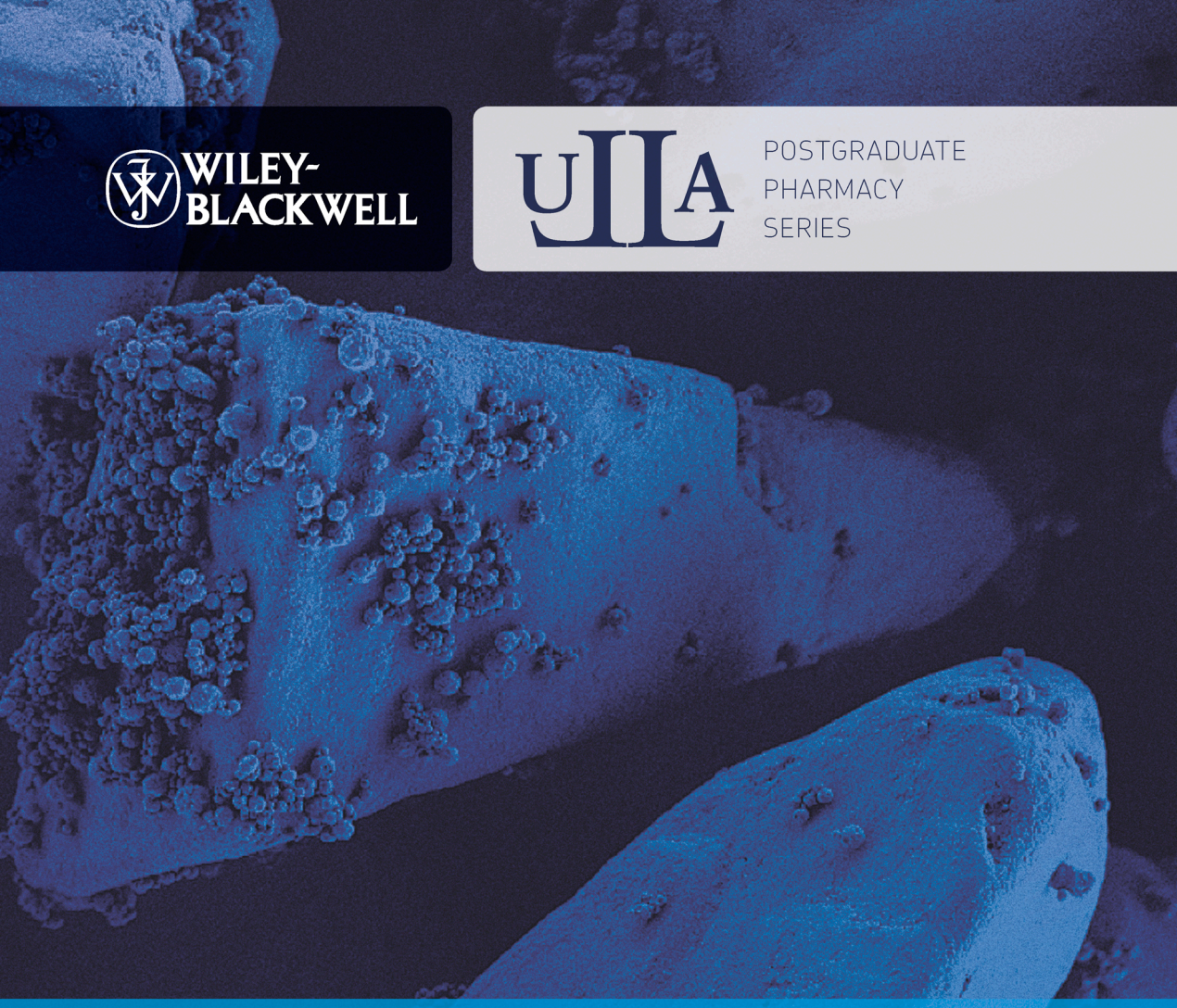

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Inhalation Drug Delivery

Techniques and Products

Editors: **Paolo Colombo**, **Daniela Traini** and **Francesca Buttini**

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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

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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.

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

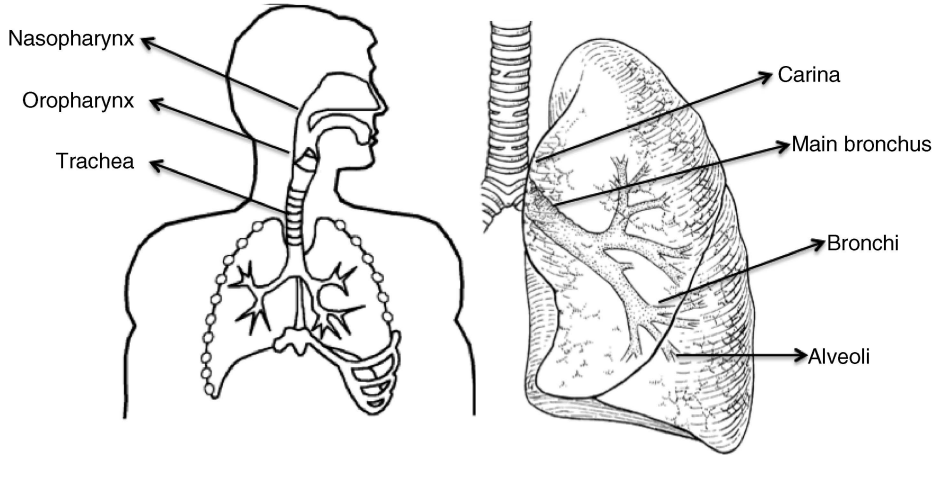

Figure 1.1 Diagrammatic representation of the structure of the human lung and airway

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).

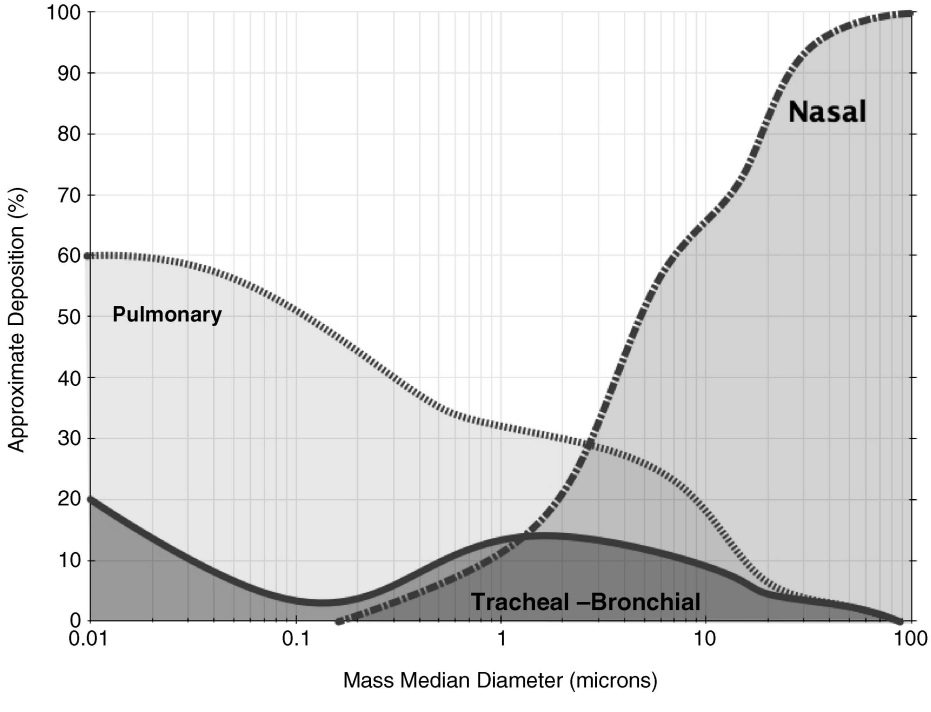

Figure 1.2 Deposition efficiency in the respiratory system as a function of the particle size