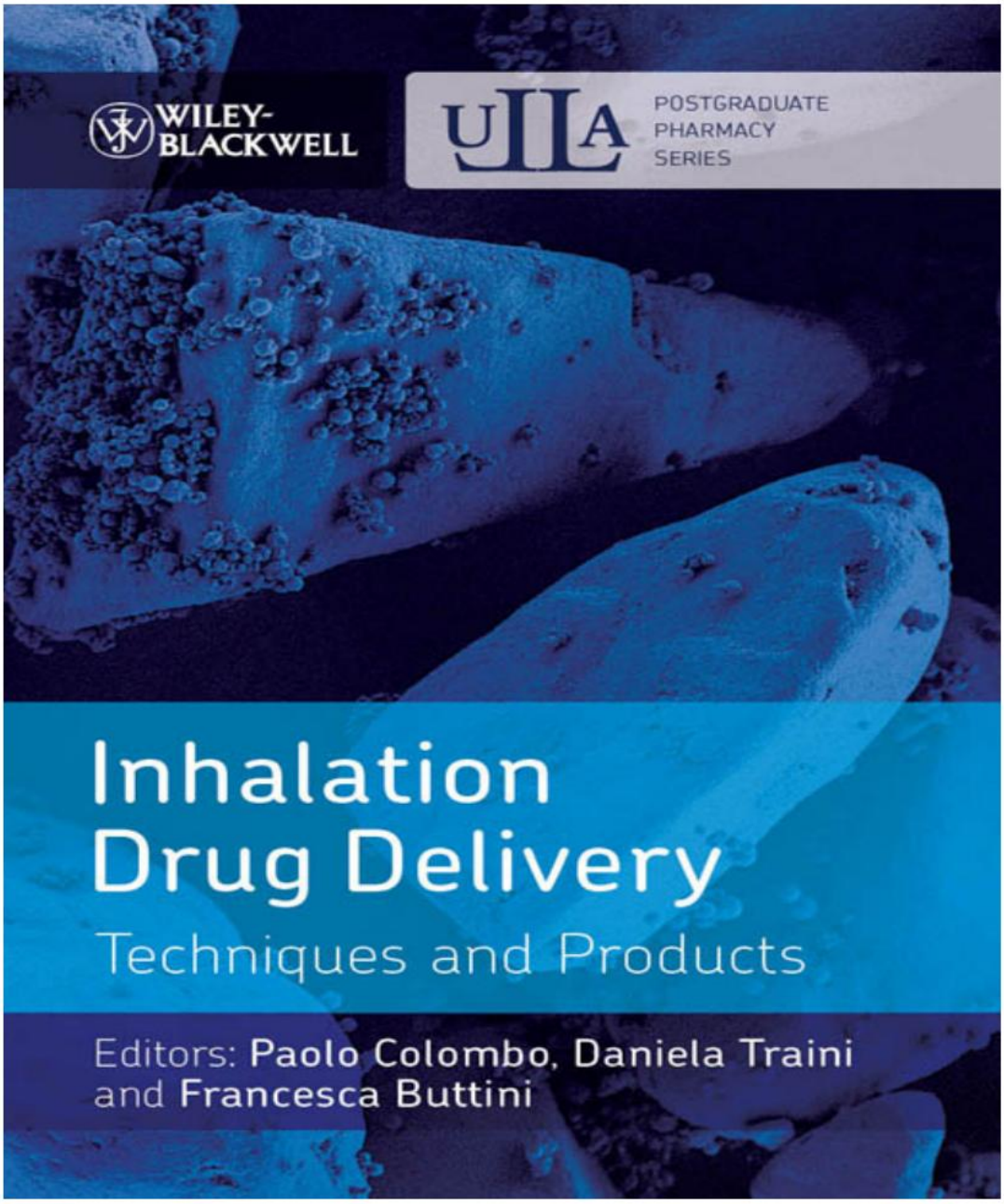
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Inhalation Drug Delivery
Techniques and Products
Editors: Paolo Colombo, Daniela Traini and Francesca Buttini

# Contents

# Inhalation Drug Delivery

## Techniques and Products

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# Preface

This book aims to provide a comprehensive and up-to-date understanding of the processes and mechanisms involved in inhalation drug delivery, with a strong focus on inhalation products and specific equipment and techniques used in laboratories today. It will accurately reflect the current state of our knowledge in the field of inhalation and will provide a good basis for the development of this knowledge. Theory will be covered, providing balanced new perspectives by drawing on research from a variety of fields and from industrial experience.

This book is intended as an aid to those studying pharmacy, pharmaceutical science and technology, or related subjects, at both undergraduate and postgraduate levels. Students will benefit from the concise presentation of a great deal of relevant information, and will find this book an invaluable tool for understanding the field of inhaled pharmaceutical aerosols.

# 1

# Inhalation Drug Delivery

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## 1.1 Introduction

The lung offers a unique and challenging route for drug delivery for the treatment of local respiratory and systemic diseases. Advances in drug formulation and inhalation device design are creating new opportunities for inhaled drug delivery as an alternative to oral and parenteral delivery methods. Nebulizers, pressurized metered-dose inhalers (pMDIs), and dry powder inhalers (DPIs) have each found a niche in the quest for optimal treatment and convenient use. While nebulizers have evolved relatively independently of the drug formulations they deliver, the current generation of pMDIs and DPIs have been developed or tailored for the specific pharmaceutical being delivered, resulting in improved performance. However, the process of delivering drugs to the lung is not simple and is related to many factors associated with the inhaled product and the patient. This chapter will briefly review the anatomy and physiology of the lungs and the various parameters that influence drug deposition.

# 1.2 Brief Review of the Respiratory System and its Physiology

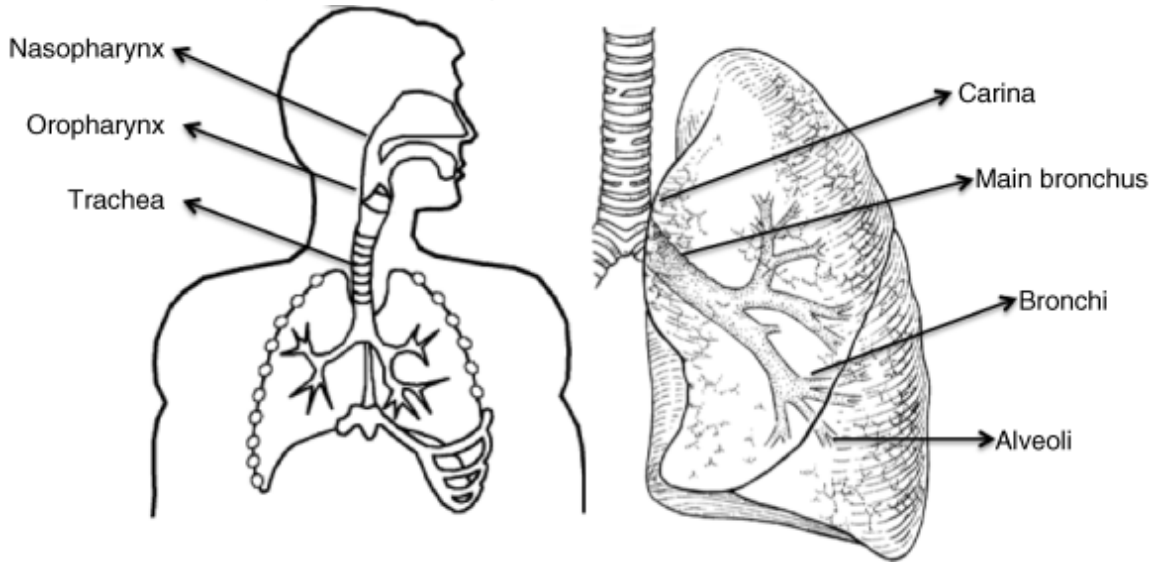
The respiratory tract comprises the conducting and the respiratory regions. The conducting region essentially consists of the nasal cavity, nasopharynx, bronchi, and bronchioles. Airways distal to the bronchioles and the alveoli constitute the respiratory region, where rapid solute exchange takes place. According to Wiebel's tracheobronchial classification [1], the conducting airways comprise the first 16 generations, and generations 17–23 include the respiratory bronchioles, the alveolar ducts, and the alveolar sacs.

The respiratory system is made up of a gas-exchanging organ (the lungs) and a pump that ventilates it. The pump consists of: the chest wall; the respiratory muscles, which increase and decrease the size of the thoracic cavity; the areas in the brain that control the muscles; and the tracts and nerves that connect the brain to the muscles. At rest, a normal human breathes 12–15 times a minute. About 500 mL of air per breath, or 6–8 L/min, is inspired and expired. This air mixes with the gas in the alveoli, and, by simple diffusion, $O_2$ enters the blood in the pulmonary capillaries, while $CO_2$ enters the alveoli. In this manner, 250 mL of $O_2$ enters the body per minute and 200 mL of $CO_2$ is excreted.

Anatomically, the respiratory system is divided into the upper and lower respiratory tract. The upper respiratory tract consists of the nose, pharynx, and larynx. The lower respiratory tract consists of the trachea, bronchial tree, and lungs. The human respiratory tract is made up of a series of bifurcating airways, starting at the oropharynx and finishing at the alveolar sacs. The airway anatomy consists of the oro, nasopharynx, larynx, trachea, two main bronchi, five lobar

bronchi (three on the right, two on the left), and 15–20 dichotomous branchings of the bronchi and bronchioles down to the level of the terminal bronchioles and the alveoli. A schematic diagram of the human respiratory tract is given in Figure 1.1.

**Figure 1.1** Diagrammatic representation of the structure of the human lung and airway




After passing through the nasal passages and pharynx, where it is warmed and takes up water vapor, the inspired air passes down the trachea and through the bronchioles, respiratory bronchioles, and alveolar ducts to the alveoli. The portion of the airways that participates in gas exchange with the pulmonary capillary blood consists of the respiratory bronchioles and the alveoli themselves. The alveoli act as the primary gas-exchange units of the lung, especially as the gas–blood barrier between the alveolar space and the pulmonary capillaries is extremely thin, allowing rapid gas exchange.

Between the trachea and the alveolar sacs, the airways divide 23 times. These multiple divisions greatly increase the total cross-sectional area of the airways, from 2.5 $cm^2$ in the trachea to 11 800 $cm^2$ in the alveoli [2].

Consequently, the velocity of airflow in the small airways declines to very low values. Oxygen can subsequently diffuse via the alveolar epithelium (a thin interstitial space) and the capillary endothelium. In simple terms, this provides a high surface area, low surface fluid coverage, thin diffusion layer, and sluggish cell surface clearance by macrophages. These properties provide an alternative delivery system to the more conventional gastrointestinal, nasal, buccal, or transdermal delivery routes [2]. Details of the anatomy and physiology of the respiratory tract are given in many texts; the reader is referred to Moren et al. [3] or a basic anatomy text [4].

# 1.3 Deposition and the Fate of Particles in the Respiratory Tract

The main factors here are the properties of the aerosol particles (particle size, aerodynamic diameter) and the mode of inspiration (breath volumes, flow rate) [5]. The most important parameter defining the site of deposition of aerosol drugs within the respiratory tract is the particle characteristics of the aerosol.

Most therapeutic aerosols are almost always heterodisperse, consisting of a wide range of particle sizes and described by the log-normal distribution with the log of the particle diameters plotted against particle number, surface area, or volume (mass) on a linear or probability scale and expressed as absolute values or cumulative percentage. Since delivered dose is very important when studying medical aerosols, particle number may be misleading, as smaller particles contain less drug than larger ones. Particle size is defined from this distribution by several parameters. The mass median aerodynamic diameter

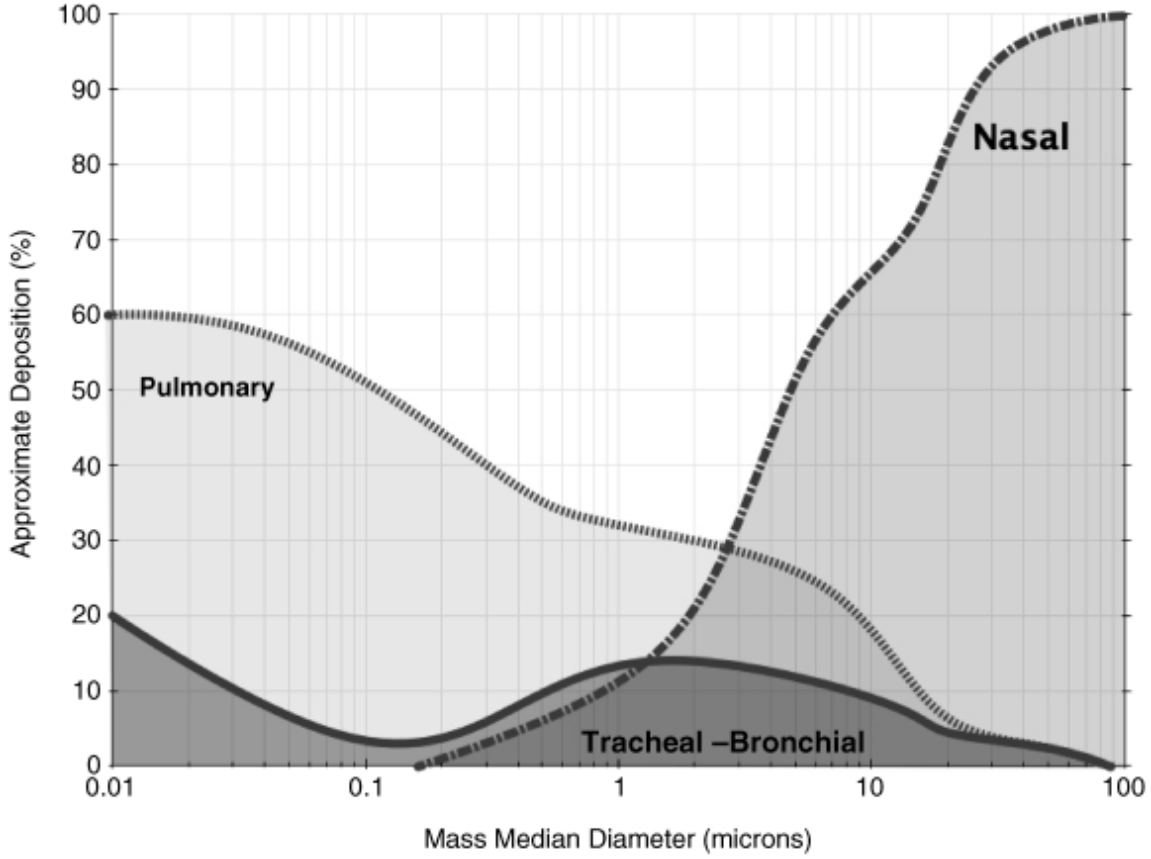
(MMAD) of an aerosol refers to the particle diameter that has 50% of the aerosol mass residing above and 50% below it. Strict control of MMAD of the particles ensures reproducibility of aerosol deposition and retention within desired regions of the respiratory tract. MMAD is read from the cumulative distribution curve at the 50% point. Geometric standard deviation (GSD) is a measure of the variability of the particle diameters within the aerosol and is calculated from the ratio of the particle diameter at the 84.1% point on the cumulative distribution curve to the MMAD. For a log-normal distribution, the GSD is the same for the number, surface area, or mass distributions. A GSD of 1 indicates a monodisperse aerosol, while a GSD of >1.2 indicates a heterodisperse aerosol.

The aerodynamic diameter relates the particle to the diameter of a sphere of unit density that has the same settling velocity as the particle of interest, regardless of its shape or density. Good distribution throughout the lung requires particles with an aerodynamic diameter between 1 and 5 μm, and thus most inhaled products are formulated with a high proportion of drug in this size range [6]. In order to target the alveolar region specifically, the aerosol droplet diameter should not be more than 3 μm. Particles with diameters that are greater than 6 μm are deposited in the oropharynx, whereas smaller particles (<1 μm) are exhaled during normal tidal breathing. Particles <2.5 μm are deposited mainly in the alveoli, where they can exert no pharmacodynamic effect and are rapidly absorbed, increasing the risk of systemic adverse events. This size range was confirmed for mild asthmatics, for whom the particle size of choice should be around 2.8 μm [7].

# 1.4 Deposition Mechanisms

As illustrated in Figure 1.2 (data from [8]), the deposition fractions of particles with different diameters in selected regions of the respiratory tract (laryngeal, upper and lower bronchial, alveolar) have been plotted as a function of particle size for particles of unit density (i.e. normalized aerodynamic diameter).

**Figure 1.2** Deposition efficiency in the respiratory system as a function of the particle size




In this context, the term “deposition” refers to the mean probability of an inspired particle being deposited in the respiratory tract by collection on airway surfaces. “Total deposition” refers to particle collection in the whole respiratory tract, and “regional deposition” to particle collection in a particular region of the respiratory tract [8].

The delivery of medicaments to the respiratory tract is not a simple process. When particles do not follow airflow

streamlines, coming in contact with surfaces, deposition occurs.

The entrainment and efficient delivery of particulates to the lung is regulated by three intrinsic physiological factors: inertial impaction, gravitational sedimentation, and diffusion (via Brownian motion) [9] (see Table 1.1).

**Table 1.1** Deposition mechanisms in the lung and the Weibel model [10, 11]. Created using data with permission from J.S. Patton and P.R. Byron. Inhaling medicines: delivering drugs to the body through the lungs. Nature Reviews Drug Discovery. 6:67–74 (2007). 11. S.W. Clarke. Medical aerosol inhalers: past present and future. In S.W. Clarke and D. Pavia (eds.), Aerosola and the lung: Clinical and experimental aspects, Butterworths, London, 1984, pp. 1–18.

| Generation | Zone | Name | Diameter (cm) | Total cross-sectional area ($cm^2$) | Mechanism of deposition |
|---|---|---|---|---|---|
| 0 | | Trachea | 1.8 | 2.54 | Impaction (inertia) |
| 1 | | Main bronchi | 1.22 | 2.33 | |
| 2 | | | 0.83 | 2.13 | |
| 3 | | | 0.56 | 2.00 | |
| 4 | | | 0.45 | 2.48 | |
| 5 | | Bronchi | 0.35 | 3.11 | Sedimentation (gravity) |
| 6 | | | 0.28 | 3.96 | |
| 7 | Conducting/ tracheobronchial | | 0.23 | 5.10 | |
| 8 | | | 0.186 | 6.95 | |
| 9 | | | 0.154 | 9.56 | |
| 10 | | | 0.130 | 13.4 | |
| 11 | | | 0.109 | 19.6 | |
| 12 | | | 0.095 | 28.8 | |
| 13 | | Bronchioles | 0.082 | 44.5 | |
| 14 | | | 0.074 | 69.4 | |
| 15 | | | 0.066 | 113 | |
| 16 | | Terminal bronchioles | 0.060 | 180 | |
| 17 | | Respiratory bronchioles | 0.054 | 300 | |
| 18 | | | 0.050 | 534 | |
| 19 | Alveolated/ respiratory | Alveolar ducts | 0.047 | 944 | Brownian diffusion |
| 20 | | | 0.045 | 1600 | |
| 21 | | Alveolar | 0.043 | 3220 | |
| 22 | | sacs | 0.041 | 5880 | |
| 23 | | | 0.041 | 11800 | |

Although deposition occurs throughout the airways, inertial impaction usually occurs in the first 10 generations of the lung, where air velocity is high and airflow is turbulent [12]. Most particles >10 μm are deposited in the oropharyngeal region, with a large number impacting on the larynx, particularly when the drug is inhaled from devices requiring a high inspiratory flow rate (DPIs) or when it is dispensed from a device at a high forward velocity (MDIs) [13]. The large particles are subsequently swallowed and contribute minimally, if at all, to the therapeutic benefit.

Inertia is the inherent property of a moving mass that resists acceleration. It depends not only on the particle density and the particle diameter, but also on the airflow velocity.

Sedimentation is the gravitational settling of particles and mainly affects particles in the size range 1–8 μm. In this case, the distance that a particle will settle in a given time increases with the mass and is a gravity-dependent process. The longer a particle remains in the respiratory system, the larger the settling distance the particle covers and hence the greater the probability that the particle will get into contact with the airspace wall.

Brownian diffusion is the irregular motion of an aerosol particle in still air, caused by random variations in the incessant bombardment of gas molecules against the particles. It affects smaller particles (<1 μm), which deposit mainly in the alveolar region. In this area, air velocity is negligible, and thus the contribution to deposition by inertial impaction is nil. Particles in this region have a longer residence time and are deposited by both sedimentation and diffusion. Particles not deposited during inhalation are exhaled. Deposition due to sedimentation affects particles down to 0.5 μm in diameter, whereas below 0.5 μm, the main mechanism for deposition is diffusion.

In summary, minimal deposition occurs in the size range between 0.1 and 1 mm, because neither impaction,

sedimentation, nor diffusion is effective in particle displacement. With decreasing particle diameter, diffusional particle displacement increases, so that particle deposition in the respiratory tract increases. With increasing particle diameter, the distance covered by sedimentation or impaction increases, so that the total particle deposition is also enhanced. The optimum size range of particulates for inhalation therapy has been shown to be 2.5–6 μm [2].

# 1.5 Parameters Influencing Particle Deposition

When designing and formulating a delivery system, the many factors that influence the deposition of drug particles need to be considered.

Increasing air velocity increases impaction deposition but decreases sedimentation and diffusion deposition. Breathing patterns – tidal volumes, respiratory time, and flow rates – all influence deposition. Total respiratory tract deposition increases with mean respiratory time and tidal volume (maximum inspiration volume). Total deposition has been shown to be dependent on the mean residence time (Tm) and the tidal volume (Vt) according to the following equation [14]:

**(1.1)** $$TDF = (DT_m)^{0.5} V_t^{0.49}$$

where D is the diffusion coefficient of the particles in air. The respiratory period and mean residence time (Tm) of particles in the respiratory tract and the tidal volume (Vt) are the two most important breathing parameters affecting deposition of particles. Deposition increases to almost the same extent with an increase in Tm or Vt [14]. Age does not influence substantially the deposition patterns of particles, except perhaps for very small particles (1–2 nm) and for very young subjects (3 years old, in vitro cast data) [15]. There are inter-

individual differences in the human population that affect the deposition and clearance, due to factors like age, existing respiratory conditions, state of the mucous layer, and exposure to other respiratory hazards (i.e. cigarette smoke) [16].

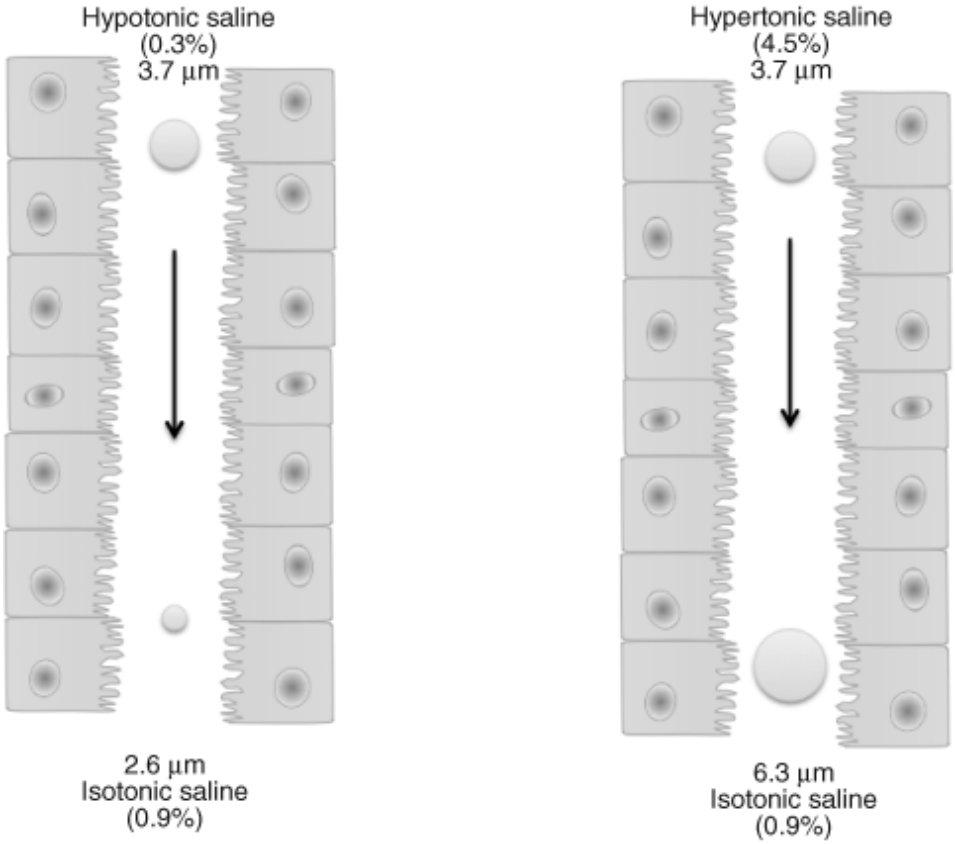
# 1.6 The Clearance of Deposited Particles

Like other parts of our organism, the lung has evolved to prevent the invasion of unwanted airborne particles into the body. Airway geometry, humidity, and clearance mechanisms contribute to this elimination process. The challenge in developing therapeutic aerosols is to produce one that eludes the lung's various lines of defense.

# 1.7 Airways Geometry and Humidity

Progressive branching and narrowing of the airways encourages impaction of particles. The larger the particle size, the greater the velocity of incoming air, the greater the bend angle of bifurcations, and the smaller the airway radius, the greater the probability of deposition by impaction [17]. It must be remembered that in deposition studies, aerosol droplets and particles are highly dynamic systems [18]. The lung has a relative humidity of approximately 99.5%. Particle size does not remain constant once it reaches the respiratory tract. Volatile aerosols become smaller with evaporation, hygroscopic aerosols grow bigger with moisture from the respiratory tract, and particulates aerosols may agglomerate (Figure 1.3).

**Figure 1.3** Hygroscopic growth and shrinkage of hypertonic and hypotonic droplets of the same initial size (3.7 µm) in the humid environment of the respiratory tract




Therefore, knowledge of primary particle size will not be enough to predict deposition, and the formulation of particles for pulmonary delivery will require knowledge of the dynamics of aerosol behavior for efficient targeting.

# 1.8 Lung Clearance Mechanisms

Once deposited on the surface of the airways, the fate of particles will depend on their solubility and the landing site (see Table 1.2).

**Table 1.2** Fate of deposited particles in the lungs.

| Type of particle | Uptake or clearance |
|---|---|
| *Soluble particle* | Dissolution and blood circulation |

| Type of particle | Uptake or clearance |
|---|---|
| *Insoluble particle* | Local action |
| *or* | Translocation, transcytosis, systemic or sensory-nerves uptake<br>Lymphatic uptake (~500 nm)<br>Clearance: macrophages and mucociliary |

Inhaled particles can be dissolved in lung fluid, can act locally or pass into the systemic system, or can be translocated out of the respiratory tract when insoluble [20–22].

The mucus that lines the pulmonary epithelium (1–10 μm thick) and the surfactant that lines the alveoli (0.1–0.2 μm thick) constitute physical barriers to pulmonary absorption of drugs. In the normal lung, the rate of mucus movement varies with the airway region and is determined by the number of ciliated cells and their beat frequency. Movement is faster in the trachea than in the small airways and is affected by factors influencing ciliary functioning and the quantity and quality of mucus. If the deposited matter is fairly soluble in the body fluids, it will enter the blood circulation.

Lipophilic molecules pass easily through the airway epithelium via passive transport. Hydrophilic molecules cross via extracellular pathways, such as tight junctions, or by active transport via endocytosis and exocytosis [23]. From the submucosal region, particles are absorbed into the systemic circulation, bronchial circulation, or lymphatic system.

For relatively insoluble matter, clearance is governed mainly by mechanical removal of particles via phagocytosis by alveolar macrophages and mucociliary transport. Niven [24] identified respiratory mucus, mucociliary clearance, alveolar lining layers, alveolar epithelia, basement membranes, pulmonary enzymes, macrophages, and other cells as barriers to pulmonary absorption of biotherapeutic agents. Although the alveolar epithelium and capillary

endothelium have high permeability to water, many gases, and lipophilic substances, the permeation of many hydrophilic substances of large molecular size and of ionic species is limited [25]. The molecular-weight cut-off of tight junctions for alveolar type I cells is 0.6 nm. Endothelial junctions allow passage of larger molecules (4–6 nm). On reaching the alveoli, most peptides and proteins are either degraded by proteases or removed by alveolar macrophages.

The retention half-time of solid particles in the alveolar region based on this clearance mechanism is about 70 days in rats and up to 700 days in humans [26]. Within 6–12 hours after deposition in the alveoli, virtually all of the particles are phagocytized, but it would appear that there are significant particle size-dependent influences on the effectiveness of this process [27]. The optimal particle size for phagocytosis by alveolar macrophages has been estimated at between 1 and 3 μm, with smaller particles resulting in a rate of phagocytosis that is progressively slower [28]. Those molecules and particles that are not removed by phagocytosis, such as nanoparticles in the deep lungs, where there are no macrophages, readily gain access to epithelial and interstitial sites, blood circulation, and even the lymphatic nodes. Once particles have translocated to the blood circulation, they can be distributed throughout the body. Different mechanisms have been proposed for uptake in systemic circulation and biological tissues. One involves transcytosis across the epithelium of the respiratory tract into the interstitium and access to the blood circulation either directly, via the lymphatic system, or through large transitory pores in the epithelium caused by cell injury or apoptosis [2, 26, 29].

Very little is known about the drug-metabolizing activities of the lung affect and how these affect the concentration and therapeutic efficacy of inhaled drugs. All metabolizing enzymes found in the liver are found to a lesser extent in the

lung (numbers of CYP450 enzymes are 5–20 times lower in lung than in liver), distributed throughout the conducting airways and alveoli [30–32]. However, for most proteins, degradation in the alveoli is not a major clearance mechanism, with >95% of proteins, including insulin, being absorbed intact from the lung periphery [29, 33].

# 1.9 Local and Systemic Drug Delivery

The lung offers a large surface area for drug absorption [2]. In addition, the alveolar epithelium is very thin (approximately 0.1–0.5 μm thick) [34], permitting rapid drug absorption. The alveoli can be effectively targeted for drug absorption by delivering the drug as an aerosol with MMAD <5 μm. Inhalation has long been established in the treatment of both local respiratory and systemic diseases, as it is an effective means of delivering drugs for both. The advantages of inhaled local versus systemic delivery of various drugs are listed in Table 1.3.

**Table 1.3** Advantages of local and systemic drug delivery to the lung.

| Local delivery | Systemic delivery |
|---|---|
| Deliver high concentration directly to the disease site, minimizing risk of systemic side-effects | Non-invasive delivery system |
| Rapid clinical response | Suitable for a wide range of substances, from small molecules to large proteins [35, 36] |
| Bypass GI absorption and first-pass metabolism in the liver | Large absorptive surface area and high permeable membrane in the alveolar region [2] |
| Achieve a similar or superior therapeutic effect at a fraction of the systemic dose | Less-harsh and low-enzymatic environment devoid of first-pass metabolism |

| Local delivery | Systemic delivery |
|---|---|
| | Reproducible absorption kinetics, since pulmonary delivery is independent of extracellular enzymes and metabolic differences, such as for the GI [36] |

Until recently, aerosol drug delivery was mostly limited to topical therapy for the lung and nose. The major contributing factor to this restriction was the inefficiency of available devices, which could deposit only 10–15% of the emitted dose in the lungs. While appropriate lung doses of local therapy can be achieved with these devices, for systemic therapies large amounts of drug are necessary in order to achieve therapeutic drug levels. Recent advances in aerosol and formulation technologies have led to the development of delivery systems that are more efficient and which produce small-particle aerosols, allowing higher drug doses to be deposited in the alveolar region of the lungs, where they are available for systemic absorption.

Several compounds of various molecular sizes can be delivered via the lung to treat a range of diseases, including respiratory and nonrespiratory conditions. A summary is presented in Table 1.4.

**Table 1.4** Compounds delivered via the pulmonary route.

| | Small molecules | Large molecules |
|---|---|---|
| **Respiratory disease** | Inhaled corticosteroids [35] | Peptide agonists/antagonists [36] |
| | $\beta_2$ agonists [37] | Antibodies (anti-IgE) [38] |
| | Anticholinergics [39] | DNA (genes) (CFTR) [40] |
| | Antibiotics [41] | Aptamers [42] |
| | Antifungals [43] | |
| **Nonrespiratory disease** | Morphine [44] | Peptide agonists/antagonists [36] |
| | Anesthetics [45] | Antibiotics [41] |
| | $5HT_{1B/1D}$ agonists (triptans)[46] | DNA (genes)[47] |
| | Adenosine A1 agonists [48] | Aptamers [42] |

| | | |
|---|---|---|
| | Small molecules | Large molecules |
| | Sildenafil [49] | Vaccines [50] |

# 1.10 Conclusion

Although not without barriers, as described briefly in this chapter, the lung is a very desirable target for drug delivery. It not only provides direct access to the site of disease for the treatment of local respiratory diseases, without the inefficiencies and unwanted effects of systemic drug delivery, but also has an enormous surface area to be utilized for the delivery of systemic absorption of medications, and a relatively low enzymatic count. Airway geometry, humidity, clearance mechanisms, and the presence of lung disease influence the deposition of aerosols and therefore the therapeutic effectiveness of inhaled medications. To provide an efficient and effective inhalation therapy, these factors must be considered.

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