observed in a cell culture model using human small airway epithelial cells onto which aerosols were sampled from an inertial impactor to achieve appropriate particle size [66].

Therapeutic Examples

A wide range of molecules have been considered for delivery to the lungs to treat a variety of systemic diseases. Interest in the lungs as a route of systemic administration existed at the onset of the biotechnology product revolution, which began in earnest in the late 1980s. In particular biological molecules that could not be delivered by the oral route and that would otherwise be injected were considered potential candidates [67, 68]. The most prominent of these candidates were insulin for the treatment of diabetes and leuprolide acetate to treat prostate cancer [11, 69]. Insulin posed some unique challenges in that it is required daily and with some discretion by the patient to control circulating glucose levels, but in other respects the patient may be healthy. The requirement for exquisite dose control to titrate efficacy safely resulted in the development of formulations and devices (mostly dry powder inhalers) that propelled pharmaceutical aerosol science into the 21st century. Leuprolide acetate, a nonapeptide

leuteinizing hormone-releasing hormone analog, was developed for the delivery in a pressurized metered dose inhaler, and as it is a relatively small peptide without secondary or tertiary structure, it did not pose such a significant formulation and stability challenge. While this product was published widely in the early 1990s, it did not proceed to the commercialization stage. A number of other proteins and peptides, including calcitonin, parathyroid hormone and growth hormone, were studied [5, 70], but none of them were commercialized.

The ability to deliver small molecular weight molecules rapidly through the lungs to relieve symptoms associated with central nervous system diseases may be traced back in modern times to a pressurized metered dose inhaler for ergotamine used to treat migraine headaches in the 1960s (3M Pharmaceuticals, St. Paul, Minn., USA) [2]. This is apparently an effective strategy since dihydroergotamine is now under development for the same purpose (Levadex; Allergan, Irvine, Calif., USA) [71]. Other agents that act in the CNS have been explored more recently, including those to treat agitation in schizophrenia (Loxapine; Alexza, Mountain View, Calif., USA) [72] and drugs used for pain relief [73].

With systemic drug delivery becoming conceptually more popular, it is not surprising that targeting a proximal site of the airways is considered. Pulmonary hypertension is a difficult disease to treat since its localization makes systemic therapy problematic. The idea of accessing the target site by direct drug delivery to the lungs is very attractive. Inhaled prostenoids have been pursued for this purpose [74].

Conclusion

The ongoing success of aerosol therapy for the treatment of pulmonary diseases has established a strong foundation for science and technology, from which to consider further applications to systemic disease, which have either proximal, e.g. in the case of pulmonary hypertension, or distal components, e.g. diabetes. Clearly, the physicochemical properties of the initial dosage form, aerosol physics leading to lung deposition and the biological barriers to presenting the drug to the circulation, all play a role in the likelihood of success in treating systemic disease. All aerosol dosage forms, e.g. pressurized metered dose inhalers, dry powder inhalers and nebulizer therapy, have the potential to deliver drugs to the lungs for systemic effects. However, macromolecules are predominantly delivered as nebulized therapy or from dry powder

inhalers. These dosage forms more readily accommodate the required doses and stability of biotechnology products. After depositing in the lungs, particles must first dissolve, and, during this period, they are being transported on the mucociliary escalator or in macrophages depending on their site of deposition and the time taken to completely convert to the molecular drug. Once dissolved, the drug will have to pass through lung lining fluid where enzyme (e.g. protease) action or binding (protein or lipid) may hinder penetration to the epithelium. Transport through or around epithelial cells may result in metabolism or transporter effects that may influence the availability of the drug in the circulation. Assuming that these potential barriers can be circumvented through judicious selection (or design) of molecules, the pulmonary route offers great potential for drugs that would otherwise be poorly bioavailable (due to their solubility or degradation in gastrointestinal fluids), toxic (due to large doses) or subject to first pass metabolism. Moreover, the pulmonary route may be considered a topical application of drugs, which does not require the invasive techniques with requisite oversight and training employed for parenteral drug administration. It may be concluded that with appropriate pharmaceutical, biological and disease state considerations, aerosol delivery of drugs to the lungs for systemic action may yet meet its full potential.

Acknowledgments

Dr. Hickey is supported in part by the National Institute of Allergy and Infectious Diseases (grant No. R01AI091882) and is principal investigator for the National Institutes of Health Nanomaterial Registry. This Registry has been funded with federal funds from the National Institute of Biomedical Imaging and Bioengineering and the following partners: the National Institute of Environmental and Health Sciences, and the National Cancer Institute, National Institutes of Health and the US Department of Health and Human Services (contract No. HHSN268201000022C).

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