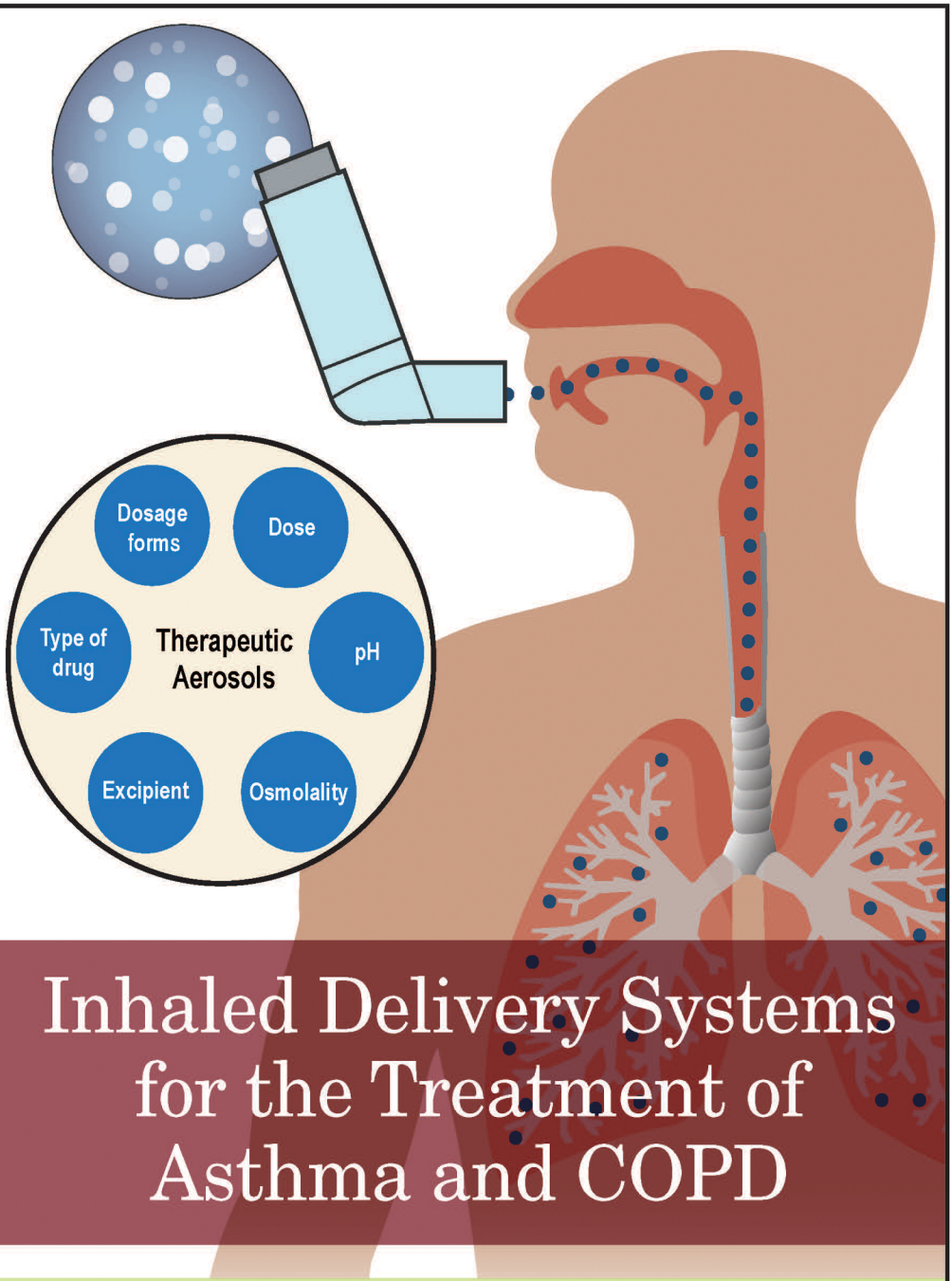

Inhaled Delivery Systems for the Treatment of Asthma and COPD

EDITED BY
Donald A. Mahler and Rajiv Dhand

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Inhaled Delivery Systems for the Treatment of Asthma and COPD

Inhaled therapies form the cornerstone for treatment of patients with asthma and COPD. Evolving technology has resulted in availability of a wide range of devices for delivery of inhaled drugs. The four different delivery systems – pressurized metered-dose inhalers, slow mist inhalers, dry powder inhalers, and nebulizers – are unique in design and require distinct inhalational instructions for correct use. This book provides current information about inhalation devices, including their advantages and disadvantages, with guidance for optimal techniques of use. The book emphasizes appropriate selection of inhalation devices based on patient and health care professional factors, as well as device attributes that allow selection of the right medication in the right inhalation device at the right time for the right patient.

Key features:

- Addresses the objective of precision medicine – the right medication in the right inhaler device at the right time.
- Inputs by international thought leaders who have published widely on inhaled medications and/or inhaled delivery systems for clinicians, trainees, and respiratory therapists.
- Discusses the development of audio-based systems and smart inhalers for patient monitoring.

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Inhaled Delivery Systems for the Treatment of Asthma and COPD

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Table of Contents

Foreword

Inhalation is the preferred route of administration of nearly all medications for the treatment of asthma and COPD via various hand-held devices or nebulizer systems. While hand-held devices are commonly used because of their relative simplicity and convenience, technical challenges to their correct use are frequently not met, resulting in ineffective delivery of these medications to the lungs, thus undermining their clinical benefit. Nebulizer systems for medication delivery, while less convenient than hand-held devices, are most often used in the hospital and emergency room settings and serve as valuable alternatives to hand-held devices in outpatients who are unable to master the technical challenges to their effective use. Asthma and COPD affect hundreds of millions of people worldwide, and COPD is the third leading cause of death globally, underscoring the vital importance of effective delivery of inhaled medications.

Drs. Donald A. Mahler and Rajiv Dhand, two widely recognized and highly respected authorities on inhaled delivery systems with whom I have had the distinct privilege to serve in various committees and conferences related to aerosol therapy, have assembled an international group of distinguished experts to contribute to their book a total of 14 chapters covering a wide range of key topics relevant to inhaled delivery systems for treating asthma and COPD, in addition to other respiratory diseases (cystic fibrosis, bronchiectasis, and pulmonary hypertension) responsive to a variety of medications deliverable by the inhaled route.

Their book is an up-to-date and comprehensive review of the mechanics and technical aspects of differing inhaled delivery systems, the requirements for their optimal use by both adult and pediatric patients, their relative advantages and disadvantages depending on host characteristics, their use in different clinical settings and for the treatment of different respiratory disorders, the ongoing development of "smart" inhalers utilizing advanced digital technology to optimize delivery technique, patient adherence, and the physician-patient relationship, and practical issues regarding cost and patient access in the current regulatory environment. As such, the book serves as a uniquely valuable resource for a variety of health care professionals, as well as inhalational device manufacturers.

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About the Editors

Donald A. Mahler (MD, FCCP) is Emeritus Professor of Medicine at Geisel School of Medicine at Dartmouth in Hanover, New Hampshire. He currently works as a pulmonary physician at Valley Regional Hospital in Claremont, New Hampshire, where he is Director of Respiratory Services.

His research interests include the evaluation/treatment of dyspnea and clinical outcomes in COPD. Under the mentorship of the late Alvin Feinstein, MD, Dr. Mahler developed and established the psychometric properties of the interviewer-administered baseline and transition dyspnea indexes (BDI/TDI), which have been translated into over 80 languages. The BDI/TDI have been used as an outcome measure in phase 3 clinical trials involving medications approved by the Food and Drug Administration and/or the European Medicines Agency for treatment of patients with COPD. These include Serevent®, Spriva®, Advair®, Brovana®, Tudorza®, Daliresp®, Arcapta®, Ultibro®, Anoro®, Striverdi®, Stiolto®, Utibron®, and Yupelri®.

In collaboration with the late John C. Baird, PhD, the interviewer administered BDI/TDI were converted into self-administered and computerized (SAC) versions, enabling patients to provide a direct rating of breathlessness during daily activities. The SAC versions have been translated into 12 languages and have been included as an outcome measure in phase 3 and 4 clinical trials evaluating therapies for patients with interstitial lung disease and COPD.

Dr. Mahler has authored/co-authored over 180 original research articles and over 100 editorials, book chapters, and non-peer-reviewed articles. In addition, he has written/edited four books on dyspnea.

In June 2014, he created the website, https://www.donaldmahler.com, with the vision "to positively affect the daily lives of those with COPD and their families." In February 2015, Dr. Mahler authored *COPD: Answers to Your Questions* (Two Harbors Press) to address the common questions posed by those with COPD, family members, and their caregivers. In January 2022, he wrote *COPD: Answers to Your Most Pressing Questions about Chronic Obstructive Pulmonary Disease* (Johns Hopkins University Press).

Dr. Rajiv Dhand (MD, FCCP, FACP, FAARC, FRSM, ATSF) serves as Professor of Medicine with tenure, the Wahid T. Hanna MD Endowed Chair of the Department of Medicine, Service Chief of the Medical Service and Associate Dean of Clinical Affairs at the University of Tennessee, Graduate School of Medicine in Knoxville, TN. Previously, he served as Division Director of Pulmonary, Critical Care, and Environmental Medicine at the University of Missouri. He is a Past President of the International Society of Aerosols in Medicine (ISAM).

Dr. Dhand is a skilled pulmonologist who is internationally recognized for his work on inhaled therapies. He helped to establish the scientific basis for the use of metered-dose inhalers in mechanically ventilated patients. He was an invited member of several Task Forces that developed Guidelines on Aerosolization of Medication that were published in *CHEST*, *European Respiratory Journal*, and *Journal of Aerosol Medicine and Pulmonary Drug Delivery*.

Dr. Dhand served as a principal investigator on many clinical trials over the past 20 years, principally related to bronchodilator therapy in patients with chronic obstructive pulmonary disease (COPD). His experience includes studies in experimental, translational, and clinical research and he is the recipient of several research grants during his career.

Dr. Dhand has been awarded Fellowships of the American College of Physicians, American College of Chest Physicians, American Thoracic Society, Royal Society of Medicine, American Association of Respiratory Care, and International Society of Aerosols in Medicine. He is Editor-in-Chief of the *ISAM Textbook of Aerosol Medicine*. Dr. Dhand has held multiple editorial appointments including *CHEST, Journal of Aerosol Medicine and Pulmonary Drug Delivery*, *Respiratory Care*, and *International Journal of COPD*. He is the Respiratory Section editor for *Advances in Therapy* and US Editor-in-Chief of *Pulmonary Therapy* Journal. He has published over 170 articles in peer-reviewed journals and has lectured at a host of national and international venues. He remains actively engaged in clinical practice as well as teaching and training medical students, internal medicine residents, and pulmonary/critical care medicine fellows.

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Introduction

Donald A. Mahler and Rajiv Dhand

Inhaled therapies are the cornerstone of treatment for individuals with asthma and COPD. To be effective, patients need to inhale the medication deep into the lower respiratory tract to activate receptors that dilate airways or reduce airway inflammation. Although both the specific molecule(s) and the delivery system are important for effective therapy, the major focus by professional respiratory organizations and pharmaceutical companies has been on development and promotion of specific molecule(s). Unfortunately, there has been limited guidance on the selection of the most appropriate inhaled delivery system for the individual patient. The four different delivery systems – pressurized metered-dose inhalers, slow mist inhalers, dry powder inhalers, and nebulizers – are unique in design and require distinct inhalational instructions for correct use by patients.

The purpose of writing this book is to address an important, but neglected topic: What should health care professionals consider when selecting an inhaled delivery system for an individual with asthma or COPD? A new resource is needed for several reasons:

1. Increased awareness of the high prevalence of incorrect inhalational technique among users.
2. The unique features of the four different inhaled delivery systems.
3. Emerging evidence that various patient factors (e.g., age, sex, cognitive function, manual dexterity, and peak inspiratory flow) affect optimal use of the inhaled delivery system.
4. The development of audio-based and digital systems for monitoring correct inhaler technique.

This book addresses the objective of precision medicine – selecting the right medication *in the right inhalation device* at the right time. The 14 chapters provide guidance for health care professionals to match an inhaled delivery system with the individual patient who has asthma and/or COPD. Moreover, this information enhances understanding about the appropriate use and care of inhaled delivery systems. Finally, we hope that the contents of the book provide a springboard for addressing new research questions.

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1 Principles of Inhaled Therapy

Omar S. Usmani and Federico Lavorini

CONTENTS

INTRODUCTION

Delivering drugs using the inhalation route to the lungs is the foundation of the everyday clinical management of patients with airway diseases (1–3). The inhaled route, as opposed to systemic drug administration, allows key therapeutic benefits. Targeting the drugs to the site of action in the lungs achieves a quicker onset of action, a reduction in the dose of drug used, and an improved therapeutic ratio (efficacy to adverse event ratio). The global pandemic has seen a seismic need for us to understand aerosol science, for example, infectious aerosols and therapeutic aerosols (4). In this chapter we discuss the physiochemical factors that control the transport, delivery, and deposition of inhaled drug within the lungs.

MECHANISMS OF DRUG DEPOSITION IN THE LUNGS

Inhaled drug deposition is an active process that requires the inspired therapeutic particles to be maximally retained within the airways of the lungs and minimize loss of drug in the exhaled air (5, 6). The chief mechanisms that control inhaled medical aerosol deposition within the airways are inertial impaction, sedimentation, and diffusion (Figure 1.1) (7, 8).

These physical mechanisms act concurrently on the inhaled drug particles as they follow the airstream on their trajectory within the respiratory tract and collectively contribute to the deposition of aerosolized drug within the lungs. The relative proportions and extent to which each mechanism contributes and predominates are dependent on the physicochemical properties of the drug particle, the pathology and geometry of the local airways, the airstream parameters, and the inhalation maneuver and pattern of breathing of the patient

Inertial Impaction

Inertial impaction of inhaled drug particles occurs when the forward momentum of an individual drug particle causes it to maintain its original path and direction of flow in the airstream leading it to impact on the surrounding airway wall, in a region of the respiratory tract where there is a change in the bulk direction of the airstream. Inertial impaction predominantly occurs with inhaled drug particles at airway bifurcations in larger branches of the airways

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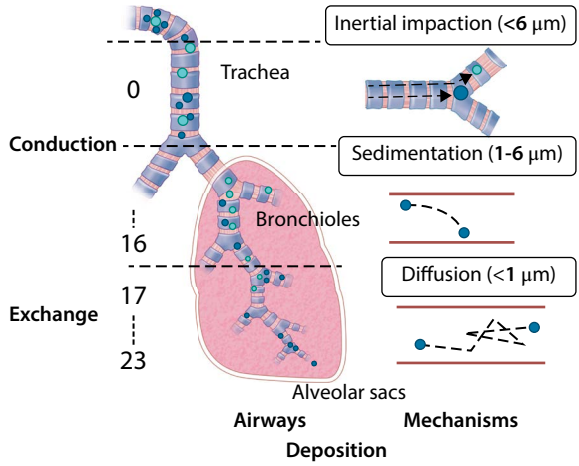

Figure 1.1 Mechanisms of aerosol deposition in the airways.

in the respiratory tract where the velocities of airflow are high and where rapid and fast changes occur in the path and direction of the airstream (Figure 1.1).

Impaction of inhaled drug particles within the lungs is beneficial. However, inertial impaction is also the prime determinant of drug depositing within the oropharynx that can lead to unwanted local adverse effects and through oral bioavailability, depending upon the pharmacokinetic behavior and metabolism of the drug systemic adverse effects. The ballistic high-velocity nature of the aerosol spray emitted from inhaler devices, such as some pressurized metered-dose inhalers (pMDIs), or inhaled with intense inspiratory force and flows by the patients, as is needed with some dry powder inhalers (DPIs), can lead to significant proportions of the emitted drug particles impacting within the oropharynx and minimal amounts, in some cases less than 20%, reaching the lungs (9–11).

Inhaler devices have evolved to slow down the emitted aerosol spray and plume velocity, such as newer pMDIs with refined drug formulations (12), the slow mist inhaler (SMI) (13), and DPIs requiring gentler inhalation flows (14) that can decrease oropharyngeal impaction. In clinical practice, valve-holding chambers (VHCs) and spacers are sometimes used and attached to pMDIs that allow an extension to the inhaler mouthpiece, and by increasing the distance the aerosol spray has to travel, VHCs slow down the velocity of the aerosol spray, which has a two-fold effect (15, 16). First, VHCs allow time for the aerosol propellant to evaporate and this results in smaller drug particles that have greater potential to reach the lower respiratory tract compared to large inhaled drug particles (17), and secondly the ballistic impact of the aerosolized drug within the oropharyngeal cavity is reduced (15). The slow mist inhaler emits an aerosol spray that is slow and steady with a longer duration compared to pMDIs containing a greater fraction of fine particles (18, 19). Inertial impaction and gravitational sedimentation are the main mechanisms that influence the deposition of large, fast-moving inhaled particles of drug between 1μm and 10μm.

Gravitational Sedimentation

Gravitational sedimentation of inhaled drug particles within the lungs occurs under the action of gravity and causes deposition within the airways when

the gravitational force acting on a drug particle overcomes the total force of air resistance. Sedimentation occurs where the velocity of the airstream is low allowing the available time for the inhaled drug particles to settle within the airway (residence time), being most efficient in the branching small airways where the distance to deposit on the airway walls is smaller compared to the larger airways (Figure 1.1). The breath-hold pause instruction often given to patients after inhalation of the aerosol enhances the action of sedimentation on inhaled drug particles in achieving greater airway deposition (20).

Diffusion

Diffusion is the random collision of gas molecules of air present in the airways with very small particles, in this case inhaled drug particles, which displaces and pushes the aerosolized drug particles about within the airways, in an irregular and erratic manner (5). As a consequence of diffusion, a drug particle in stationary air continues to move around in a random manner, even in the absence of gravity, and this can lead the inhaled drug particles to contact and deposit on the surrounding airway wall. Diffusion predominantly occurs in the distal small airways and alveoli, where airflow velocities are at their lowest, the residence time within the airways is long, and the distance an inhaled particle has to travel before hitting the airway wall is short (Figure 1.1). Diffusion is the main deposition determinant of slow-moving, small submicron (<1 μm) particles.

FACTORS AFFECTING DEPOSITION

Many factors can influence the deposition of inhaled aerosolized drug particles within the airways and they can generally be divided into aerosol characteristics and patient variables (Table 1.1).

Table 1.1: Factors Affecting Airways Deposition of Inhaled Medical Aerosols

Aerosol Factors	Patient Factors
Drug particle characteristics: • particle density • particle electrostatics • particle shape • particle size and fraction	Inhalation maneuver: • breathing frequency • breath-hold pause • chin lift • degree of lung inflation • exhalation to end tidal breath before inhalation • inhaled aerosol volume • inspiratory flow • nose vs. mouth breathing
Drug formulation: • hygroscopicity • surfactant • molecule charge	Airway features: • adult vs. pediatric • airways disease type • diameter and obstruction • severity of disease
Aerosol generation system: • inhaler device type • maintenance of device	Healthcare features: • competency of healthcare to teach, train and instruct patient • inhaler regimen • patient adherence • patient technique

Aerosol Properties

Of the physicochemical aerosol properties, drug particle size, or mass median aerodynamic diameter (MMAD) for therapeutic aerosols, is the most significant factor that determines the overall amount of inhaled drug particles depositing within the lungs and also the distribution of aerosolized drug within the airway regions. The branching airway system of the respiratory tract acts primarily as a defense mechanism analogous to a series of filters sequentially removing harmful airborne particulate matter from the inspired airstream. Inhaled drug particles therefore need to overcome the barriers to achieve effective drug deposition. Generally, inhaled particles >100 microns in size are usually trapped in the upper airway nasal cavity, where those >10 micron typically deposit in the oropharyngeal region, and particles between 2 and 6 microns deposit in the conducting airways. Extra fine inhaled drug particles, defined as those less than 2.1 microns (21), have the best potential to reach the small airways and distal lung region.

It is clear that modulating the particle size of inhaled drug can optimize drug delivery to the lungs and the clinical benefit experienced by the patients in terms of impact on their disease (22–24). Indeed, this will depend upon the drug class and pharmacological action of the drug and also the lung region it is thought best to target the drug with respect to receptors for the drug (25, 26). In a landmark *in vivo* study investigating the effect of inhaled drug particle size in patients with asthma using short-acting beta-agonist, the authors observed aerosolized particles of 6- and 3-micron MMAD of monodisperse aerosol achieved a good bronchodilator response as assessed with the forced expiratory volume in one second (FEV_1), whereas the 1.5-micron MMAD aerosols achieved less airways bronchodilation with FEV_1 (10). However, overall the smaller particles achieved greater total lung deposition of drug compared to the larger particles. The authors explained this paradox by noting that the larger particles achieved a better bronchodilator response as the short-acting beta-2 agonist particles were preferentially depositing in the proximal large conducting airways where the beta-2 receptors were associated with a greater density of airway smooth muscle and the endpoint used to asses bronchodilator response, the FEV_1, was relatively more selective for eliciting a response in this lung region compared to the smaller aerosols depositing in the distal smaller conducting airways (10, 27, 28). Indeed, FEV_1 in spirometry is a marker of large airways (29). Since this study, the importance of targeting drug to the small conducting airways has been established, where small-airway dysfunction can be accurately assessed, occurs in obstructive airways diseases of asthma and COPD, and contributes to patient symptom burden and patient outcomes (24, 25). Importantly, inhaler formulations have been engineered to allow commercial devices that can be prescribed to patients that target drug to the large and also small airways, the whole airway tree, and have been shown to improve clinical outcomes compared to large particle therapy (23). In vitro studies have shown that small particles can be exhaled, with values documented as high as 70%; however, these used modes and breathing conditions that did not replicate the human lung and particles that were not therapeutic aerosols. Subsequent in vivo studies using inhaled drug particle show that small therapeutic drug particles are minimally exhaled 4–6% and in similar proportions to large drug particles exhaled 1–3%.

Other physicochemical properties that have been engineered to enhance deposition of inhaled drug particles have been altering the shape of the particles (30), utilizing electrostatic charge on particles (31), using low-density gases, such as helium (32), and changing aerosol properties with low-density large porous

particles (33). Particle size may not remain constant as a generated aerosol moves through a delivery system and the respiratory tract. Volatile aerosols may become smaller through evaporation droplets of pure water that evaporate rapidly even under conditions of 100% humidity because of increased pressure inside a small droplet caused by surface tension. For example, a 1-micron droplet of water will evaporate within 0.5 s at room ambient temperature, even under saturated conditions. A 10-micron droplet will evaporate within approximately 1 min (34). It has been shown that the humid airway environment may cause water-soluble hygroscopic drug particles to increase their size causing aerosolized particles to deposit more proximally compared to inert non-hygroscopic particles, yet this phenomenon of "hygroscopic growth" has been shown only using non-pharmacological aerosols in vitro experimentally and in healthy subjects in vivo, but not with therapeutic drug particles in actual patients with respiratory disease (35, 36).

Recent pharmaceutical engineering and developments in drug chemistry have focused on the formulation in pMDIs with respect to their propellants. The Montreal Protocol Treaty in 1989 established the need to eradicate the use of chlorofluorocarbons (CFCs) as propellants in the formulation in pMDIs to protect the ozone layer in the stratosphere, with consequent reformulation of pMDIs with non-ozone depleting propellants, such as hydrofluoroalkanes (HFAs) (37, 38). Reproducible delivery of inhaled drug had to be shown and also clinical outcomes, so some pMDI incorporated improved actuator design, new compatible elastomeric valve components, and changes in the orifice geometry (39, 40). The Kigali amendment of 2019 extends the coverage to HFA and there is innovation in low global warming potential propellants to replace the existing HFA propellants in pMDIs.

Patient Variables

The way each subject breathes also affects drug deposition in the airways. Respiratory frequency, tidal volume, and lung volume will affect the residence time of aerosols in the lungs, and hence the probability of deposition by gravitational and diffusional forces. Changing lung volume will also alter the dimensions of the airways and parenchyma. High level of ventilation during exercise and breath-holding represents extremes of breathing patterns which give rise to markedly different deposition patterns. The results of experiments measuring the effect of breathing pattern on the distribution of aerosol deposition indicate that a) total deposition decreases as breathing frequency increases; b) slow, deep breathing produces uniform deposition throughout the lung, but with little aerosol collection in the large airways; c) rapid, shallow ventilation results in enhanced large-airway deposition and marked heterogeneity in deposition distribution; and d) slow, shallow breathing at high end-expiratory volumes enhanced small-airway deposition (41). In clinics, the most important patient variable affecting inhaled aerosol deposition in the lungs is the breathing maneuver, which influences deposition efficiency and therapeutic efficacy of the inhaled drug particles. For pMDIs and the SMI a slow and steady inhalation over 5 seconds is optimal (42), and patients should be instructed to inhale "slowly, steadily, naturally, deeply and comfortably" [Usmani, personal communication]. It has been shown that a fast, rapid, and quick inhalation decreases aerosol in the lungs and increases oropharyngeal impaction (43). Actuation of pMDIs at the start of the inhalation maneuver during low lung volumes has been shown to enhance the deposition of inhaled drug within the lungs (44). It is important that prior to inhalation from any device that patients lift their chin up, in order to open the airway (45) and

also exhale to end tidal functional residual capacity in order to have enough inhaled volume to carry the drug particles in the inspiratory airstream (46). A greater inhaled volume on inspiration allows more aerosolized particles to be effectively deposited within the lungs and carried toward the peripheral airways (47). Instruction to patients to exhale the aerosol via the nose and not the mouth may be beneficial [Usmani, personal communication], where data show the dose of nasal corticosteroid may be significantly reduced in asthma patients with rhinitis (48). In contrast to pMDIs, DPIs are dependent upon the patient's inspiratory flow to operate and require quicker, faster inspiratory inhalation flows to generate sufficient peak inspiratory flow (PIF) and optimally de-aggregate the powdered drug from its carrier molecule and effectively aerosolize the powder into respirable inhaled particles in order to achieve adequate lung deposition (49). The internal resistance of a DPI, and hence the flow required to overcome this resistance, varies with different DPI designs (50). Of note, findings from observational studies (51, 52) suggest that 32–47% of inpatients admitted for exacerbations of COPD demonstrated a suboptimal PIF (<60 L/min) prior to discharge; suboptimal PIF was also reported in 19–78% of stable outpatients with COPD. Taken together, these findings suggest that many patients do not generate sufficient inspiratory force to overcome the resistance of prescribed DPIs. Several independent predictors for suboptimal PIF have been identified, including patient effort, female gender, shorter height, and older age (53, 54).

With the conventional nebulizers the ideal breathing maneuver is relaxed tidal breathing by the patient, and where some new nebulizer devices assess the patient's breathing maneuver and pulse to deliver aerosolized drug only during the inhalation phase leading to a more efficient system and less drug wastage. As discussed, at the end of the inhalation maneuver the breath-hold pause enhances the deposition of inhaled drug in the lungs, with the required airway residence time for the aerosolized particles to make contact with the airway walls through the deposition mechanisms of gravitational sedimentation and diffusion (44).

The configuration of the lungs and airways is important since the efficiency of deposition depends, in part, upon the diameters of the airways, their angles of branching, and the average distances to alveolar walls. Furthermore, along with the inspiratory flow, airway anatomy specifies the local velocity of the airstream, and thus whether the flow is laminar or turbulent. There are inter-intra-species differences in lung morphometry; even within the same individual, the dimensions of the respiratory tract vary with changing lung volume, with aging, and with pathological processes. A highly significant change in the effective anatomy of the respiratory tract occurs when there is a switch between nose and mouth breathing or when the nose is bypassed by a tracheostomy or by an endotracheal tube. The nose has a major role as a collector of inhaled aerosol particles. The combination of a small cross-section for airflow, sharp curves, and interior nasal hairs helps maximize particle impaction. The loss of filtering capacity of the nose may be involved in the exercise-induced asthma. With rising levels of exercise and increasing ventilation, the high-resistance nasal pathway will be abandoned in favor of the low-resistance oral pathway, thus increasing the exposure to more aerosol particles particularly large particles, such as pollen particles. Respiratory diseases markedly influence the distribution of inspired particles. Bronchoconstriction will lead to diversion of flow to non-obstructive airways. With advancing diseases, the remaining healthy airways may be exposed increasingly to inspired particles. Narrowing by inflammation or mucus can increase linear velocities of airflow, enhance