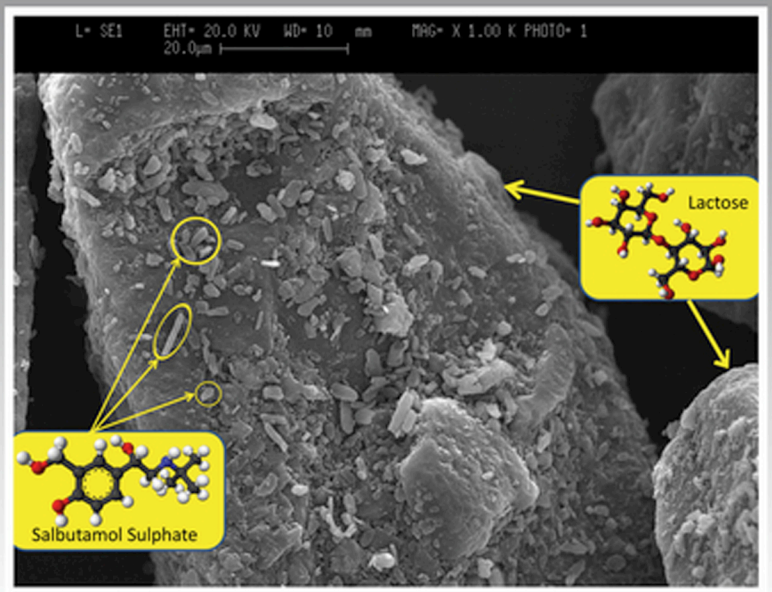
ADVANCES IN PHARMACEUTICAL TECHNOLOGY

Editors
Ali Nokhodchi
Gary P. Martin

Pulmonary Drug Delivery

Advances and Challenges



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Pulmonary Drug Delivery

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Advances in Pharmaceutical Technology

Series Preface

The series *Advances in Pharmaceutical Technology* covers the principles, methods, and technologies that the pharmaceutical industry use to turn a candidate molecule or new chemical entity into a final drug form and hence a new medicine. The series will explore means of optimizing the therapeutic performance of a drug molecule by designing and manufacturing the best and most innovative of new formulations. The processes associated with the testing of new drugs, the key steps involved in the clinical trials process, and the most recent approaches utilized in the manufacture of new medicinal products will all be reported. The focus of the series will very much be on new and emerging technologies and the latest methods used in the drug development process.

The topics covered by the series include:

Formulation: The manufacture of tablets in all forms (caplets, dispersible, and fast-melting) will be described, as will capsules, suppositories, solutions, suspensions and emulsions, aerosols and sprays, injections, powders, ointments and creams, sustained release, and the latest transdermal products. The developments in engineering associated with fluid, powder and solids handling, solubility enhancement, colloidal systems including the stability of emulsions and suspensions will also be reported within the series. The influence of formulation design on the bioavailability of a drug will be discussed and the importance of formulation with respect to the development of an optimal final new medicinal product will be clearly illustrated.

Drug Delivery: The use of various excipients and their role in drug delivery will be reviewed. Amongst the topics to be reported and discussed will be a critical appraisal of the current range of modified-release dosage forms currently in use and also those under development. The design and mechanism(s) of controlled release systems including; macromolecular drug delivery, microparticulate controlled drug delivery, the delivery of biopharmaceuticals, delivery vehicles created for gastro-intestinal tract targeted delivery, transdermal delivery, and systems designed specifically for drug delivery to the lung will all be reviewed and critically appraised. Further site-specific systems used for the delivery of drugs across the blood brain barrier including dendrimers, hydrogels, and new innovative biomaterials will be reported.

Manufacturing: The key elements of the manufacturing steps involved in the production of new medicines will be explored in this series. The importance of crystallization; batch and continuous processing, seeding; mixing including a description of the key engineering principles relevant to the manufacture of new medicines will all be reviewed and reported. The fundamental processes of quality control including good laboratory practice (GLP), good manufacturing practice (GMP), quality by design (QbD), the Deming cycle; regulatory requirements and the design of appropriate robust statistical sampling procedures for the control of raw materials will all be an integral part of this book series.

An evaluation of the current analytical methods used to determine drug stability, the quantitative identification of impurities, contaminants, and adulterants in pharmaceutical materials will be

described as will the production of therapeutic bio-macromolecules, bacteria, viruses, yeasts, molds, prions, and toxins through chemical synthesis and emerging synthetic/molecular biology techniques. The importance of packaging including the compatibility of materials in contact with drug products and their barrier properties will also be explored.

Advances in Pharmaceutical Technology is intended as a comprehensive one-stop shop for those interested in the development and manufacture of new medicines. The series will appeal to those working in the pharmaceutical and related industries, both large and small, and will also be valuable to those who are studying and learning about the drug development process and the translation of those drugs into new life saving and life-enriching medicines.

Dennis Douroumis
Alfred Fahr
Juergen Siepmann
Martin Snowden
Vladimir Torchilin

Preface

One of the first axioms imparted to students interested in formulating drugs for human and animal administration is that a drug (or active pharmaceutical ingredient) itself does not comprise a medicine. The drug has first to be formulated into a medicine that can be ingested by the patient. The most popular medicinal form (both with patient and healthcare workers), easiest to take or administer, dose-reproducible, cheapest, most stable, and safest form is generally acknowledged to be the tablet. To achieve these desirable characteristics, a large number of excipients (or 'non-pharmacologically active' materials) have to be included. These could include, for example, fillers, lubricants, glidants, disintegrants, colours, coating agents, etc.

However the challenges of treating diseases, such as asthma, chronic obstructive pulmonary disease, cystic fibrosis, infections, tuberculosis, and lung cancer which involves the airways, render the tablet a less advantageous choice compared with the patient employing an inhaled formulation as a means of therapeutic management. This is because an inhaled drug can be delivered locally at a lower dose and hence with fewer side-effects compared to that taken via the gastrointestinal tract. In addition, it might appear initially that some of the formulation issues might be reduced because most inhaled formulations comprise either none or possibly only one or two excipients (in addition to the drug). However this tenet is clearly false. For example currently, over 40% of patients suffering from asthma and chronic obstructive pulmonary disease use dry powder inhaler (DPI) formulations and this number is expected to grow in the future; and despite extensive research on DPIs during the last 40 years, some of these formulations may only delivery 10–20% of the inspired drug to the lungs. A core requirement for the effective clinical management of such respiratory diseases often, therefore, depends on the efficient delivery of aerosolised drugs to the airways. For efficiency to be optimised prior to the innovation of a new medicinal aerosol, a closely integrated triumvirate of fundamental factors, namely the patient, the formulation and the device, have to be considered both individually and holistically in the development process. One of the first steps of a development process should be to define the product specifications which combine these three essential factors into a user-requirement specification. Such a specification must encompass an appreciation of the patient requirements, involving an understanding of the structure of the airways and the challenges of separate patient groups such as children and the elderly, and acknowledge the impact of disease (e.g. lung cancer) upon the delivery of the drug. To this end, the functional imaging of the airways might assist in improving pulmonary delivery. As regards the formulation of drugs for inhaled dosage forms, then the challenges are many and encompass the following: the methods by which the efficiency of delivery (and dissolution) of such medicines can be assessed *in vitro*; the strategies for formulating poorly soluble active agents; the development of novel macromolecular, micro- and nanoparticulate systems; and the techniques which are developed to assess satisfactory powder blending. The importance of understanding the physicochemistry (including surface roughness) of the so-called inactive excipients, such as lactose, in dry powder formulations and the manner in which these can be manipulated (by particle engineering) is often under-appreciated. However improvements in formulating the drug in powder or suspended form cannot be carried out without appreciating the capabilities of

the device in which it is to be both packaged and presented. The development of the aerosol medicine can then proceed according to quality by design approaches.

As editors, we have been privileged to gain the cooperation of leading expert scientists to contribute to this book, providing both an overview of their research knowledge and presenting first-hand experiences of medicine design. We believe that this proffers an accessible overview to this fast-moving and complex field, and provides the readers with a sound basis for understanding some of the key issues involved. We hope that it will inspire future scientific and technological endeavour to improve the formulation of inhaled dosage forms such that ultimately they will possess all the desirable characteristics of the tablet form (discussed earlier).

The book is written primarily for postgraduate (PhD/Masters) level for readers who require a fast-route basic understanding of the current key issues of pulmonary drug delivery formulation, including device design, powder and particle engineering, and patient considerations. This book is useful for pharmacy students at their final year, pharmaceutical sciences degree courses, postgraduate students working in the inhalation field and scientists working in the industrial sector.

Ali Nokhodchi
Gary P. Martin
April, 2015

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Lung Anatomy and Physiology and Their Implications for Pulmonary Drug Delivery

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Abbreviations

List of Abbreviations

ABC	ATP binding cassette
BCRP	Breast cancer resistance protein
CF	Cystic fibrosis
COPD	Chronic obstructive pulmonary disease
CFD	Computational fluid dynamics
CFPD	Computational fluid-particle dynamics
GIT	Gastro intestinal tract
GR	Glucocorticoid receptors
ICRP	International Commission on Radiological Protection
MCC	Mucociliary clearance
MRP1	Multidrug resistant protein
OAT	Organic anion transporters
OCT	Organic cation transporters
P(D)	Probability by diffusion
P(I)	Probability by impaction
P-gp	P-glycoprotein
PR	Prostacyclin receptor

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Pulmonary Drug Delivery: Advances and Challenges, First Edition. Edited by Ali Nokhodchi and Gary P. Martin.

P(S)	Probability by sedimentation
SLC	Solute carrier
TEER	Trans-eoithelial electric resistance
TEER	Trans-epithelial electric resistance

1.1 Introduction

The pulmonary route of administration is a noninvasive, rapid, and effective approach to deliver therapeutic agents both locally and systemically [1]. Inhaled drug therapy is generally used locally to treat airway disease, such as asthma, bronchitis, cystic fibrosis (CF), and chronic obstructive pulmonary disease (COPD). On the other hand, inhalation also offers a great potential for systemic delivery because the lungs have a huge surface area available for absorption, and, abundant vasculature [2]. Moreover, drug-metabolizing enzymes are in much smaller amounts in the lungs as compared to the liver and gastro intestinal tract (GIT). These properties create conditions that are well suited for efficient drug absorption, offering a potential conduit for systemic drug delivery. However, pulmonary drug delivery is a challenging route of administration. First, the effectiveness of the inhalation therapy depends upon the site of deposition of the drug in the lung. Deposition of inhaled drugs is a complicated process that relies on lung anatomy and physiology, the physicochemical properties of the drug, the nature and characteristics of the formulation, and the type of the delivery system used for administration [3]. The flow and deposition of aerosol particles in the lungs are strongly influenced by the geometry of the airways along the respiratory tract. Only particles of a specific size (generally 1–5 μm) and shape will deposit in the alveolar region, the main site of absorption [2, 4].

Patho-physiological changes in the airways that are induced by respiratory tract infections may alter the deposition pattern of inhaled therapeutic aerosols. Therefore, the prediction of drug deposition in the respiratory tract is crucial to optimize drug delivery by inhalation and to evaluate its possible therapeutic effectiveness [5]. Several mathematical models are available to illustrate the deposition and distribution of inhaled aerosols based on airways dimensions, flow dynamics, breathing pattern of the subject and the shape of aerosol particles [6]. However, delivering drugs via the inhalation route requires a deep understanding of the intricate anatomy and physiology of the lungs and the movement of particles within the complexity of the airways. This chapter discusses the influence of the macro- and microstructures of the human respiratory tract on the dynamics and kinetics of drug delivery to the lungs and considers the implications this might have for effective inhaled therapy.

1.2 Anatomy and Physiology of Lungs

The respiratory tract starts at the nose, and this is followed more distally by the pharynx, larynx, and trachea, which divides into left and right bronchi. Each of the latter further divides into smaller bronchioles and the tract is ended via terminal bronchioles deep in the lung, at the alveolar sacs. There are several formats for the classification of various regions of the respiratory tract. One of the most commonly used categorizations is to divide the respiratory tract into two main parts: the upper respiratory tract, consisting of the nose, nasal cavity, and pharynx; and the lower respiratory tract, consisting of the larynx, trachea, bronchi, and alveoli [7].

1.2.1 Macro- and Microstructure of the Airways and Alveoli as It Pertains to Drug Delivery

The airways can also be divided into two distinct functional zones: the conducting airways and the respiratory airways. Several mathematical models of bronchial morphometry based on bronchial luminal

diameter, bronchial length, and angles have been developed to simulate the function of the lungs. Weibel-A, a symmetric lung model, is one of the most commonly used models that divides the lungs into 24 compartments, each compartment corresponding to a generation of the model. Such compartments are adopted for the calculation of deposition fractions of inhaled aerosols. The Weibel-A model assumes that each generation of the airways branches symmetrically into two similar smaller branches. The conducting region of the airways comprises generations 0 (trachea) to 16 (terminal bronchioles) [8]. The respiratory region is composed of respiratory bronchioles, the alveolar ducts, and the alveolar sacs, including generations 17 to 23. As a result of the discrete biological properties and the variable dimensions of different divisions along the respiratory tree, each compartment will respond differently to aerosol flow and deposition [8–10].

- **Conducting airways**
  The conducting airways are composed of the nasal cavity, pharynx, larynx, trachea, bronchi and terminal bronchioles. The function of these airways is to filter and condition the inspired air. Progressing from the trachea to the terminal bronchioles, the number of airways multiply in a dichotomous branching pattern. In addition, the airway dimensions are reduced with each bifurcation [11, 12]. The trachea (generation 0) begins at the edge of the larynx and divides at the end into right and left bronchi, one bronchus going to each lung. It facilitates air passage from the nasopharyngeal region to the bronchi and finally to the lungs. The tracheal epithelium is composed of ciliated cells, mucus secreting goblet cells and mucus secreting glands. In the tracheobronchial region, a high proportion of the epithelial cells are ciliated such that there is nearly a complete covering of the central airways by cilia. Each ciliated cell has about 200 cilia with numerous interspersed microvilli, of about 1–2 μm in length. Cilia are hair-like projections of about 0.25 μm in diameter and 5 μm in length. They are submersed in an epithelial lining fluid, secreted mainly from the serous cells in the submucosal glands. The tips of the cilia project through the epithelial lining fluid into a layer of mucus secreted by goblet cells. Mucin is a glycoprotein that imparts to mucus its 'sticky' nature. During mucociliary clearance (MCC), the mucus together with the entrapped particles is swept up out of the respiratory tract by the synchronized movements of the cilia, toward the pharynx. In order for this to occur, the gel–sol layer or the layer of mucus and the perciliary fluid through which the cilia beats must be of a convenient consistency to allow for efficient propulsive motion of the cilia. The synchronized sweeping movement of cilia in the upward direction propels the mucus and other foreign particulate matter to the larynx where they are either removed by coughing or swallowing. Inside each lobe of the lungs, the bronchi undergo further division into airways of smaller caliber: the bronchioles, which branch in the lungs forming passageways for air [13]. The bronchi are composed of the same tissue structure as the trachea. Serous cells, brush cells, and Clara cells also populate the epithelia of the bronchi, whereas the bronchioles are mainly lined with ciliated cuboidal cells, without cartilages or glands. Progressing more distally, the cartilages become irregular in shape and are absent at the bronchiolar level [7, 11]. In addition, the number of serous and goblet cells decreases, while the occurrence of Clara cells increases. The conducting zone ends with terminal bronchioles (generation 16], the smallest airways devoid of alveoli. The main function of those bronchioles is to allow the flow of air into and out of the lungs during each breath [14].
- **Respiratory airways**
  The respiratory region consists of respiratory bronchioles, alveolar ducts and alveolar sacs. It also includes interstitial lymphatic tissues and lymph vessels as well as bronchial lymph nodes. The gas exchange region is represented by the alveolar sacs, which are closed at the periphery by a group of alveoli [9]. The target cells in the alveolar–interstitial region are the secretory (Clara) cells of the respiratory bronchiole and the type I and type II epithelial cells covering the alveolar surface [15].
- **Alveoli**
  There are approximately 300 million alveoli in each lung. Alveoli are tiny structures and thus offer a large surface area in total ($\sim 100\,m^2$) for an efficient gas exchange. The blood barrier between the alveolar space and the pulmonary capillaries is very thin to allow for rapid gas exchange [15].

The alveoli are devoid of mucus and have a much flatter epithelium, of simple squamous type, 0.1–0.5 μm thick. The alveolar surface is lined with a surface-active component that contains phospholipids [16], termed lung surfactant; its role is discussed later.

The rate and amount of drug absorption vary along the length of the respiratory tract. Absorption in different regions is affected, for example, by different areas of each region (~2 m^2 conducting airways but ~140 m^2 alveolar surfaces) [17]. Moreover, epithelial thickness and cell population in the airways and alveolar region are dissimilar. The airway epithelium is covered by a mucus gel, while the alveolar surface is coated with a surfactant layer. The presence of mucus and surfactant influences deposition and clearance of aerosolized particles, and these also affect the dissolution, solubility and absorption of drugs. The ciliated cells together with the mucus provide a major mechanism for drug clearance from trachea and bronchi, whereas macrophages play an important role in clearance from the deep lung. These processes present a physical barrier to aerosolized delivery of drugs to the airways, since the overall therapeutic effect of an aerosol is dependent upon the amount of drug deposited and distributed within the lungs. Accordingly, knowledge of the anatomy and physiology of the lung are necessary for a precise understanding of the role of each physiological region with respect to the final drug absorption [18].

The surface of the alveoli is lined with two types of pneumocytes: type I pneumocytes, which are thin squamous cells forming part of the barrier to gas exchange with capillaries, and type II pneumocytes, which are larger cuboidal cells; they occur more diffusely than type I cells and are responsible for secreting lung surfactant [18]. Alveolar (phagocytic) macrophages, accounting for ~3% of cells in the alveolar region, scavenge and transport particulate matter to either the mucociliary escalator or the lymph [19].

1.2.2 Lung Surfactant

The pulmonary airways are lined with pulmonary surfactant, a lipoprotein complex consisting of 90% lipid and 10% protein, which is synthesized, secreted, and recycled by type II epithelial cells in the alveoli. The surfactant film of the lung plays a dual role of reducing surface tension and being a host defence against inhaled pathogens and particles. By reducing the alveolar surface tension at the air–liquid interface, the alveoli are stabilized against collapse and thus a large surface area for gas exchange is maintained. Surfactant also facilitates oxygen penetration through the lung surface lining and into the blood. Without the lung surfactant, it would be extremely hard to breathe since the diffusion of oxygen through the lung surface lining would be hindered [20]. Lung surfactants also have anti-inflammatory and antioxidant effects. Furthermore, pulmonary surfactants enable the movement of deposited particles to the upper airways of the bronchial tree. However, interactions between the phospholipids of the lung surfactant and inhaled drugs have been reported. Lung surfactant has been shown to enhance the solubility of steroidal drugs (glucocorticosteroids), which influenced their residence time in the lung [21], and other studies have shown that some antibiotics may influence the activity of pulmonary surfactant [22–24]. Therefore, such interactions between the antibiotic and lung surfactant should be carefully evaluated before administering antibiotics via inhalation [25, 26]. In addition, possible interactions between deposited nanoparticles and lung surfactants may influence the biophysical surfactant function, surfactant metabolism and particle clearance, or cause particle-induced toxicity [27, 28]. It is suggested that there is a reduction in the activity of the lung surfactant in the presence of a large number of aerosolized insoluble particles (e.g., polymer microparticles) [29]. This can interrupt the physiological role of the surfactant, including retarding the clearance of particles from burdened lungs [30]. Lung surfactant may cause large molecules, such as protein therapeutics, to aggregate which could enhance their ingestion and digestion by alveolar macrophages [17]. When aerosol particles settle in the lung, they become enveloped by a monolayer of lung surfactant. Such opsonized particles are rapidly digested by macrophages and subsequently cleared from the alveolar region. Some recent reports suggest that the lung surfactant may slow down the diffusion of

drug out of the alveoli. The inclusion of exogenous surfactant into the inhaled formulation enhances the distribution of drug particles deeper into the lung lumen [31].

1.2.3 Pulmonary Blood Circulation

The blood to the lung bronchi and smaller air passages is supplied by branches of the right and left bronchial arteries, whereas the venous return is mostly through the bronchial veins. The lung receives the entire cardiac output and hence is the most perfused organ of the body. Only the alveolar region and respiratory bronchioles receive most of the pulmonary circulation, whereas the blood flow in the larger airways (i.e., trachea to terminal bronchioles) is through the systemic circulation which receives only 1% of the cardiac output. The exact role of the pulmonary circulation in distributing aerosolized drugs to lung regions distal from the site of deposition is still unknown. Supposedly, aerosolized drugs absorbed into the pulmonary circulation from the upper airways region can be redistributed into remote areas of the lung which might enhance aerosolized drug efficacy. However thus far, no experimental work in humans has been conducted in order to investigate the role of pulmonary circulation in aerosolized drug distribution in the lungs or its effect on therapeutic efficacy [32].

1.3 Mechanisms of Aerosol Deposition

The size of pharmaceutical aerosol particles can range from 10^{-2} to 10^{2} μm in diameter [33]. Particles intended to be administered by the pulmonary route are generally categorized, based on their size, into coarse particles ≥5 μm, fine particles between 0.1 and 5 μm, and ultrafine particles ≤0.1 μm. For optimal deposition and more specific targeting in the desired region of the lung, a narrow particle size distribution or monodisperse aerosol is required.

Most aerosol particles are poly-disperse in size, but an aerosol with particles of equal size (monodisperse) is more desirable [34]. The phenomenon of aerosol deposition of inhaled particles in different regions of the respiratory system is influenced by many factors such as the particle size, particle shape, breathing rate, lung volume, respiration volume and health condition of the individual [35, 36]. Figure 1.1 represents the different mechanisms of aerosol deposition in the respiratory tract.

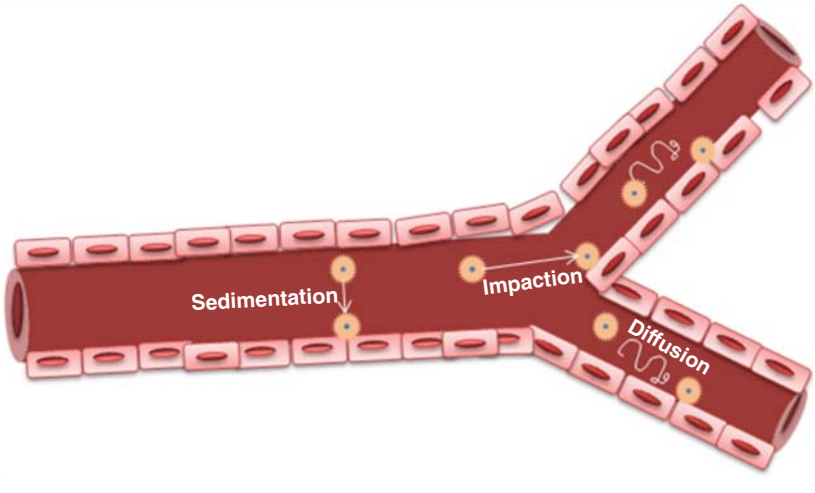

Figure 1.1 *Mechanism of deposition of particles in the respiratory tract (See insert for color representation of this figure)*

Depending on the particle size, airflow, and location in the respiratory system, particle deposition can occur via one of the following principal mechanisms: impaction, sedimentation, interception, and diffusion.

1.3.1 Impaction

Impaction is a flow-dependent mechanism that is determined by the aerodynamic diameter of the particles. The phenomenon of inertial impaction is important for large particles or droplets (≥5 μm). Large particles with high velocity do not follow the trajectory of the air stream due to inertia causing them to impact the wall of the airways and deposit there. This mechanism is common in the upper respiratory tree of the lung (oropharyngeal and trachea-bronchial region), where air velocity is high and the airflow is turbulent [37, 38]. Particles with a size >10 μm deposit in the upper airways and are rapidly removed by the mucociliary escalator, assisted also by coughing to the trachea and are subsequently swallowed [12, 36]. The deposition probability by impaction [$P(I)$] in cylindrical airways is calculated as [12]:

$$p(I) = 1 - \frac{2}{\pi}\cos^{-1}(\theta\ St) + \frac{1}{\pi}\sin[2\cos^{-1}(\theta\ St)] \tag{1.1}$$

$$St\ (\text{Stoke number}) = \frac{\rho d^2 v}{18\mu D} \tag{1.2}$$

where θ is the branching angle, ρ is the density of the particle, μ is the viscosity of fluid, v is the velocity of particle, D is the diameter of airways, and d is the particle diameter.

1.3.2 Sedimentation

The deposition of particles via sedimentation occurs in the lower bronchial airways and the alveolar region where airflow is slower. Particles of size in the range of 0.5–5 μm may avoid impaction in the upper airways and they could then deposit by sedimentation and impaction in the lower tracheobronchial and alveolar regions. If the aerosol particle size is between 3 and 5 μm, then deposition is most likely to occur in the trachea-bronchial region [39]. If the particles are of size smaller than 3 μm, then appreciable deposition in the alveolar region might be anticipated. Sedimentation of particles is governed by the (higher) gravitational force acting on the particles being more dominant than the (lower) dragging force imposed by the airflow [12]. The rate of sedimentation deposition increases with an increase in particle size and a decrease in flow rate. This mechanism is especially important for particles of size greater than 0.5 μm [38, 40]. The deposition probability by sedimentation [$P(S)$] in cylindrical airways is calculated as [12]:

$$P(S) = 1 - e^{\frac{4.g.C.\rho.d^2.L.Cos\phi}{9.\pi.\mu.R.v}} \tag{1.3}$$

where g is the acceleration due to gravity, Φ is the angle relative to gravity, L is the tube length, ρ is the density of the particle, C is the Cunningham slip angle correction factor, d is the radius of the particle, R is the radius of the airways, and μ is the viscosity of fluid.

1.3.3 Interception

The particles of acicular shapes (fibers) are efficiently deposited on the wall of the small airways by the mechanism of interception. In contrast to impaction, particles deposited by interception do not diverge from their air stream. Due to their elongated shape, particles are deposited as soon as they contact the airway wall. The aerodynamic diameters of these fibers are smaller relative to their size, so they usually deposit within the lower (smaller diameter) airways [39, 40].

1.3.4 Diffusion

Diffusion is the key mechanism of deposition for particles of size less than 0.5 μm caused by Brownian motion. This motion increases with decreasing particle size and airflow rate, and thus becomes an important mechanism for particle deposition in the lower airways and alveolar region. Here particles move from high concentration to low concentration across the streamline and deposit upon contact with the airway wall. This mechanism is governed by the geometric rather than the aerodynamic size of the particles [12, 39, 41]. Nanoparticles deposit via diffusion due to displacement when they collide with air molecules. The deposition probability by diffusion [$p(D)$] in the cylindrical airways [12] is calculated as:

$$p(D) = \sqrt{(2KTC/3\pi\eta d/R} \tag{1.4}$$

where R is the airway diameter, k is the Boltzmann constant, T is the absolute temperature, η is the gas viscosity, and d is the particle diameter.

1.4 Drug Absorption

The pulmonary membrane is naturally permeable to small molecule drugs and many therapeutic peptides and proteins. The epithelium of the lung is the major barrier to the absorption of inhaled drugs. It is thick (50–60 μm) in the trachea, but its thickness decreases to 0.2 μm in the alveoli. As mentioned in Section 1.3, the change in cell types and morphology when progressing distally from trachea, bronchi, and bronchioles to alveoli is very dramatic. The lungs are more permeable to macromolecules than any other portal of entry into the body [42]. A number of peptides, particularly those that have been chemically altered to inhibit peptidase enzymes, have demonstrated a very high bioavailability through the pulmonary route [2, 43]. Small molecules can exhibit prolonged absorption if they are highly cationic [44]. Although the rapid absorption of molecules in the lungs has many conceivable medical uses, there are situations when one might need to slow the absorption rate of inhaled small molecules either to keep them acting locally in lung, or to control their absorption into the body. Very insoluble molecules that slowly dissolve from the inhaled particle may remain in the lung for many hours or even days [38].

1.4.1 Mechanisms of Drug Absorption from the Lungs

The lung shares many of the mechanisms of absorption that occur in organs involved in other routes of administration [45]. In general, absorption of the inhaled drugs can be either paracellular or transcellular. Paracellular absorption occurs through tight junctions which are integral proteins of claudins and occludins that extend in the paracellular space in between lung epithelial cells [46]. Studies have shown that the apical to basal trans-epithelial electric resistance (TEER), which indicates the degree of tightness of the cells, decreases from the tracheal region to the distal airways before it increases again in the alveolar region. Thus, paracellular absorption is most likely to occur in the distal bronchioles. Many hydrophilic drugs with quite small molecular weights such as insulin (Mwt: 5808 Da) have been reported to be absorbed through paracellular transport in the lungs [3]. Several approaches have been shown to be capable of enhancing the paracellular transport of drugs, for example the administration of compounds such as chitosan reversibly decreases the tightness of the paracellular junctions allowing for the passage of larger molecules [47].

Transcellular transport accounts for most of the drug absorption that occurs through the lungs, in which the drug has to diffuse through the cells in order to be absorbed [45]. For hydrophobic drugs, absorption mainly occurs through passive diffusion where the drug diffuses through the phospholipid

bilayer of cellular membranes from a high extracellular to a lower intracellular concentration [48]. Transcellular transport also involves a carrier-mediated transport which occurs via transporter molecules expressed at the surface of cellular membranes. There is a relative paucity of information relating to lung transporters, as compared to intestinal, liver or kidney transporters [49]. Many of the transporter expression studies were carried out *in vitro* which may not guarantee a precise description of the degree of expression or the distribution of transporters *in vivo*. Furthermore, there is still a lack of knowledge concerning the degree of involvement of such transporters in the absorption kinetics of many drugs.

There are two main classes of transporters expressed in lung cells: the solute carrier (SLC) and ATP binding cassette (ABC) transporters [50]. The SLC family are capable of transporting organic cationic or anionic molecules through organic cation transporters (OCT) and organic anion transports (OAT), respectively [51]. Salbutamol (albuterol), a positively charged bronchodilator at the lung physiologic pH, was found to be absorbed through OCTs [52], but OAT expression has not yet been verified in the lungs [53]. PEPT2, an SLC transporter expressed by type II pneumocytes in the alveoli, is capable of transporting peptide drugs [54]. The ABC family of transporters includes some of the most important efflux transporters that act in an energy-dependent manner. Multidrug resistant protein (MRP1), breast cancer resistance protein (BCRP), and P-glycoprotein (P-gp) are the most commonly expressed efflux transporter in the lung [55–57]. Depending on the location of expression of such receptors, either on the apical side at the airway lumen or the basolateral side facing the blood capillaries endothelium, they can either enhance or hinder the absorption of the drugs. There is a huge diversity in the substrates for such transporters which makes these receptors an essential issue to consider during dosing calculations [45].

Another possible mechanism of absorption is vesicular transport which involves formation of invaginations in the cellular plasma membrane that separate out later into individual vesicles engulfing the particles inside [58]. Vesicular transport can be either caveolin- or clathrin-mediated, depending on the particle size. Caveolin-mediated transport usually involves particles of size less than 120 nm, while the clathrins transport bigger particles of size in the range 150–200 nm [59].

1.5 Physiological Factors Affecting the Therapeutic Effectiveness of Drugs Delivered by the Pulmonary Route

1.5.1 Airway Geometry

The deposition of aerosol droplets/particles in the lungs is heavily influenced by the architecture of the airways in the respiratory tree. Each bifurcation, branching, and decrease in the lumen diameter of the airways in the respiratory tract promotes the possibility of deposition of particles by impaction and decreases the fraction of aerosol available for the therapeutic effect [5]. The shape of the pharynx and larynx influence the airflow in the trachea and bronchi. The sudden decrease in the downstream diameter at the bifurcations in the upper respiratory tree leads to the generation of turbulent airflow which increases particle deposition in the upper airways [9].

1.5.2 Inhalation Mode

The mode of inhalation considerably influences the extent and region of particle deposition in the respiratory tree. Nose breathing enhances the possibility of deposition of fine particles ($\leq$10 μm) in the peripheral alveolar region of the lung, because larger particles are retained in the nose and pharynx, whereas mouth breathing increases the chances of deposition of coarse particles ($\geq$10 μm) in the upper tracheobronchial region [60]. Holding the breath increases the time between inspiration and exhalation, which facilitates sedimentation of aerosol in the lung periphery [61].

1.5.3 Airflow Rate

The variation in the inspiratory airflow rate significantly influences the regional deposition of aerosol in the respiratory tree. Fast and turbulent airflow reduces the residence time of the particles in the airways by enhancing the deposition of aerosol in the oropharynx region and upper airways, whereas slow inhalation leads to deposition in the lower peripheral airways [38]. In addition, increasing the airflow rate is accompanied by a lower deposition proportion of fine particles and vice versa. The inhalation of an aerosol at a very slow airflow rate decreases the possibility of particle/droplet impaction, which in turn reduces aerosol deposition in the upper respiratory tract and targets the lower airways by sedimentation and diffusion. Lastly, increasing the tidal volume (volume of air displaced between normal inspiration and expiration when extra effort is not applied) enhances the deposition of aerosol particles into the lower bronchial and alveolar regions. These are the main reasons why patients are advised to breathe slowly and deeply and hold their breath when inhaling a medication [62].

1.5.4 Mechanism of Particle Clearance

After inhalation of aerosol particles via the lungs, the particles are either cleared from the lungs, absorbed into blood/lymphatic circulation or degraded by drug metabolism [63]. The various clearance mechanisms that are used in different regions of the respiratory tract to eliminate foreign particles (Figure 1.2) are reviewed in the following sections.

1.5.4.1 Mucociliary Clearance (MCC)

MCC provides an important defence mechanism for removing insoluble inhaled particles from the respiratory tract and acts as a potential physical barrier for drug penetration. The majority of the deposited particles in the trachea-bronchial region of the respiratory tract are cleared within 24 h of inhalation in healthy subjects. MCC is prevalent in the upper airways as compared to the lower airways [63].

1.5.4.2 Mechanical Clearance

This includes coughing, sneezing or swallowing of inhaled particles in the upper region of the respiratory tract. This mechanism occurs instantly after the deposition of particles in the larger

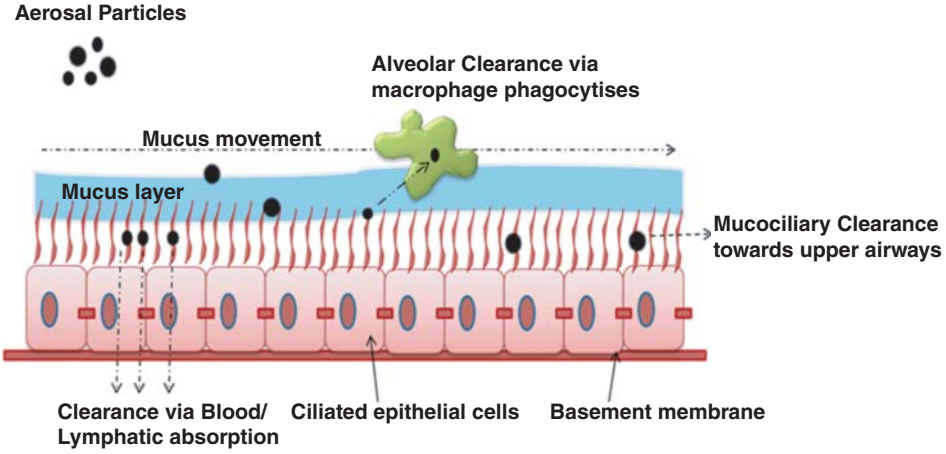

Figure 1.2 *Clearance mechanisms for particles deposited in the respiratory tract (See insert for color representation of this figure)*

airways. When a particle of size ≥10 μm is inhaled, coughing is spontaneously provoked. For efficient coughing clearance, a high airflow rate is needed, and since this is only available in the upper airways, it is only in this region that it is effective. In respiratory disease conditions such as bronchitis, asthma or pneumonia where MCC becomes impaired, cough turns into the major mechanism of clearance. Thus, it is important to maintain aerosols in sizes ≤10 μm for the optimum drug effect [40, 64].

1.5.4.3 Enzymatic Degradation

Despite the level of degrading enzymes in the lungs being much less than that in the liver, many inhaled drugs are substrates for the CYP450 enzymes present in the lung epithelia [65]. Some isoforms such as CYP2S and CYP2F have been identified as being lung specific [66]. In addition, Phase II metabolic enzymes such as esterases and peptidases are also expressed in the lung. The concentrations of such enzymes differ significantly between different cell types lining the different regions in the lungs [67].

1.5.4.4 Alveolar Macrophages

The housekeeping function of alveolar macrophages can severely limit the efficacy of an inhaled treatment [68]. If the inhaled drug has poor solubility and particles remain in the alveoli for sufficient time, they can be cleared by macrophages reducing the amount of drug available for a therapeutic effect. Clearance by alveolar macrophages is still the main obstacle to achieve controlled drug release in the alveoli. Most of the materials used to prepare particles that can sustain the release of a drug for the extended period are rigid and have all the physicochemical characteristics that make them an ideal target for macrophage uptake [40, 64].

1.5.5 Lung Receptors

Many inhaled drugs interact with specific receptors expressed by pulmonary cells. The efficiency of pulmonary delivery can be enhanced by targeting specific cells with low risk of systemic side effects. Hence, recognizing the different cellular receptors in the lungs builds a potential for a more effective pulmonary therapy. The most important receptor classes are β-adrenergic receptors, muscarinic receptors (M3), histaminic receptors (H1 and H2), glucocorticoid receptors (GR), leukotriene 1 receptors and prostacyclin receptors (PR), none of these being uniformly distributed throughout the lung [69–74]. Most of the β-adrenergic receptors are located in the epithelium of the alveolar walls, some bronchi and the terminal bronchioles. β_2-Adrenergic receptor agonists (salbutamol (albuterol), terbutaline and isoprenaline) are drugs that act on the β_2-adrenergic receptor, causing smooth muscle relaxation and dilation of bronchial passages [72]. A high density of M3 receptors are present in the submucosal glands and lung lymph nodes, while there is a lower proportion in the smooth muscle of the airways, bronchi and in the alveolar region. Methacholine acts through M3 receptors to contract the smooth muscles [74]. H1 and H3 receptors are both found primarily in the bronchial smooth muscle in the human respiratory tract. These receptors are involved in mediating increased vascular permeability and contraction of the smooth muscle in the respiratory tree [75]. High concentrations of GR have been reported in the alveolar walls, endothelium, and smooth muscle cells of bronchial vessels. These receptors can be the potential targets for steroidal anti-inflammatory drugs and glucocorticosteroids such as betamethasone, and may control airway inflammation in asthma by inhibiting many aspects of the inflammatory process [69]. In the case of inhaled corticoids, the treatment seems to be more beneficial when more of the drug is dispersed throughout the lungs, as inflammatory cells such as eosinophils, lymphocytes and macrophages are present throughout the respiratory tract and alveoli in asthma patients [76]. The location of these receptors in the lung suggests that ipratropium bromide should be deposited in the conducting airways in order to elicit greater effectiveness;

meanwhile, salbutamol (albuterol) should be deposited more peripherally (in the middle and small airways) to produce an adequate therapeutic effect [69, 70]. Many novel receptors, including orphan receptors [77], have now been identified as future targets for developing novel therapies for asthma and COPD.

1.5.6 Disease States

In respiratory diseases, bronchial obstruction and narrowing of airways occur due to mucus accumulation and inflammation. CF is a genetic disease in which the epithelial cells of the lungs produce thick mucus in high quantities reducing the lumen diameter in all airways [78]. Chronic bronchitis is characterized by excessive mucus generation, alveolar wall thickening, and occlusion of small bronchi [79]. Asthma is a chronic inflammatory disease characterized by airflow obstruction, due to constriction of the bronchial airways in response to a stimulus (pollutants, allergens, or exercise). This constriction may also in turn result in a thickened mucus layer and subepithelial fibrosis [80]. All of these disease conditions change the airways geometry resulting in variable airflow velocities, air resistance and turbulence, which influence the aerosol deposition pattern in the lungs. This usually leads to the accumulation of aerosols in the larger airways and healthy areas in the lungs. In such conditions, the aerosolized drug is deposited more in the upper airways by the inertial impaction mechanism instead of there being a uniform distribution in the lungs. Particles of size larger than 5 μm are mainly trapped in the oropharyngeal region and unable to reach to the lungs, whereas particles of size smaller than 1 μm are mostly exhaled without deposition. This altered deposition pattern might lead to loss of drug efficacy [81]. A noticeable increase in the deposition of ultrafine particles has been reported in the lungs of patients with bronchitis and asthma compared to the healthy lungs. Inhaled ultrafine particles were found to cause lung inflammation, oxidative stress and genetoxicity [82]. Any accumulation of thick mucus in the airways can impair the MCC resulting in the patient being more susceptible to airways infections and the latter might be expected to modify drug absorption [83]. A higher rate of inhaled drug degradation has been reported to occur in response to smoking which increases the expression of metabolic enzymes [84]. Other diseases may affect the degree of expression of either absorption or efflux transporters, hence changing the bioavailability of the inhaled drugs [67].

1.5.7 Effect of Age and Gender Difference

The age of the subject influences aerosol deposition in the human lung, because of the anatomical changes that occur at progressive ages causing dissimilarities in airway geometry. Studies have shown that children have an enhanced upper airway deposition of coarse particles compared to adults, but that total deposition amounts are quite comparable [61, 85]. Healthy adults can have a larger amount of aerosol deposited in the alveolar region as compared to children due their higher lung volume [86].

Anatomical differences in the larynx and airways between males and females are related to gender disparities in aerosol deposition patterns with females having more upper airway deposition compared to males. Studies have shown that females have a higher deposition of coarse particles (>5 μm) as compared to males at a similar flow rate, whereas fine particle (0.5 to 3 μm) aerosols show similar deposition patterns regardless of the gender [39, 86].

1.6 Computer Simulations to Describe Aerosol Deposition in Health and Disease

Deposition of inhaled aerosol particles in the human lung can be measured by both experimental method and theoretical calculation. The deposition of aerosol in different regions of the respiratory tract is predicted theoretically by the use of various deterministic computational models. The model is

validated by the extensive comparison of experimental and numerical results [12]. However, computational simulations of the respiratory tract are not straightforward due to the complexity of airways geometry and physiology. The wide range of overlapping and interrelated physiological factors makes it even more complicated. Mathematical models can illustrate the deposition of aerosol on the basis of particle size, inspiratory airflow rate, and the airways geometry of the respiratory tree. The predicted results are helpful to interpret experimental results and can also guide the design of targeted delivery procedures for formulation scientists. Therefore, accurate simulations and predictions of airflow structures and related aerosol-phase depositions in realistic models of the human respiratory system are of fundamental importance [87]. Aerosol deposition models can be categorized as empirical, deterministic, trumpet, stochastic or computation fluid dynamics-based.

1.6.1 Semiempirical Models

Semiempirical models are based on fitting numerical relationships to experimental data. A semiempirical model was designed by the International Commission on Radiological Protection (ICRP), using algebraic equations for the prediction of regional deposition and clearance of inhaled airborne radionuclides in the respiratory tract of some workers [88]. This model treats the respiratory tract as a sequence of compartments (e.g., tracheobronchial, central and peripheral) through which particles pass during inhalation and are filtered. Regional deposition fractions are calculated using semiempirical equations, employing particle size and flow rate as functions. Using this method, deposition in the entire lungs, as well as regional deposition in the respiratory tract, can be predicted. The main advantage of such an approach is its mathematical simplicity with lesser computational work. However, this model lacks universality, since it does not explain some of the important factors such as particle trajectory [89, 90].

1.6.2 Deterministic Models

1.6.2.1 Deterministic Symmetrical Single Path Model

This model considers the respiratory tree as a simple branched structure where each parent airway divides into two identical daughter airways. Therefore, it is assumed that aerosols will equally deposit in identical airways since they have equal diameters. Such a model is simple and does require thorough knowledge of the daughter airway structure, and, in addition, both the lung geometry and airflow dynamics are considered for calculating aerosol deposition in the lungs [89, 91].

1.6.2.2 Deterministic Asymmetrical Multipath Model

Unlike the symmetric model, this model considers an asymmetric dichotomous branching pattern and heterogeneity of ventilation in the airways of the lungs. This assumption aids in understanding the regional variation in aerosol deposition along the respiratory tract. Thus, it provides a more pragmatic approach to calculating particles deposition in the lung as compared with the symmetrical modelling procedure [91].

1.6.3 Trumpet Models (One-Dimensional)

Trumpet models are single-path models based upon the Weibel symmetric lung model, where the whole respiratory tract is considered a one-dimensional channel with a variable cross-sectional area for each generation (similar to a trumpet). As a result of deposition, the concentration of aerosol particles in the channel varies with position and time. This model simulates the breathing process as the movement of air in and out of the channel, since airways and alveoli expand and contract uniformly [92]. This model uses convection–diffusion-type differential equations to calculate the transport and deposition of aerosol particles onto the respiratory tract [12, 92, 93].

1.6.4 Stochastic, Asymmetric Generation Models

In a stochastic, asymmetric model, the geometry of the lung airways along the conduit of an inspired particle is selected randomly and deposition possibilities are calculated using deterministic formulae. This model makes use of the asymmetric nature of the branching pattern of the lung and also demonstrates the statistical relationships between parent and daughter airway dimensions [94]. The geometry of the airways (length, lumen diameter, airway angles and asymmetry) is varied randomly based on experimental observations. The paths of inspired particles through a lung model are traced by randomly selecting a sequence of airways for each individual particle using the stochastic modelling technique [95].

1.6.5 Computation Fluid Dynamics (CFD)-Based Model

Computational fluid-particle dynamics (CFPD) involves the study of particle movement by computational fluid dynamics (CFD) simulations. CFD has emerged as a valuable tool for the prediction of airflow and particle transport within the human lung airways. Furthermore, it provides information about aerosol deposition patterns within selected structural elements of the human respiratory systems [96]. This model follows a mathematical process known as discretization, where the airways are segmented into many discrete elements or volumes. CFPD methods are used to study the effects of multifaceted flow patterns on particle motion and its deposition in the lungs. In each element, the calculation of regional deposition is carried out using differential and algebraic equations that describe the fluid motion. CFD models utilize detailed three-dimensional fluid flow and particle transport equations. Most CFD-based models explain aerosol deposition in the upper respiratory tracts or alveolar regions only [43, 96].

1.7 Conclusions

A considerable body of literature is available on a variety of formulations for aerosolized delivery of drugs to the lungs; many of these involve particle engineering techniques applied to the powder and a large number more to the many applicable delivery devices that are available. However, a better understanding of the overlap of anatomical, physiological, and pathological factors is required and also the manner in which these interact with the physicochemical factors of the drug and the drug delivery devices. Some of these factors that influence the efficiency of pulmonary drug delivery have been identified, but the complexities of the overall process have yet to be appreciated. In order to optimize aerosol therapy, it is essential to consider the influence of the variable airway geometry and the airflow rates through the various regions of the respiratory tract. The effect of age difference and the health condition on airway caliber and airflow patterns also requires consideration. Computational simulations of the particle deposition can assist, but they still suffer from limitations that hinder their universal usage and application.

Perhaps one of the most important challenges is the lack of a suitable animal model that truly mimics drug delivery to humans. Due to variation in the breathing pattern of animals and differences in airways branching, animal models are not representative of the situation in the human. Hence, it is very difficult to extrapolate results from animal models to humans and even more difficult to extrapolate these results to young children and elderly adults. Future challenges comprise the necessity to develop more sensitive tests for airway flow to match passive inhalation studies in animals to those in humans. Finally, our understanding of the mechanisms of drug absorption in the lungs is still relatively poor, especially those involving transporters, such as Pgp, OCT, PEPT and OATP. The recognition of the expression of various transporters in different regions in the lung can lead to efficient targeted drug delivery to specific receptors and thus improve the therapeutic outcomes.

References

1. Courrier HM, Butz N, Vandamme TF. Pulmonary drug delivery systems: recent developments and prospects. *Critical Reviews in Therapeutic Drug Carrier Systems*. 2002;**19**(4–5):425–98.
2. Byron PR, Patton JS. Drug delivery via the respiratory tract. *Journal of Aerosol Medicine*. 1994;**7**(1):49–75.
3. Patton JS, Byron PR. Inhaling medicines: delivering drugs to the body through the lungs. *Nature Reviews Drug Discovery*. 2007;**6**(1):67–74.
4. Byron PR, Hindle M, Lange CF, *et al*. *In vivo–in vitro* correlations: predicting pulmonary drug deposition from pharmaceutical aerosols. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*. 2010;**23** (Suppl. 2):S59–69.
5. Newman SP. Aerosol deposition considerations in inhalation therapy. *Chest*. 1985;**88** (Suppl. 2):152S–60S.
6. Martonen TB. Mathematical model for the selective deposition of inhaled pharmaceuticals. *Journal of Pharmaceutical Sciences*. 1993;**82**(12):1191–9.
7. Gehr P. Respiratory tract structure and function. *Journal of Toxicology and Environmental Health*. 1984;**13**(2–3):235–49.
8. Weibel ER. Morphometry of the Human Lung. Academic Press, New York, 1963.
9. Horsfield K. Diameters, generations, and orders of branches in the bronchial tree. *Journal of Applied Physiology*. (1985). 1990;**68**(2):457–61.
10. Kleinstreuer C, Zhang Z, Donohue JF. Targeted drug-aerosol delivery in the human respiratory system. *Annual Review of Biomedical Engineering.* 2008;**10**:195–220.
11. Horsfield K, Cumming G. Morphology of the bronchial tree in man. *Journal of Applied Physiology*. 1968;**24**(3):373–83.
12. Yeh HC, Schum GM. Models of human lung airways and their application to inhaled particle deposition. *Bulletin of Mathematical Biology*. 1980;**42**(3):461–80.
13. Wailoo MP, Emery JL. Normal growth and development of the trachea. *Thorax*. 1982;**37**(8): 584–7.
14. Macklem PT. The physiology of small airways. *American Journal of Respiratory and Critical Care Medicine*. 1998;**157**(5 Pt 2):S181–3.
15. Massaro GD, Massaro D. Formation of pulmonary alveoli and gas-exchange surface area: quantitation and regulation. *Annual Review of Physiology.* 1996;**58**:73–92.
16. Angus GE, Thurlbeck WM. Number of alveoli in the human lung. *Journal of Applied Physiology*. 1972;**32**(4):483–5.
17. Patton JS, Fishburn CS, Weers JG. The lungs as a portal of entry for systemic drug delivery. *Proceedings of the American Thoracic Society*. 2004;**1**(4):338–44.
18. Plopper CG. *Structure and Function of the Lung*. In: *Jones TC, Dungworth DL, Mohr U*, eds., Springer, Berlin 1996:135–50.
19. Itoh H, Nishino M, Hatabu H. Architecture of the lung: morphology and function. *Journal of Thoracic Imaging*. 2004;**19**(4):221–7.
20. Hamm H, Fabel H, Bartsch W. The surfactant system of the adult lung: physiology and clinical perspectives. *Clinical Investigation*. 1992;**70**(8):637–57.
21. Liao X, Wiedmann TS. Solubilization of cationic drugs in lung surfactant. *Pharmaceutical Research*. 2003;**20**(11):1858–63.
22. Caldwell EJ, Piper DS. Influence of a pulmonary surfactant on the in vitro activity of tobramycin against *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 1999;**43**(12):3044.
23. Wiedmann TS, Bhatia R, Wattenberg LW. Drug solubilization in lung surfactant. *Journal of Controlled Release*. 2001;**65**(1–2):43–7.
24. van 't Veen A, Mouton JW, Gommers D, *et al*. Influence of pulmonary surfactant on in vitro bactericidal activities of amoxicillin, *ceftazidime, and tobramycin. Antimicrob Agents Chemother*. 1995;**39**(2):329–33.

25. Silverman JA, Mortin LI, Vanpraagh AD, *et al*. Inhibition of daptomycin by pulmonary surfactant: in vitro modeling and clinical impact. *The Journal of Infectious Diseases*. 2005; **191**(12):2149–52.
26. Davies MJ, Brindley A, Chen X, *et al*. A quantitative assessment of inhaled drug particle–pulmonary surfactant interaction by atomic force microscopy. *Colloids and Surfaces B: Biointerfaces*. 2009;**73**(1):97–102.
27. Schleh C, Hohlfeld JM. Interaction of nanoparticles with the pulmonary surfactant system. *Inhalation Toxicology*. 2009;**21** (Suppl. 1):97–103.
28. Schleh C, Muhlfeld C, Pulskamp K, *et al*. The effect of titanium dioxide nanoparticles on pulmonary surfactant function and ultrastructure. *Respiratory Research.* 2009;**10**:90.
29. Sosnowski TR, Garden L., Podgorski, A. Influence of insoluble aerosol deposits on the surface activity of the pulmonary surfactant: a possible mechanism of alveolar clearance retardation? *Aerosol Science and Technology*. 2000;**32**(1):52–60.
30. van't Veen A, Mouton JW, Gommers D, Lachmann B. Pulmonary surfactant as vehicle for intratracheally instilled tobramycin in mice infected with *Klebsiella pneumoniae*. *British Journal of Pharmacology*. 1996;**119**(6):1145–8.
31. Evander E, Wollmer P, Jonson B, Lachmann B. Pulmonary clearance of inhaled 99mTc-DTPA: effects of surfactant depletion by lung lavage. *Journal of Applied Physiology* (1985). 1987;**62**(4):1611–4.
32. Wilson Ra. Anatomy and Physiology in Health and Illness. Allison WAaG, editor: Churchill Livingstone, Spain.
33. Chow AH, Tong HH, Chattopadhyay P, Shekunov BY. Particle engineering for pulmonary drug delivery. *Pharmaceutical Research*. 2007;**24**(3):411–37.
34. Yu CP, Taulbee DB. A theory of predicting respiratory tract deposition of inhaled particles in man. *Inhaled Particles*. 1975;**4** (1):35–47.
35. Heyder J, Rudolf G. Deposition of aerosol particles in the human nose. *Inhaled Particles*. 1975;**4** (1):107–26.
36. Schulz H, Brand, P., and Heyder, J. Particle deposition in the respiratory tract. In: Gehr P, and Heyder J., eds, *Particle–Lung Interactions*, Marcel Dekker, Inc., New York, 2000.
37. Heyder J. Alveolar deposition of inhaled particles in humans. *American Industrial Hygiene Association Journal*. 1982;**43**(11):864–6.
38. Heyder J. Particle transport onto human airway surfaces. *European Journal of Respiratory Diseases Supplement.* 1982;**119**:29–50.
39. Kim CS, Hu SC. Regional deposition of inhaled particles in human lungs: comparison between men and women. *Journal of Applied Physiology* (1985). 1998;**84**(6):1834–44.
40. Lippmann M, Yeates DB, Albert RE. Deposition, retention, and clearance of inhaled particles. *British Journal of Industrial Medicine*. 1980;**37**(4):337–62.
41. Lourenco RV, Cotromanes E. Clinical aerosols II. *Therapeutic aerosols. Archives of International Medicine.* 1982;**142**(13):2299–308.
42. Patton J. Mechanisms of macromolecular absorption by the lungs. *Advanced Drug Delivery Reviews.* 1996;**19**: 3–36.
43. Comer JK, Kleinstreuer C, Hyun S, Kim CS. Aerosol transport and deposition in sequentially bifurcating airways. *Journal of Biomechanical Engineering*. 2000;**122**(2):152–8.
44. Niven RW, Whitcomb KL, Shaner L, Ip AY, *et al*. The pulmonary absorption of aerosolized and intratracheally instilled rhG-CSF and monoPEGylated rhG-CSF. *Pharmaceutical Research*. 1995;**12**(9):1343–9.
45. Ibrahim M, Garcia-Contreras L. Mechanisms of absorption and elimination of drugs administered by inhalation. *Therapeutic Delivery*. 2013;**4**(8):1027–45.
46. Schneeberger EE, Lynch RD. The tight junction: a multifunctional complex. *American Journal of Physiology Cell Physiology*. 2004;**286**(6):C1213–28.

47. Vllasaliu D, Casettari L, Fowler R, *et al*. Absorption-promoting effects of chitosan in airway and intestinal cell lines: a comparative study. *International Journal of Pharmaceutics*. 2012;**430**(1–2):151–60.
48. Sporty JL, Horalkova L, Ehrhardt C. *In vitro* cell culture models for the assessment of pulmonary drug disposition. *Expert Opinion on Drug Metabolism and Toxicology*. 2008;**4**(4):333–45.
49. Bo Olsson EB, Lars B, Staffan E, *et al*. Pulmonary drug metabolism, clearance, and absorption. In: Hickey AJ, Smith HDC, eds. *Controlled Pulmonary Drug Delivery, 21*, Springer Science and Business Media, LLC, New York, NY, 2011.
50. Bosquillon C. Drug transporters in the lung – do they play a role in the biopharmaceutics of inhaled drugs? *Journal of Pharmaceutical Science*. 2010;**99**(5):2240–55.
51. Gumbleton M, Al-Jayyoussi G, Crandon-Lewis A, *et al*. Spatial expression and functionality of drug transporters in the intact lung: objectives for further research. *Advanced Drug Delivery Reviews*. 2011;**63**(1–2):110–8.
52. Salomon JJ, Ehrhardt C. Organic cation transporters in the blood-air barrier: expression and implications for pulmonary drug delivery. *Therapeutic Delivery* . 2012;**3**(6):735–47.
53. Bo Olsson EB, Lars B, Staffan E, *et al*. Pulmonary drug metabolism, clearance, and absorption. In: *Hugh DC, Smyth AJH, eds. Controlled Pulmonary Drug Delivery*: Springer, Berlin, 2011. pp. 21–50.
54. Groneberg DA, Nickolaus M, Springer J, *et al*. Localization of the peptide transporter PEPT2 in the lung: implications for pulmonary oligopeptide uptake. *The American Journal of Pathology*. 2001;**158**(2):707–14.
55. Ehrhardt C, Kneuer C, Laue M, *et al*. 16HBE14o- human bronchial epithelial cell layers express *p*-glycoprotein, lung resistance-related protein, and caveolin-1. *Pharmaceutical Research*. 2003;**20**(4):545–51.
56. Endter S, Becker U, Daum N, *et al*. P-glycoprotein (MDR1) functional activity in human alveolar epithelial cell monolayers. *Cell and Tissue Research*. 2007;**328**(1):77–84.
57. Forbes B, Asgharian B, Dailey LA, *et al*. Challenges in inhaled product development and opportunities for open innovation. *Advanced Drug Delivery Reviews* . 2011;**63**(1–2):69–87.
58. Parkar NS, Akpa BS, Nitsche LC, *et al*. Vesicle formation and endocytosis: function, machinery, mechanisms, and modeling. *Antioxidants Redox Signaling*. 2009;**11**(6):1301–12.
59. Herd H, Daum N, Jones AT, *et al*. Nanoparticle geometry and surface orientation influence mode of cellular uptake. *ACS Nano*. 2013;**7**(3):1961–73.
60. Rodenstein DO, Perlmutter N, Stanescu DC. Infants are not obligatory nasal breathers. *The American Review of Respiratory Disease*. 1985;**131**(3):343–7.
61. Becquemin MH, Swift DL, Bouchikhi A, *et al*. Particle deposition and resistance in the noses of adults and children. *European Respiratory Journal*. 1991;**4**(6):694–702.
62. Verbanck S, Kalsi HS, Biddiscombe MF, *et al*. Inspiratory and expiratory aerosol deposition in the upper airway. *Inhalation Toxicology*. 2011;**23**(2):104–11.
63. Houtmeyers E, Gosselink R, Gayan-Ramirez G, Decramer M. Regulation of mucociliary clearance in health and disease. *European Respiratory Journal*. 1999;**13**(5):1177–88.
64. Oberdorster G. Pulmonary deposition, clearance and effects of inhaled soluble and insoluble cadmium compounds. *IARC Scientific Publications.* 1992 (**118**):189–204.
65. Thum T, Erpenbeck VJ, Moeller J, *et al*. Expression of xenobiotic metabolizing enzymes in different lung compartments of smokers and nonsmokers. *Environmental Health Perspectives* . 2006;**114**(11):1655–61.
66. Pacifici GM, Franchi M, Bencini C, *et al*. Tissue distribution of drug-metabolizing enzymes in humans. *Xenobiotica*. 1988;**18**(7):849–56.
67. Somers GI, Lindsay N, Lowdon BM, *et al*. A comparison of the expression and metabolizing activities of phase I and II enzymes in freshly isolated human lung parenchymal cells and cryopreserved human hepatocytes. *Drug Metabolism and Disposition* . 2007;**35**(10):1797–805.

68. Lombry C, Edwards DA, Preat V, Vanbever R. Alveolar macrophages are a primary barrier to pulmonary absorption of macromolecules. *American Journal of Physiology Lung Cellular Molecular Physiology*. 2004;**286**(5):L1002–8.
69. Adcock IM, Gilbey T, Gelder CM, *et al*. Glucocorticoid receptor localization in normal and asthmatic lung. *American Journal of Respiratory and Critical Care Medicine*. 1996;**154** (3 Pt 1):771–82.
70. Wilson SM, Shen P, Rider CF, *et al*. Selective prostacyclin receptor agonism augments glucocorticoid-induced gene expression in human bronchial epithelial cells. *Journal of Immunology*. 2009;**183**(10):6788–99.
71. Barnes PJ. Beta-adrenergic receptors and their regulation. *American Journal of Respiratory and Critical Care Medicine*. 1995;**152**(3):838–60.
72. Bai TR. Beta 2 adrenergic receptors in asthma: a current perspective. *Lung*. 1992;**170**(3):125–41.
73. Simons FER SK. Antihistamines. In: Middleton E Jr,, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds., Allergy Principles and Practices. Mosby-Year Book, St. Louis, 1993.
74. Casale TB, Ecklund P. Characterization of muscarinic receptor subtypes on human peripheral lung. *Journal of Applied Physiology (1985)*. 1988;**65**(2):594–600.
75. Slack RJ, Russell LJ, Hall DA, *et al*. Pharmacological characterization of GSK1004723, a novel, long-acting antagonist at histamine H(1) and H(3) receptors. *British Journal of Pharmacol*. 2011;**164**(6):1627–41.
76. Carroll N, Cooke C, James A. The distribution of eosinophils and lymphocytes in the large and small airways of asthmatics. *European Respiratory Journal*. 1997;**10**(2):292–300.
77. Barnes PJ. Distribution of receptor targets in the lung. *Proceedings of the American Thoracic Society*. 2004;**1**(4):345–51.
78. Robinson M, Eberl S, Tomlinson C, *et al*. Regional mucociliary clearance in patients with cystic fibrosis. *Journal of Aerosol Medicine*. 2000;**13**(2):73–86.
79. Yeates DB, Gerrity TR, Garrard CS. Particle deposition and clearance in the bronchial tree. *Annals of Biomedical Engineering*. 1981;**9**(5-6):577–92.
80. Bateman JR, Pavia D, Sheahan NF,*et al*.. Impaired tracheobronchial clearance in patients with mild stable asthma. *Thorax*. 1983;**38**(6):463–7.
81. Sakagami M. In vivo, in vitro and ex vivo models to assess pulmonary absorption and disposition of inhaled therapeutics for systemic delivery. *Advance Drug Delivery Reviews*. 2006;**58**(9–10):1030–60.
82. Donaldson K, Brown D, Clouter A, *et al*. The pulmonary toxicology of ultrafine particles. *Journal of Aerosol Medicine*. 2002;**15**(2):213–20.
83. Samet JM, Cheng PW. The role of airway mucus in pulmonary toxicology. *Environal Health Perspectives*. 1994;**102** (Suppl. 2):89–103.
84. Kroon LA. Drug interactions with smoking. *American Journal of Health-System Pharmacy*. 2007;**64**(18):1917–21.
85. Isaacs KK, Martonen TB. Particle deposition in children's lungs: theory and experiment. *Journal of Aerosol Medicine*. 2005;**18**(3):337–53.
86. Pritchard JN, Jefferies S, Black A. Sex-differences in the regional deposition of inhaled particles in the 2.5–7.5 μm size range. *Journal of Aerosol Science.* 1986;**17**:385–89.
87. Kim CS, Brown LK, Lewars GG, Sackner MA. Deposition of aerosol particles and flow resistance in mathematical and experimental airway models. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology.* 1983;**55**(1 Pt 1):154–63.
88. ICRP. *Human Respiratory Tract Model for Radiological Protection*. ICRP Publication, Elsevier Science Ltd, *Oxford*, 1994, Vol. **24**, pp. 1–3.
89. Asgharian B, Wood R, Schlesinger RB. Empirical modeling of particle deposition in the alveolar region of the lungs: a basis for interspecies extrapolation. *Fundamental and Applied Toxicology*. 1995;**27**(2):232–8.