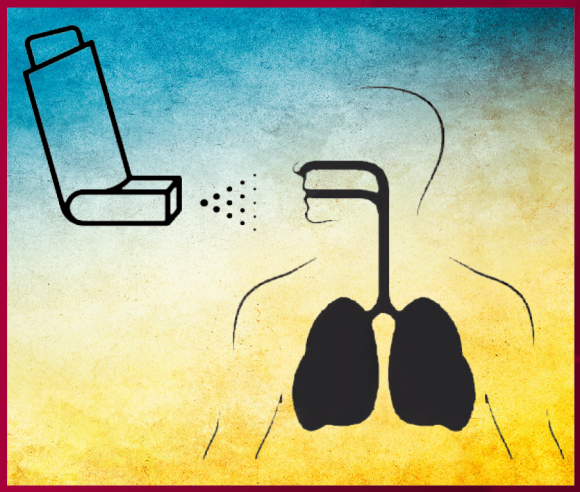
DRUGS AND THE PHARMACEUTICAL SCIENCES

PHARMACEUTICAL INHALATION AEROSOL TECHNOLOGY

Third Edition



Edited by

Anthony J. Hickey

Sandro R.P. da Rocha

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Pharmaceutical Inhalation Aerosol Technology

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Preface

Two previous editions of the book *Pharmaceutical Inhalation Aerosol Technology* (PhIAT) were published in 1993 and 2004. The first edition appeared at a time when few books on aerosol technology were available, notably those of WC Hinds (*Aerosol Technology*, Wiley) and PC Reist (*Introduction to Aerosol Science*) that had only been available for a decade. There were few general texts on medical aerosols, and those were in specialized areas, notably several volumes by Stephen Newman. With this background, the original PhIAT book was intended to broadly cover all aspects of the field from lung biology (pharmacology, physiology, and anatomy) to drug product manufacturing, performance, and clinical applications. In the intervening decades many new volumes have appeared and much more has been published on aerosol physics, formulation and device development, and therapeutic strategies, supported by the commercialization of many new drug products.

This edition of PhIAT not only provides an update on many topics addressed in the 2nd edition, but also expands the "technology" focus of the original volumes to address the title more directly. Since the major purpose of any book should be its utility to the reader, it is logical to look at the topic from the perspective of clear unmet needs. The new text covers all aspects of product development and manufacturing encompassing the important areas of preformulation, formulation, device selection, and drug product evaluation. In order to expand the scope to consider previously unaddressed aspects of pharmaceutical inhalation aerosol technology, considerations of the patient interface have been restricted to those aspects of aerosol delivery, lung deposition, and clearance that are used as measures of effective dose delivery.

The introduction of Dr. Sandro da Rocha as co-editor of the new edition reflects the intention to bring engineering principles to bear on this important topic and to stress the importance of pharmaceutical engineering as a foundational element of all inhaler products and their application to pulmonary drug delivery.

We are grateful to the publishing staff, in particular, Hilary LaFoe and Jessica Poile for their assistance in navigating the manuscript through the process.

This book is dedicated in memory of Professor Paul Myrdal, outstanding scientist, educator, family man, and friend. He is missed by all.

Anthony J. Hickey
Chapel Hill, NC

Sandro R.P. da Rocha
Richmond, VA
September 2018

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Editors

Anthony J. Hickey is Distinguished RTI Fellow at the Research Triangle Institute, Emeritus Professor of Molecular Pharmaceutics of the Eshelman School of Pharmacy (2010–present, Professor 1993–2010), and Adjunct Professor of Biomedical Engineering in the School of Medicine at the University of North Carolina at Chapel Hill. He obtained PhD (1984) and DSc (2003) degrees in Pharmaceutical Sciences from Aston University, Birmingham, United Kingdom. Following postdoctoral positions, at the University of Kentucky (1984–1988), Dr. Hickey joined the faculty at the University of Illinois at Chicago (1988–1993). In 1990 he received the AAPS Young Investigator Award in Pharmaceutics and Pharmaceutical Technology. He is a Fellow of the Royal Society of Biology (2000), the American Association of Pharmaceutical Scientists (2003), the American Association for the Advancement of Science (2005), and the Royal Society of Biology (2017). He received the Research Achievement Award of the Particulate Presentations and Design Division of the Powder Technology Society of Japan (2012), the Distinguished Scientist Award of the American Association of Indian Pharmaceutical Scientists (2013); the David W. Grant Award in Physical Pharmacy of the American Association of Pharmaceutical Scientists (2015); Thomas T. Mercer Joint Prize for Excellence in Inhaled Medicines and Pharmaceutical Aerosols of the American Association for Aerosol Research and the International Society for Aerosols in Medicine (2017). He has published numerous papers and chapters (over 250) in the pharmaceutical and biomedical literature, one of which received the AAPS Meritorious Manuscript Award in 2001. He has edited five texts on pharmaceutical inhalation aerosols and co-authored three others on "pharmaceutical process engineering," "pharmaceutical particulate science," and "pharmaco-complexity." He holds 25 United States patents on a variety of inhaler device technologies, pulmonary, and oral drug delivery formulation technologies. He is founder (1997, and formerly President and CEO, 1997–2013) of Cirrus Pharmaceuticals, Inc., which was acquired by Kemwell Pharma in 2013; founder (2001, and formerly CSO, 2002–2007) of Oriel Therapeutics, Inc, which was acquired by Sandoz in 2010; founder and CEO of Astartein, Inc. (2013–present); member of the Pharmaceutical Dosage Forms Expert Committee of the United States Pharmacopeia (USP, 2010–2015, Chair of the Sub-committee on Aerosols); and formerly Chair of the Aerosols Expert Committee of the USP (2005–2010). Dr. Hickey conducts a multidisciplinary research program in the field of pulmonary drug and vaccine delivery for treatment and prevention of a variety of diseases.

Sandro R.P. da Rocha is a full professor in the Department of Pharmaceutics in the School of Pharmacy and director for Pharmaceutical Engineering—School of Pharmacy at Virginia Commonwealth University (VCU). He also holds a joint appointment in Chemical and Life Science Engineering and is a full member of the Massey Cancer Center at VCU. He obtained his BSc and MSc in Chemical Engineering at USFM and UFSC, respectively, in Brazil, and a PhD in 2000 from the University of Texas at Austin in Chemical Engineering. After a postdoctoral position in Chemistry and Biochemistry also at the University of Texas at Austin, Dr. da Rocha joined the faculty at Wayne State University in Detroit, MI, where he worked until 2015. Professor da Rocha has contributed extensively to the area of pulmonary drug delivery, particularly through the development of novel pressurized metered dose inhaler formulations and of nanotherapeutics for pulmonary drug delivery, both areas having potential applications in the treatment of a variety of pulmonary disorders. Professor da Rocha has received numerous awards and recognition for his work, including visiting appointments at foreign institutions where he has developed collaborative efforts and taught in the area of nanomedicine and pulmonary drug delivery. Professor da Rocha has delivered a number of lectures nationally and internationally in the area of pulmonary nanotherapeutics and has written manuscripts and book chapters with his collaborators that include visiting faculty, postdoctoral fellows, PhD, undergraduate, graduate, and high-school students, who now hold key positions in the industry, academia, and government in various areas including pulmonary pharmaceutics.

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1

Introduction

Anthony J. Hickey and Sandro R.P. da Rocha

A number of outstanding texts on foundational elements of the topics discussed in this book exist, and the reader is encouraged to familiarize themselves with these materials, as they describe basic principles (Finlay, 2001), specific (Purewal and Grant, 1997, Srichana, 2016 and Zeng et al, 2000) and general dosage forms (Colombo et al., 2013, Hickey, 2007, Newman, 2009, Smyth and Hickey, 2011), and analytical methods (Tougas et al., 2013).

The advances in pharmaceutical inhalation aerosol technology occurring since the turn of the millennium have increased the potential of pulmonary drug delivery substantially. While some of the new developments had their origins in earlier work, we have seen the appearance of new propellants and new regulations considering the phase out of what we still consider new propellants, new dry powder inhalers, nebulizers, and a new category of product, soft mist inhalers.

In parallel with these new products, the breadth of application has increased to include the treatment of chronic obstructive pulmonary disease, a range of infectious diseases, diabetes, idiopathic pulmonary fibrosis, and pulmonary arterial hypertension. Pre-clinical studies and clinical trials covering yet a range of other potential applications of orally inhaled products include the use of a broader range of biologics and also nanomaterials that may help further advance the pulmonary drug delivery market.

Successful aerosol therapy has given research and development a boost, and the prospects of even greater opportunities for disease management is emerging from patient compliance, adherence tools, and new classes of drugs for local and systemic delivery through the lungs.

This text is focused on the active pharmaceutical ingredient, formulation development, device design, process and product engineering, and analytical methods to assess critical quality attributes underpinning safe and efficacious dosage forms.

Figure 1.1 depicts the sequence in which these topics will be presented, which follows the product development pathway. The conclusion of the volume is a discussion of bioequivalence testing and the interface between the dosage form and the patient. This reflects the point at which design and engineering controls, which are embedded in a regulated environment of quality by design, give way to biological factors.

It is intended that the materials covered in subsequent sections familiarize the reader with the underlying science and engineering associated with the design and characterization of complex dosage forms required to deliver orally inhaled aerosols. The platform of knowledge will be useful in considering options for specific applications and is a point from which to launch new technologies that will frame future developments in the field as described in a companion text (Hickey and Mansour, in press).

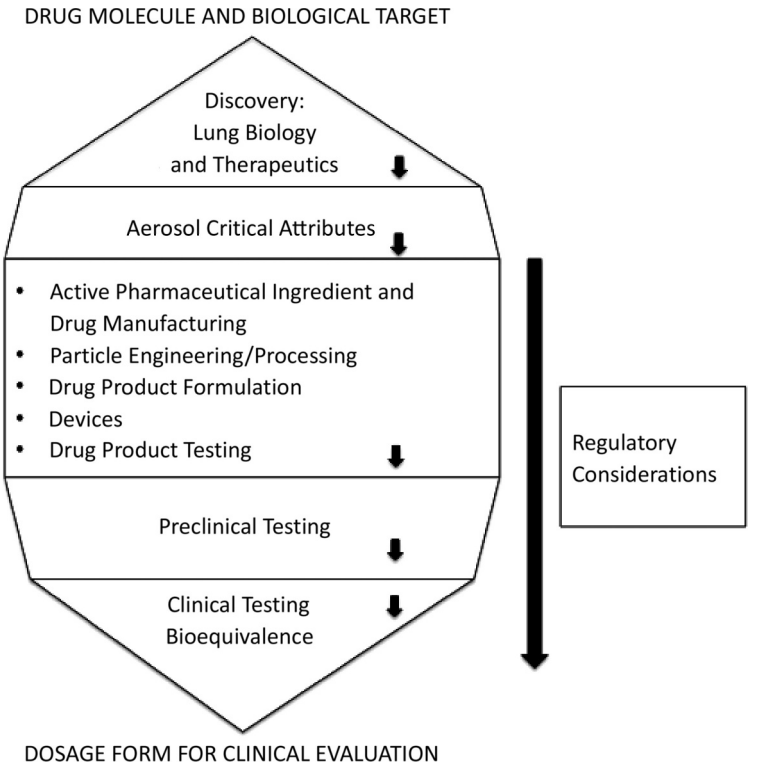

FIGURE 1.1 Product development themes in pharmaceutical inhalation aerosol technology.

REFERENCES

Colombo P, Traini D, Buttini F. *Inhaled Drug Delivery: Techniques and Products*. New York: Wiley-Blackwell; 2013.

Finlay W. *The Mechanics of Inhaled Pharmaceutical Aerosols: An Introduction*. New York: Academic Press; 2001.

Hickey A. *Inhalation Aerosols, Physical and Biological Basis for Therapy*. 2nd ed. New York: Informa Healthcare; 2007.

Hickey A J, Mansour H H, Eds. *Inhalation Aerosols, Physical and Biological Basis for Therapy*, Third Edition. Boca Raton, FL: CRC Press; in press.

Newman S. *Respiratory Drug Delivery: Essential Theory and Practice*. Richmond, VA: RDD Online; 2009.

Purewal T, Grant D. *Metered Dose Inhaler Technology*. Boca Raton, FL: CRC Press; 1997.

Smyth H, Hickey A. *Controlled Pulmonary Drug Delivery*. New York: Springer; 2011.

Srichana T. *Dry Powder Inhalers: Formulation, Device and Characterization*. Hauppauge, NJ: Nova Science Publishers; 2016.

Tougas T, Mitchell J, Lyapustina S, Eds. *Good Cascade Impactor Practices, AIM and EDA for Orally Inhaled Products*. New York: Springer; 2013.

Zeng X, Martin G, Marriott C. *Particulate Interactions in Dry Powder Formulations for Inhalation*. New York: CRC Press; 2000.

Section I

Discovery

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2

Physiology of the Airways

Anthony J. Hickey and David C. Thompson

CONTENTS

2.1 Introduction

The airways represent a unique organ system in the body, their structure allowing air to come into close contact with blood, is one of the principal adaptions permitting the existence of terrestrial life. This adaptation also makes the airways a useful route of administration of drugs in the inhaled or aerosol form. This chapter provides an overview of the physiology of the airways excluding that of the nasopharyngeal regions of the airways. Aspects considered relevant to the practical and theoretical application of inhaled substances are emphasized.

2.2 Anatomy of the Airways

The airways (constituting the lungs) may be viewed as a series of dividing passageways originating at the trachea and terminating at the alveolar sac. In the context of aerosol design and delivery, such a "static" overview represents a satisfactorily simple model. However, many factors beyond the anatomy of the airways are relevant to the therapeutic use of aerosols.

2.2.1 Structure

The airways are often described as the pulmonary tree in that their overall form resembles a tree. The tree trunk is analogous to the trachea of the airways that bifurcates to form main bronchi. These divide to form smaller bronchi that lead to individual lung lobes: three lobes on the right side and two on the left side. Inside each lobe, the bronchi undergo further divisions to form new generations of smaller caliber airways: the bronchioles. This process continues through the terminal bronchioles (the smallest airway not involved with an alveolus), the respiratory bronchioles (which exhibit alveoli protruding from their walls), alveolar ducts, and terminates with the alveolar sacs. In the classic model of the airways, as described by Weibel (1963), each airway divides to form two smaller "daughter" airways (Figure 2.1), and, as a result, the number of airways at each generation is double that of the previous generation. The model proposes the existence of 24 airway generations in total, with the trachea being generation 0 and the alveolar sacs being generation 23.

In passing from the trachea to the alveolar sac, two physical changes occur in the airways that are important in influencing airway function. Firstly, the airway caliber decreases with increasing generations, for example, tracheal diameter ≈ 1.8 cm versus alveolar diameter ≈ 0.04 cm (Figure 2.2). This permits

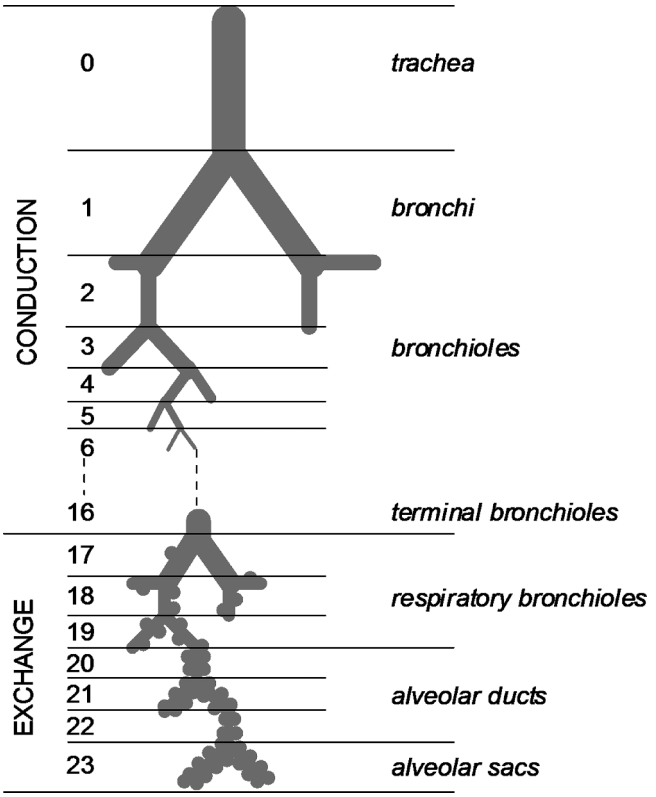

FIGURE 2.1 Model of airway. (With kind permission from Taylor & Francis: *Morphometry of the Human Lung*, Berlin, Germany, Springer-Verlag, 1963, Weibel, E.)

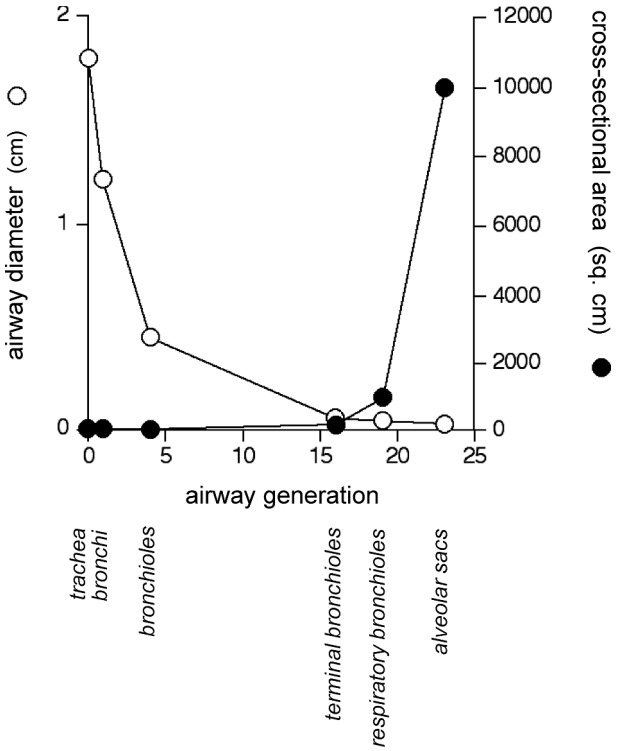

FIGURE 2.2 Graph of airway diameter and cross-sectional are as a function of airway generation.

adequate penetration of air to the lower airways for a given expansion of the lungs. Secondly, the surface area of the airways increases with each generation to the extent that the total area at the level of the human alveolus is in the order of 140 m^2 (Gehr et al., 1978). The alveolus is the principal site of gas exchange in the airways, a function compatible with the increased surface area that promotes extensive and efficient diffusional gas exchange between the alveolar space and the blood in alveolar capillaries (*vide infra*). The relatively small change in cross-sectional area that occurs over the 19 generations of airways between the trachea and the terminal bronchiole (from 2.5 cm^2 to 180 cm^2) (Bouhuys, 1974) fosters the rapid, bulk flow of inspired air down to the terminal bronchiole. By contrast, the cross-sectional area increases greatly in the four generations between the terminal bronchiole and the alveolar sac (from 180 cm^2 to 10,000 cm^2) (Bouhuys, 1974), which results in a significant decrease in the velocity of airflow to the extent that the flow velocity fails to exceed that of diffusing oxygen molecules (Weibel, 1984). Accordingly, diffusion assumes a greater role in determining the movement of gases in these peripheral airways.

The various levels of the airways may be categorized functionally as being either conducting or respiratory airways. Those airways not participating in gas exchange constitute the conducting zone of the airways and extend from the trachea to the terminal bronchioles. This region is the principal site of airway obstruction in obstructive lung diseases, such as asthma. The respiratory zone includes airways involved with gas exchange and comprises respiratory bronchioles, alveolar ducts, and alveolar sacs. As such, conducting and respiratory zones of the airways may be distinguished simply by the absence or presence of alveolar pockets (which confer gas exchange function). Regions within each zone may be classified further on a histological basis. For example, the contribution of cartilage to the airway wall is one means of differentiating the trachea from bronchi and bronchioles because cartilage exists as incomplete rings in the trachea, regresses to irregularly shaped plates in bronchi, and is absent from bronchioles. Also, respiratory bronchioles may be discriminated from terminal bronchioles by the presence of associated alveoli.

Other histological changes are evident downward throughout the pulmonary tree, and the cellular profile of each region has distinctive effect on functional aspects of the airways under physiological and pathophysiological conditions.

2.2.1.1 Epithelium

The epithelium of the airways is a continuous sheet of cells lining the lumenal surface of the airways. It separates the internal environment of the body (i.e. subepithelial structures) from the external environment (i.e. airway lumen). The lumenal surface of the epithelium is, therefore, exposed to inhaled substances, such as gases, particulates, or aerosols. Connecting adjacent epithelial cells are specialized tight junctional processes (Inoue and Hogg, 1974; Williams, 1990) that limit the penetration of inhaled substances by the intercellular route of administration. Under normal or physiological conditions, larger molecules must past through the epithelial cell. Therefore, the epithelium serves the important function of limiting access of inhaled substances to the internal environment of the body. Under pathophysiological conditions, the epithelium may be damaged, enhancing penetration of substances present in the airway lumen (Godfrey, 1997).

The airway epithelium comprises a variety of cell types (Table 2.1), the distribution of which confers different functions on the airways region. The lumenal surface of the airways are lined by ciliated cells from the trachea to the terminal bronchus. Mucus, a viscous fluid containing mucin glycoproteins and proteoglycans, floats on a watery layer of periciliary fluid (or sol) and covers the lumenal surface of the epithelium. The secretions fulfill four important functions. Firstly, it protects the epithelium from becoming dehydrated. Secondly, the water in the mucus promotes saturation of inhaled air. Thirdly, the mucus contains antibacterial proteins and peptides, such as defensins and lysozyme that suppress microbial colonization of the airways (Finkbeiner, 1999; Schutte and McCray, 2002). Fourthly, the mucus is involved in airway protection from inhaled xenobiotics or chemicals. Coordinated beating of the epithelial cilia propels the blanket of mucus towards the upper airways and pharynx where the mucus may either be swallowed or ejected. The rate of mucus propulsion varies according to the airway region such that movement in the smaller airways is slower than in the larger airways, a situation that arises from the proportionally larger number of ciliated cells in the larger airways and the higher ciliary beat frequency in the larger airways (Gail and L'enfant, 1983). Syllogistically, this process is advantageous, given that many small airways converge on the larger, more central airways whose mucus clearance rate would have to be greater to accommodate the large volumes of mucus being delivered by the smaller distal airways. This process of

TABLE 2.1

Cells of the Airway Epithelium

Cell	Putative Function
Ciliated columnar	Mucus movement
Mucous (goblet)	Mucus secretion
Serous	Periciliary fluid; mucus secretion
Clara (nonciliated epithelial)	Xenobiotic metabolism; surfactant production
Brush	Transitional form of ciliated epithelial cell
Basal	Progenitor for ciliated epithelial and goblet cells
Dendritic	Immunity
Intermediate	Transitional cell in differentiation of basal cell
Neuroendocrine (Kultschitsky or APUD)	Chemoreceptor; paracrine function
Alveolar type I	Alveolar gas exchange
Alveolar type II	Surfactant secretion; differentiation into type I cell
Alveolar macrophage	Pulmonary defense
Mast	Immunoregulation

Sources: Holt, P. et al., *Clin. Exp. Allergy*, 19, 597–601, 1989; Jeffrey, P., *Am. Rev. Respir. Dis.*, 128, S14–S20, 1983; Scheuermann, D., *Microsc. Res. Tech.*, 37, 31–42, 1997.