Lung Biology in Health and Disease

Inhalation Aerosols

Physical and Biological Basis for Therapy

Third Edition

edited by
Anthony J. Hickey
Heidi M. Mansour

CRC Press
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Preface

Inhalation aerosols continue to be the basis for successful lung therapy for a variety of diseases. Since the turn of the millennium, many new products have been approved. Arguably the most substantial have been the first approved inhaled drugs and drug combinations for the treatment of chronic obstructive pulmonary disease (COPD). More recently, the development of drugs to treat pulmonary infection and diabetes has continued the translation of drug therapy to aerosol technology. With this background, it is evident that technological advancements and therapeutic strategies have evolved since the first two editions of this book were published. The original focus on asthma as the most significant target of inhaled therapy has broadened to include numerous local and systemic diseases. And the range of technology forming the basis for novel inhaler design has expanded significantly.

In this text, rather than simply expand and update the original two editions, we decided to address the close integration of technology with its application. An introductory section (Part I) on the fundamental science acts as a transition from past volumes to the present text by presenting briefly the general considerations that apply to physical chemistry, device technology, aerosol physics, lung deposition, clearance, physiology, and pharmacology. Part II represents a new approach in which a disease and therapeutic agent focus is employed to illustrate the application of a technology. It is evident from the number of chapters in this section (13) that the opportunities for the application of aerosol drug delivery have increased dramatically in recent years. Finally, an integrated strategies section (Part III) draws the major points from the applications regarding disease targets and drug products in the form of generalizations that may be valuable to readers.

In modifying the approach to the structure of the book, we are aligning with the translational imperative that has emerged in the last decade. In addition, this third edition is aligned with the latest scientific initiatives on precision medicine that has been gaining much attention recently. This approach encompasses precision pulmonary medicine. The ability to extract knowledge rapidly and effectively from study data and apply it in a therapeutically relevant manner is considered an urgent demand of the scientific and clinical research community. In presenting the content as described in this preface, we hope that relevance to development and clinical evaluation can be established.

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Editors

Anthony J. Hickey, PhD, DSc, is Distinguished RTI Fellow at the Research Triangle Institute (2010–present), Emeritus Professor of Molecular Pharmaceutics of the Eshelman School of Pharmacy (1993–2010), and Adjunct Professor 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 then joined the faculty at the University of Illinois at Chicago (1988–1993). In 1990, he received the American Association of Pharmaceutical Scientists (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), the 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 U.S. patents on a variety of inhaler device technologies, and 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; and founder and CEO of Astartein, Inc. (2013–present). He is a member of the Pharmaceutical Dosage Forms Expert Committee of the United States Pharmacopeia (USP, 2010–2015, Chair of the Subcommittee 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.

Heidi M. Mansour, PhD, RPh, is a tenured Associate Professor of Pharmaceutical Sciences in the College of Pharmacy with joint faculty appointments in the BIO5 Research Institute and the College of Medicine in the Division of Translational and Regenerative Medicine at The University of Arizona (UA) in Tucson, Arizona. Dr. Mansour has faculty member affiliations in the UA Institute of the Environment, and the UA NCI Comprehensive Cancer Center. She lectures in the BS Pharmaceutical Sciences undergraduate program, the Pharm. D. professional program and in the Pharmaceutics and Pharmacokinetics track of the graduate program at The University of Arizona. In addition to teaching, Dr. Mansour serves as Faculty Advisor in the Pharm. D./PhD Dual Degree Joint Program and Director of the Pharmaceutics and Pharmacokinetics track in the Pharmaceutical Sciences graduate program in The UA College of Pharmacy. Dr. Mansour has published over 80 peer-reviewed scientific journal papers, 9 book chapters, 2 edited books, and over 100 scientific conference abstracts. She serves on the editorial advisory boards of the Royal Society of Chemistry *Molecular Systems Design & Engineering*, APhA/FIP *Journal of Pharmaceutical Sciences*, and *Pharmaceutical Technology*.

Dr. Mansour is an annual Faculty Instructor at International Society of Aerosols in Medicine (ISAM) Aerosol School, instructor in two online webinars on inhalation aerosol drug delivery, and instructor in Buchi Advanced Spray Drying short courses. She was recently Co-Chair of the Drug Delivery: New Devices & Emerging Therapies Group in ISAM, and has been an expert member of the National Institutes of Health (NIH) NICHD U.S. Pediatric Formulations Initiative New Drug Delivery Systems Aerosols Working Group for several years. Dr. Mansour currently serves on the Drug/Device Discovery and Development (DDDD) Committee of the American Thoracic Society (ATS). She regularly serves as an expert reviewer for scientific journals and grant funding agencies,

including NIH study sections; Department of Defense (DOD) study panels; National Science Foundation (NSF) study panels; American Association for the Advancement of Science (AAAS); Catalent Drug Delivery Institute; and international funding agencies such as the German–Israeli Foundation, German International Exchange Service (DAAD), Cochrane Airways Group of the National Health Service (London, United Kingdom), Engineering and Physical Sciences Research Council (London, United Kingdom), PRESTIGE Postdoc Fellowship Programme of the European Commission (Paris, France), and the Biomedical Innovation Program of the French National Research Agency (Paris, France).

In addition to serving on NSF study panels, NIH study sections, and international study panels in the European Union and Great Britain, her innovative research program continuously attracts competitive funding awards from federal sources (NIH, NSF, FDA, DOD) and the pharmaceutical industry. In addition to lecturing in the BS Pharmaceutical Sciences undergraduate, PhD graduate, and Pharm. D. professional programs, Dr. Mansour leads her research labs where she trains postdoctoral scholars, visiting scholars, visiting professors, graduate students, Pharm. D. student researchers, and physician-scientist (MD/PhD) fellows. As Major Professor and mentor, her research program has successfully graduated several PhDs. Her innovative research program has produced assistant professors employed at research universities in the United States and in the Republic of South Korea, and senior research scientists employed at major pharmaceutical companies in the United States.

Dr. Mansour is an active, long-time member of several scientific organizations and elected member to honor societies, including the Sigma Xi Scientific Research Honor Society, Rho Chi Pharmaceutical Honor Society, and Golden Key International Honor Society. A registered pharmacist for over 20 years, she earned her BS in pharmacy with honors and distinction, a PhD minor in advanced physical and interfacial chemistry (Department of Chemistry), and a PhD major in drug delivery/pharmaceutics (School of Pharmacy) from the University of Wisconsin–Madison. Also at the University of Wisconsin–Madison, she was a clinical instructor for a few years. Having completed postdoctoral fellowships at the University of Wisconsin–Madison and at the University of North Carolina–Chapel Hill, she was awarded the University of North Carolina–Chapel Hill Postdoctoral Award for Research Excellence from the Office of the Vice-Chancellor, the AAPS Postdoctoral Fellow Award in Research Excellence, and the PhRMA Foundation Postdoctoral Fellowship Award. As an instructor, she served on the Graduate Faculty at the University of North Carolina–Chapel Hill.

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Introduction

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The evolution of inhalation aerosol technology over the last half-century has created unique opportunities to treat disease. The fundamentals of pharmaceutical aerosol generation and delivery are well established and require the consideration of physical pharmacy, aerosol physics, device technology, process and product engineering, and pulmonary biology. The latter includes knowledge of lung deposition, clearance, and local and systemic pharmacology of delivered drugs.

As the use of aerosols in the treatment of disease has been explored, a greater understanding of the best therapeutic approaches has been developed. The nature of questions regarding selection of technologies has progressed from a desire to be informed about performance specifications to greater curiosity about the suitability of the technology for a specific disease therapy. The facility with which particular technologies can be adapted for use allows the optimization of all elements of the inhaled drug product to meet the needs of the biological and therapeutic endpoints.

A number of outstanding texts on the subject of aerosols and aerosol technology have been published (1–7). In the field of inhalation aerosols, the focus varies from fundamental science (8,9) and technology (10–15), and expands to clinical application (16–18) and the entire topic of drug delivery and translation to the clinic (19). The present text is arranged to cover some basic principles and then to focus extensively on translation of pharmaceutical inhalation aerosol technology into the clinic to treat specific diseases. Figure I.1 indicates the sequence of topics this volume covers.

The fundamental aspects of medicinal aerosol delivery may be considered as a sequence of events that first involve the formation of the aerosol from a variety of formulations and devices, each of which is optimized for a specific application. Once the aerosol is formed, the physicochemical properties and airborne behavior of the aerosol interacts with the pulmonary physiology to dictate deposition and disposition of drugs from the lungs. These properties and parameters can be modeled to predict deposition of particles and droplets in the lungs, and these predictions can be supplemented with experimental measures of deposition achieved by radiological imaging. After deposition, disposition can be followed by considering local transport and metabolism in the context of the systemic appearance of drugs in pharmacokinetic studies. Each of the common therapeutic aerosol systems can be evaluated for its potential to serve the needs of particular diseases.

A major debilitating lung disease, asthma has been the primary focus of aerosol treatment since the 1950s. As the understanding of key elements of effectiveness was identified, aerosol treatment has been expanded to include a wide range of diseases. Chronic obstructive pulmonary disease (COPD) was a logical target for treatment as manifestations of this disease are similar to asthma. As the vision of aerosol therapy broadened and new drug and biochemical targets were identified, other areas such as genetic disorders, airway remodeling, vascular disease, and infectious disease have received considerable attention, from which new products have been developed.

As in other areas of human endeavor, the discoveries that have occurred in the parallel field of research serve to inform each other in a manner that synergistically moves the field in a sometime discontinuous or disruptive manner. Several recent events have promoted discoveries and inventions. The most substantial was the implication of chlorofluorocarbon (CFC) propellants in ozone depletion and their subsequent phase-out, which resulted in the development of hydrofluoroalkane (HFA) alternatives. A similar phenomenon is now occurring as the role of HFAs in global warming is evident and the desire for potential alternatives is driving new developments. A second event of arguably similar magnitude to the propellant replacement was the desire for methods to deliver the products of biotechnology that were difficult to prepare as stable formulations, that were difficult to deliver by other routes of administration, or that would simply benefit from the characteristic disposition from the lungs. The need for a stable formulation and dose considerations resulted in a focus on dry powder inhalers (DPIs), which were until the late 1980s were poorly designed and inefficient systems with respect to the needs for macromolecule delivery. The innovations arising from the research of the following twenty years, particularly that focused on insulin delivery, elevated the field significantly and positioned the technology for the many successes that have occurred since 2000. Finally, the same drivers in the context of aqueous solution aerosol delivery resulted in an evolution from the dominant theme of air jet and ultrasonic

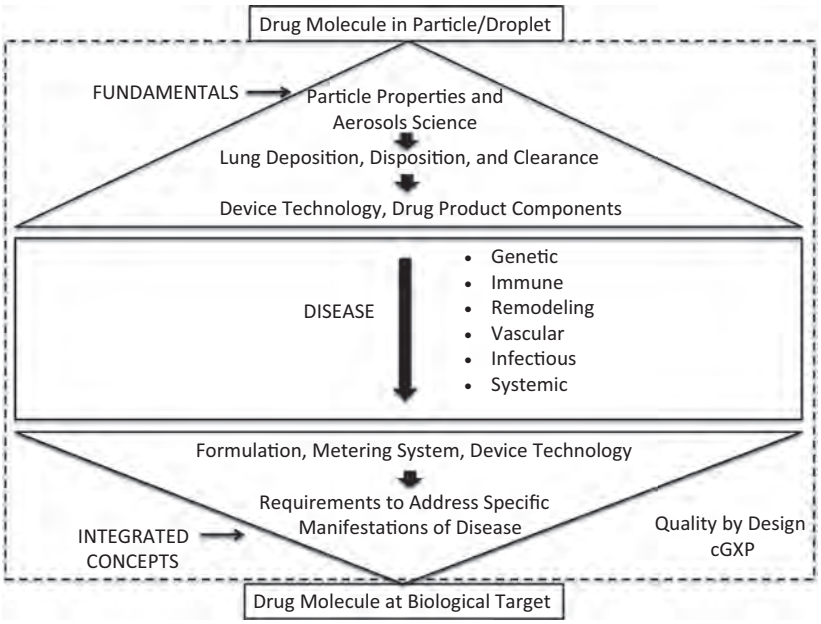

Figure I.1 The sequence of topics addressed in this text. Fundamental considerations are the foundation for the adoption of technologies to treat specific diseases. Knowledge gained from these experiences can be integrated to establish general principles that may be used prospectively in transferring the drug molecule from its starting environment to the proximity of its biological target. Many of the intervening steps are controlled either in manufacturing or in patient training.

nebulizers to smaller, more efficient vibrating mesh nebulizers and ultimately to handheld soft mist inhalers (SMIs).

As progress has been made to apply the fundamental understanding of the dosage forms and the route of administration to the context of specific diseases, an integrated body of knowledge can now be drawn together to make general observations about the foundation of technology available and its impact on certain aspects of disease.

The complexity of inhaled products and the multitude of factors that affect their performance requires a quality by design (QbD) approach if overall quality is to be ensured. The spatial (chemical and physical structure) and temporal (motion and disposition) behaviors of the product are subject to change by a range of variables, and each variable requires sufficient monitoring and control to meet product specifications and regulatory approval. The efficacy and safety of the product are linked to quality metrics, since the characteristic therapeutic needs of each disease are matched to the performance of the drug product.

Subsequent chapters of the book will guide the reader through the fundamentals (Part I) into specific disease considerations with translation to precision pulmonary medicine (Part II) from which integrated expositions on the nature of technology and the impact of disease considerations will be concluded. The importance of developing products in a controlled environment and the ways in which this might be translated into a uniform therapeutic outcome are discussed (Part III). This systematic method ideally accounts for the drug molecule from its starting environment, accounting for adjacencies, to its presentation to the molecular therapeutic target, controlling as many of the intervening variables as possible.

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PART I

Fundamentals

1

Physicochemical properties of respiratory particles and formulations

BORIS SHEKUNOV

INTRODUCTION: PHYSICOCHEMICAL PARTICLE PROPERTIES AND INHALER PERFORMANCE

Drug delivery by inhalation can be considered as a sequence of three equally important stages: particle aerosolization within an inhaler device (as solid particles or liquid droplets); particle deposition/distribution in the airways and, finally, drug release/particle uptake/clearance at the site of action. The anatomy of respiratory tract presents a natural barrier to any particulate matter and, if particles penetrate into the deeper lungs, they tend to be rapidly removed by one of the physiological defense mechanisms (1,2). Consequently a major goal of respiratory drug delivery is to optimize physicochemical particle properties in order to achieve the maximum efficacy and safety of these dosage forms. The physicochemical properties of respiratory formulations can also be classified in accordance with their material characterization level and in relationship with their biopharmaceutical effects as illustrated in Table 1.1. This table also contains information pertinent to regulatory considerations during development, quality control and bioequivalence studies of inhalation drug products (3–6). Particle size distribution, in combination with the particle density and shape factor, is the most important critical attribute for any respiratory formulation and at each drug delivery stage: it determines the ability of formulation to be efficiently aerosolized at predefined inspiratory flow rates, controls the particle deposition profile, drug dissolution and particle uptake rates. Particle inertial deposition is typically associated with the fine particle fraction (FPF) between 1 and 5 μm in terms of the aerodynamic diameter, d_A, with maximum deposition in alveoli region between 1 and 2 μm. It is also known that particles with $d_A \approx 100$ nm also exhibit a peak related to the deposition by Brownian diffusion mechanism (1), although generating such nanosize aerosols is rather hypothetical. Particles in the micron, and especially the submicron, range are very cohesive. Small variations in size, surface and morphology, and some environmental conditions can significantly affect the powder aerosolization leading to low or, even worse, inconsistent FPF. Particles that deposit into the alveolar region are removed by phagocytosis, which may influence the efficacy of drug formulation (2,7). For this uptake, the volume-weighted particle diameter, d, and surface-to-volume shape factor, α_{sv}, are important: for example, spherical particles 1–5 μm are taken at a greater extent than smaller or larger particles, or particles of acicular shape, or those with modified surface and charge. By using different means of particle engineering it is therefore theoretically possible to optimize most drug delivery characteristics. There are, however, very significant practical limitations to that imposed by the inherent material properties of active pharmaceutical ingredients (APIs) and carriers, their toxicology, the inhaler design, the patient variability, as well as by the stringent requirements of drug product manufacturing and pharmaceutical quality control.

Table 1.1 Different levels of physicochemical functionality in relationship to major biopharmaceutical and drug delivery characteristics, combined with its regulatory considerations for development, bioequivalence, and quality control of inhalation drug products

Physicochemical characteristics	Affected biopharmaceutical parameters	Related regulatory considerations
Solid State		
Molecular structure, impurities; crystal form/crystallinity/amorphous content; equilibrium solubility, intrinsic dissolution rate; hygroscopicity / moisture content	Physical and chemical stability, potency, safety; systemic bioavailability and/or local drug concentration; bioequivalence (for generics)	Physicochemical characterization of API(s) and excipients relevant to their functionality in drug product; compatibility with diluents[c]; effects of environmental moisture[a,b], low temperature[b]; temperature cycling[b,d]; moisture content[a,b]; sameness/therapeutic equivalence of API (generics).
Particulate and Surface		
Volume or mass-weighted particle size distribution (PSD); shape factor and specific surface area; porosity/density; rugosity/asperity and rigidity; specific surface free energy, work of cohesion and adhesion; electrostatic charge or zeta potential; dissolution rate; dose delivered (emitted dose); fine particle dose/mass (*FPD*); aerodynamic particle size distribution (APSD): *MMAD/GSD; FPF*	*In vivo* regional deposition profiles; dose delivered; dose uniformity/ consistency; rate of particle uptake/ clearance and toxicity; systemic bioavailability (AUC/C_{max}) and/or local drug concentration; bioequivalence (for generics)	PSD (for APIs and carriers); ASPD; single actuation *FPD*[a,b,d]; (delivered) dose content uniformity (*DCU*)[a,b,d] (containers intra- and inter-batch) or uniformity of dosage units[a,c,d]; *DCU* and *FPD* at various flow rates[a] and at various lifestages (i.e., beginning, middle, end)[a,b,d]; *FPD* with spacer[b]; actuator/mouthpiece deposition[a,b,d]; shaking requirements; drug delivery rate and total drug delivered[c]; foreign particulate matter.
Formulation		
Type of formulation, dosage form and packaging presentation; carrier(s)[a,b], composition and coating[a,b]; dispersion media[b,c,d]; powder triboelectric charge, bulk and tapped density[a]; aggregate structure, density and strength; impact of processing/mixing; bulk flow properties/powder handling/filling[a].	Mode of administration; immediate, sustained or controlled drug delivery; dose metering, devise retention; dose uniformity/consistency; systemic bioavailability and/or local drug concentration; therapeutic efficacy and therapeutic index; ADME; safety/ toxicology/ irritability; storage stability/ shelf life; bioequivalence (for generics).	Assay, mean delivered dose vs. label claim[a,b,d]; *DCU*[a,b,d]; dose proportionality (for different strengths and/or APIs); formulation/ inhaler robustness; drug product stability; qualitative (Q1) sameness and quantitative (Q2) equivalence of excipients and media physicochemical similarity[c] (generics).

[a] DPIs.
[b] pMDIs.
[c] Nebulizers.
[d] Non-pressurized metered-dose inhalers; otherwise generally applicable.

The medical science of respiratory drug delivery is discussed in the following chapters of this book. The present chapter is concerned with material science—physicochemical particle properties that directly impact formulation and inhaler design, especially for dry powder inhalers (DPIs). Although other type of devices such as pressurized metered-dose inhalers (pMDIs), nebulizers and non-pressurized metered-dose inhalers/soft mist inhalers are very important; the range of material science issues with them is much narrower. The fundamental reasons for this observation will also be discussed. DPIs certainly belong to the cutting technological edge, due to the wide range of different active ingredients, doses, formulations as well as current and potential therapeutic applications (8). They also present the greatest challenges in pharmaceutical development, and from the regulatory viewpoint, are considered one of the most complex drug products (4). Since the early application of DPIs in the 1960s, there has been a great body of work done and literature accumulated for this technology, but there are still many unresolved fundamental issues. In recent reviews, for example, it has been pointed out that

lack of understanding of powder dispersion mechanisms is a major obstacle to improved inhaler performance (9). Several misconceptions are highlighted in relationship to optimal inhaler performance with the air-flow independent therapy (8), device resistance and application of high-resistance devices by patients with reduced lung function (8,10). It was noted that surprisingly little attention has been given to the improvement of inhaler designs and new integrated device-formulation systems, with most modern inhalers still delivering only 20%–30% FPF of the label claim (10). For the carrier-based formulations, the consensus is that the relationship between properties of the starting materials, the mixing process, and dispersion performance is not well understood and constitutes a mostly empirical endeavor (11). This list of misconceptions can further be extended to other areas of inhalation material science including, for example, mechanisms of interparticle interaction, dispersion, particle dissolution and solid-state stability of amorphous formulations, as discussed in this chapter.

Although the complexity of interactions within the triad "formulation—airflow—inhaler design" should not be underestimated, in the author's opinion many of these gaps are methodological. For instance, one may consider independence of FPF from the airflow as a desirable characteristic for any respiratory formulation, but this point needs to be clarified in conjunction with a specific inhaler design. If formulation is readily fluidizable and dispersible at any flow rate, this implies a low "threshold energy" (or, more precisely, minimal stresses required for powder disaggregation, see the section called "Major factors affecting particle aerosolization") with very high FPF approaching the ideal 100%. Also for such particles, the inertial impaction parameter is sufficiently small to bypass deposition in the upper respiratory tract resulting in low *in vivo* variability (12). In practice, however, neither formulation nor inhaler are perfect, so if FPF increases steadily with flow or pressure drop, this most likely indicates a cohesive formulation and variable dispersion mechanism, whereas a steady but low FPF value may suggest a problem with either formulation or inherent inhaler design and may, in fact, be attributed to the fundamental properties of turbulent flow, as shown below. A significant issue here is that flow rate, pressure drop and inhaler resistance are usually not related quantitatively to the material characteristics of the formulation (e.g., particle adhesion/cohesion and aggregate strength), flow regime (character and intensity of turbulence) or the inhaler performance in terms of FPF or other measurable aerosolization parameters. Indeed, the most widely used approach consists of an array of empirical studies, oriented towards proving how certain formulation properties are important for better inhaler performance. Even when supported by the design of experiments (DoE), these studies often lead to contradictory conclusions and, by their nature, cannot result in generalized models (13). Of course, such studies may solve some short-term problems of industrial development or commercial production. On the other hand, more recent applications of computational fluid dynamics (CFD) predominantly concentrate on the description of aerodynamic flow fields, but usually do not contain principal closure equations of particle aerosolization and dispersion. Understanding of these mechanisms, in turn, requires a purposeful experimental methodology to determine the key material and fluid dynamic parameters, rather than statistical correlations.

The major objective of this chapter is not to review previous developments of inhalation particle technology or formulations, an extensive topic already covered by multiple recent publications (e.g., 1,8,10,11,14–17). Although a comprehensive assessment is also difficult to accomplish in a single chapter, the main intention here is to provide the reader with a systematic quantitative description of the key physicochemical parameters and, when possible, relate these parameters to the inhaler performance using analytical concepts developed for this work. In what follows, the definitions are introduced and mechanisms discussed by which the physicochemical properties of solid particles and liquid drops are translated into the drug delivery characteristics of pharmaceutical aerosols, most important, the FPF. This is concluded with a brief review of different formulation approaches and optimization strategies, and future perspectives in this important and fast-growing therapeutic field.

MAJOR FACTORS AFFECTING PARTICLE AEROSOLIZATION

Aerodynamic diameter and Stokes number

Particles for inhalation may not only have different geometric size (usually defined through the volume-equivalent diameter, d, [18]) but also exhibit different shape, density/porosity and aggregate structure. In order to standardize the fluid dynamic equations for different kinds of particles, the concept of aerodynamic diameter, d_A, is introduced. It is defined as the diameter of spheres of unit density, which undergo the same acceleration in the air stream as non-spherical particles of arbitrary density, therefore moving along the same streamlines. Following this definition, the general dynamic equation leads to the following relationship:

$$d_A = d\frac{\rho}{\rho_1}\frac{1}{\alpha_{sv}}\frac{C_d\left(Re_A\right)}{C_d\left(Re\right)}\frac{C_c\left(Re\right)}{C_c\left(Re_A\right)} \tag{1.1}$$

where ρ_1 is the unit density (e.g., 1 g/cm^3) and ρ is the particle density. C_d is the particle drag coefficient which is a function of the particle Reynolds number, $Re = ud/\upsilon$, where υ is the air kinematic viscosity, u is the particle (slip) velocity relative to the air stream. Re_A and Re denote numbers for particles with diameters d_A and d, respectively. C_c is the Cunningham slip correction factor dependent on the particle diameter (18,19). Experimentally, the aerodynamic particle size distribution (APSD) is typically measured using cascade impactor devices such as Andersen cascade impactor, next generation cascade impactor (NGI) and muti-stage liquid impinger (MSLI), all of which operate on the principle of particle classification by using a series of jets and collection plates with different Stokes numbers (see below). APSD can also be measured using time-of-flight (TOF) techniques (18).

Surface-to-volume shape factor, α_{sv}, is the ratio of the characteristic particle cross-section with equivalent diameter, d_s, to that of the particle with volume-equivalent diameter, d:

$$\alpha_{sv} = \left(\frac{d_s}{d}\right)^2 \tag{1.2}$$

Equations (1.1) and (1.2) define this shape factor through the particle geometry, whereas the drag coefficients are written for the spherical particles, thus decoupling these quantities. This definition is different from the dynamic shape factor considered elsewhere (18,19). The advantage is that it can be determined experimentally from microscopic image analysis, or from other measurements given independent assessment of both d and d_s. These parameters are usually measured through a combination of laser diffraction and microscopic imaging studies. For solid particles with density ρ_p, it is useful to define α_{sv} (for randomly oriented particles) through the specific surface area (SSA) which are related through the well-known Cauchy theorem stipulating that the mean projected area is equal to quarter of the surface area, leading to the following expression:

$$\alpha_{sv} = \frac{1}{6} SSA\, \rho_p d \tag{1.3}$$

whereby SSA can be determined from the Brunauer–Emmett–Teller (BET) gas adsorption measurements.

The general equation (1.1) is solved numerically and equally applicable to droplets, solid particles, porous particles and aggregates provided that the particle density (or void fraction for aggregates) and particle shape factor are known. The flow regimes applicable to respiratory delivery or measurements can be defined as Stokesian ($Re < 0.1$) and ultra-Stokesian ($0.5 < Re < 100$). For the spherical particles in the Stokesian flow regime, the drag coefficient assumes the well-known relationship: $C_d = 24/Re$. Also, taking $C_c \approx 1$ for the micron particle size range (the estimated error <10% for particles approximately 2 µm in size [19]), Eq. (1.1) leads to the simplified expression for Stokes aerodynamic diameter widely used in the aerosol literature:

$$d_A(Stokes) = d\left(\frac{\rho}{\alpha_{sv}\rho_1}\right)^{1/2} \tag{1.4}$$

Thus non-spherical particles and porous particles have a smaller aerodynamic diameter than solid spherical particles of the same mass. For liquid aerosols, such as nebulizer and pMDIs sprays, the droplet particle shape is also not completely spherical due to deformation by air stresses, as will be discussed in the following sections.

The dimensionless Stokes number (given here as the generalized effective Stokes number, Stk_e), can be viewed as the ratio of the characteristic particle relaxation time under the drag, to the characteristic flow time around the obstacle (20). At small $Stk_e << 1$, a particle follows the fluid streamlines whereas at $Stk_e >> 1$, particle follows its initial trajectory and impact the obstacle. This definition depends on the particle Re number (20,21):

$$Stk_e = \psi\left(Re\right) Stk \tag{1.5}$$

where Stk is this number in the Stokesian flow regime ($\psi = 1$):

$$Stk = \frac{\rho d_A^2 u}{18\,\mu L} \tag{1.6}$$

$\mu = \upsilon\rho_0$ is the dynamic air viscosity and L is the characteristic dimension of an obstacle. The non-Stokesian particle drag correction factor, ψ, can be calculated numerically (21). The importance of the Stokes number is that it can describe at least three categories of events:

1. Deposition by inertial impaction in the upper airways defining the fine particle dose (FPD) delivered to the lungs. The "inertial impaction parameter," $d_A^2 Q$ (according to Eq. [1.6]), is often used to describe the mouth-throat deposition (12).
2. Measurements of the aerodynamic particle diameters (e.g., mass-median aerodynamic diameter [MMAD]) and fine particle fraction (FPF) with different cascade impactors or liquid impingers, typically used for *in vitro* R&D studies and industrial quality control of different inhalers; and applied for recalibration of impactor cut-off diameters at different flow rates Q (18).
3. Efficiency of particle deaggregation within the DPIs, in particular those purposely designed for particle impaction.

One may consider possible deviations introduced in Eqs. (1.1) and (1.5) in the ultra—Stokesian flow regime. Although the particle Re is much smaller than corresponding numbers for airflow within both the human respiratory system and inhalation devices, it can reach levels sufficiently high to introduce non-Stokesian corrections. For example, for a turbulent flow (at least at the peak airflow rate) in the mouth-throat, $Re \approx 1$, for particles below 10 µm, which give the value of $\psi \approx 0.9$, so the effect on the throat deposition is likely to be minimal. However, for the turbulent flow within the inhaler itself, and for larger aggregates, Re may reach one or two orders of magnitude higher (see the section called "Modelling of dry powder dispersion"), thus $\psi \approx 0.4$–0.8, introducing a significant correction, for example, in assessing the particle impaction on an inhaler grid. Similarly, calculations of the precise cut-off diameters in the cascade impactors may require application of complete Eqs. (1.1) and (1.5) (18).