RESEARCH PAPER

Principles of lung physiology, deposition mechanism for pulmonary drug delivery

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ABSTRACT

This method of drug delivery to the lungs is scientifically and clinically of relevance in treatment and management of respiratory diseases as therapeutic agents get exposed to direct exposure of the lungs. A rational development of the inhalable preparations that are efficient necessitates a detailed understanding of the lung physiology and means of aerosol deposition, which defines the movement, deposition, and retention of drugs in the system. A highly branched airways, large alveolar surface area, thin air-blood diffusion barrier, the lining of the pulmonary surfactant as well as the presence of dense capillary network characterize the respiratory system, and thus affect the deposition, dissolution and absorption of drugs. Irrespective of these benefits, the physiological defense system e.g. mucociliary clearance within the airways conducting the flying as well as the alveolar macrophage phagocytosis of the deep lungs serve as significant obstacles to protracted pulmonary delivery and therapeutic efficacy. The inherent processes such as inertial impaction, gravitational sedimentation, and Brownian diffusion contribute a great deal in the inhaled particle deposition, which is strongly dependent on the aerodynamic properties of particles, their density and breathing specificities of a patient. The local distribution of drugs by these deposition processes and have a significant role to play in attaining the desired targeting in the deep lung, which houses many respiratory diseases such as pulmonary tuberculosis.

The chapter introduced a mechanistic approach that connects the physiology of the lungs, together with aerosol deposition, which provides the scientific basis underlying rational approaches in design and optimization.

Keywords: Pulmonary drug delivery, Lung physiology, Aerosol deposition, Inhalable drug delivery systems, Particle deposition mechanisms, Pulmonary tuberculosis, Respiratory drug delivery

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INTRODUCTION

Respiratory diseases are one of the greatest global health burdens, as a group of diseases that affect more than one billion people worldwide. Asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), pulmonary tuberculosis (TB), idiopathic pulmonary fibrosis (IPF), and lung cancer are conditions that cause enormous morbidity, mortality and social economic costs [1,2]. The COVID-19 outbreak only highlighted the susceptibility of the respiratory system and motivated the world to become interested in pulmonary therapy and mucosal vaccines delivery [3].

The pulmonary route of drug delivery presents a list of benefits in comparison with the traditional oral and parenteral routes that is hard to resist. The therapeutic agents direct to their target site- the airway epithelium or alveolar space- allows high local concentrations and greatly reduces systemic exposure, leading to minimal off-target toxicity [4,5]. The huge surface area of the lung (~80100 m 2) is highly vascularized with a thin diffusion barrier and lacks hepatic first-pass metabolism, making it an ideal portal not only to local respiratory therapy but also to systemic delivery of biologics including insulin, peptides and monoclonal antibodies [6,7].

Although these benefits exist, successful drug delivery to the lungs is complicated by a complex of physiological obstacles which the respiratory system has adapted to keep out of the breathing system foreign particles. The combined

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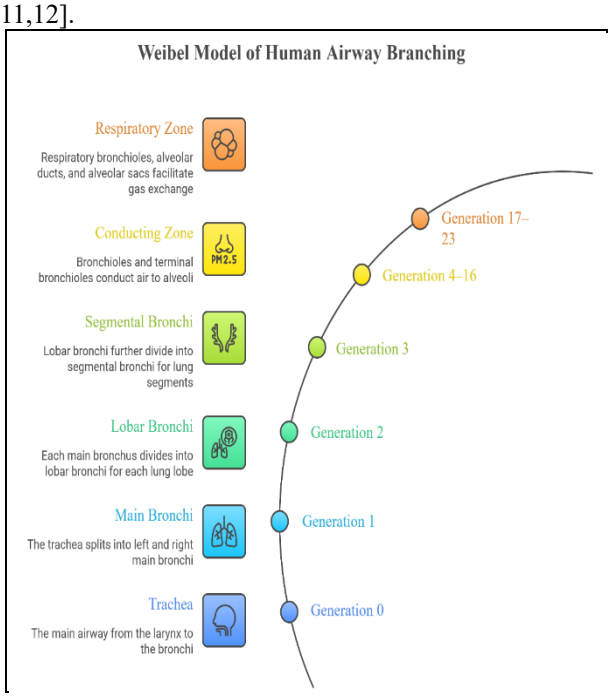
effects of mucociliary clearance, alveolar macrophage phagocytosis, enzyme metabolism and the mucus-surfactant continuum contribute to restricting the residence time and bioavailability of inhaled therapeutics [8,9]. The aerosol deposition science (including inertial impaction, gravitational sedimentation, and Brownian diffusion) further determines the location in the respiratory tract in which a drug particle eventually settles, which has a significant impact on its therapeutic effect [10].

Inhalable formulation rational design requires a combined knowledge of lung anatomy, cellular physiology, aerosol physics and patient-patient specific factors including breathing patterns and changes in disease states. The chapter contains a mechanistic explanation that bridges the gap between lung physiology and deposition science, acting as a scientific basis to designing and optimizing future pulmonary drug delivery systems. It pays special attention to deep lung targeting approaches, especially in pulmonary tuberculosis - disease, the pathogen of which is located exactly in the alveolar macrophages of the deep lung [11,12].



2. Anatomy and physiology of the respiratory system

2.1 Structural Organization of the Airways

The human respiratory system is structurally beautiful, hierarchically branched structure that is optimized in bidirectional exchange of gases. It is traditionally subdivided into the conducting zone (generations 0-16) and the respiratory zone (generations 17-23), a classification based on the seminal symmetric dichotomous branching model of 1963 of Weibel a model that is still at the heart of aerosol deposition models today [13].

Its origin is the trachea (generation 0), a cartilage-strengthened tube with a diameter of about 1.8 cm, which runs through the primary bronchi (generation 1), lobar bronchi (generation 2), segmental bronchi (generation 3), and smaller bronchioles to the terminal bronchioles (generation 16). The cumulative cross-sectional area of this region is exponentially generational, which changes to laminar airflow as it nears the terminal bronchioles [14]. More importantly, the conducting zone is the anatomical site of mucociliary clearance and is the main site of deposition of large aerosol particles (>5 μm) through inertial impaction [15].

The respiratory zone starts with the respiratory bronchioles (generation 17), the first to contain alveoli, then by alveolar ducts (generation 22) into the alveolar sacs (generation 23). This gradual development of alveoli in this area produces an exponential expansion in surface area, which reaches a high of the 480 million alveoli in the adult human lung providing a total alveolar surface area of 80100 m2 [16]. The therapeutic target of deep lung delivery plans and systemic drug absorption is this huge surface area equivalent to a tennis court.

2.2 Cellular Architecture Relevant to Drug Delivery

The epithelium of the airways is a ciliated columnar layer, which is pseudostratified in the trachea and bronchi and becomes a simple cuboidal epithelium in the terminal bronchioles. It consists of ciliated epithelial cells, goblet cells that produce mucus, Club cells (Clara cells) that carry out xenobiotic metabolism and the release of surfactant-proteins, and basal progenitor cells [17]. Goblet cell density, and thus mucus production, is significantly increased in inflammatory diseases like asthma and COPD, enhancing barrier properties and making aerosol penetration challenging [18].

Two types of pneumocytes predominate on the alveolar surface. Gas exchange is carried out by type I pneumocytes, which cover approximately 95% of the alveolar surface area and are made of thin, squamous cells (0.1-0.2 μm thick). They are very thin, which makes the air-blood diffusion barrier essentially sub-micron; this property is clinically used in pulmonary delivery in biologics and systemic drugs [6]. Alveolar repair Type II pneumocytes are less abundant, but synthesize and secrete pulmonary surfactant and act as progenitor cells. The sentinel immune cell of the lung is the alveolar macrophage (AM), which is located in the alveolar lumen and performs the functions of phagocytosis of inhaled foreign particles and being a crucial defense mechanism, as well as an intracellular reservoir of the pathogen in the case of Mycobacterium tuberculosis infection [19,20].

2.3 Biophysical Parameters Critical to Drug Delivery

The destiny of drugs inhaled is directly dependent on several biophysical characteristics of the lung. This large absorptive surface (alveolar surface area, 80100 m^2) has an enormous absorptive interface, much greater than the gastrointestinal surface area used to deliver drugs orally (200 m^2), but with the added benefit of a much smaller epithelial capillary distance (0.20.5 m vs. millimeters in the gut wall) [21]. The large capillary system- the pulmonary blood flow is approximately 5 L/min at rest- guarantees fast absorption of drugs systemically which are able to penetrate the alveolar epithelium [22].

The ionization and solubility of drugs deposited in the alveolar lining fluid (ALF) depends in part on the pH of the fluid (around 6.9), which is a few tenths of units less than plasma pH . ALF volume is incredibly low (about 10 to 30 mL), which implies the dynamic nature of drug dissolution and concentration at the alveolar surface and its reliance on

such physicochemical factors as lipophilicity and solubility [23]. Relevant lung volumes in drug delivery are tidal volume (0.5 L) and functional residual capacity (FRC -2.5 L) and total lung capacity (TLC -6 L); breathing rate and pattern are also critical in determining the depth of aerosol penetration and residence time..

2.4 Pulmonary Surfactant System

Coating the alveolar surface is a thin film of pulmonary surfactant; a complex of lipids and proteins that Type II pneumocytes secrete. Dipalmitoylphosphatidylcholine (DPPC) is the major lipid molecule (approximately 40 percent) and the rest of the lipid molecules include phosphatidylglycerol, cholesterol and minor lipids. Four surfactant-associated proteins (SP-A, SP-B, SP-C, SP-D) play a vital role in important activities such as surface tension, film formation, innate immunity, and particle opsonization [24,25].

Surfactant has a significant effect on behavior of inhaled particles. When the particles are deposited into the alveolar space, they are quickly covered with the surfactant film, changing their surface characteristics and affecting the cellular uptake and dissolution kinetics. Hydrophobic particles can be integrated with the surfactant monolayer and the hydrophilic may destabilize it. The SP-A and SP-D are collectins, which opsonize inhaled particles and enable their recognition and subsequent phagocytosis by alveolar macrophages- a phenomenon that formulation scientists should consider when developing macrophage-evasive nanocarriers [26,27]. Also, surfactant-based components may be used as endogenous excipients in dry powder inhaler (DPI) formulations, and DPPC-mimicking lipids are used as inhaled excipients to take advantage of the biocompatibility.

3. Physiological barriers to pulmonary drug delivery

3.1 Mucociliary Clearance

The major mechanical defense of the conducting airways is called mucociliary clearance (MCC) which is a continuous conveyor-belt mechanism to eliminate deposited particles to the oropharynx to be expectorated or swallowed [28]. The airway surface liquid (ASL) is layered into two functionally distinct layers: a low-viscosity periciliary sol layer (PCL, ~7 μm thick) whereby the cilia beat freely at 1215 Hz, and a viscoelastic mucus gel layer floating on top of the PCL, pushed towards the oropharynx at 420 mm/min [29].

Mucus is mainly comprised of large polymeric glycoproteins (mucins, mainly MUC5B and MUC5AC) and water (some 95%), salts, immunoglobulins, lipids and defense proteins (lysozyme and lactoferrin). The viscoelastic properties of it, which are important in cilia transport, change considerably in disease. In CF, impaired CFTR-mediated chloride secretion results in dehydrated and hyperconcentrated mucus with significantly increased viscosity that inhibits MCC and favoring chronic bacterial colonization. Likewise, in COPD, hyperplasia of goblet cells enhances the production of mucus but ciliary dysfunction decreases the ability to transport particles, resulting in the retention of drug particles in the conducting airways instead of reaching their destination therapy [30,31].

Formulation-wise, the mucus layer is a powerful resistance to diffusion, especially to large hydrophilic macromolecules and charged nanoparticles. PEGylation of surfaces of nanoparticles- taking advantage of steric and lubricating influences- has become the most prevalent strategy to increase mucus penetration, transforming entangled nanoparticles into mobile mucus-penetrating particles (MPP) that diffuse through mucus pores instead of binding to mucin fibers [32].].

3.2 Alveolar Macrophage Phagocytosis

The initial cellular immunological response in the deep lung is the alveolar macrophages (AMs). Normal human lung has an average of 1.410-2.310 AMs spread across the alveolar lumen which can quickly phagocytose deposited particles through Fc-receptor, complement, and pattern-recognition receptor-mediated pathways (e.g., MARCO, CD206, SR-A) [19,20]. The phagocytosis process is most effective with particles between 1 and 5 μm, a size range that is also ideal to deep lung deposition- a very deep paradox that characterizes one of the key issues of alveolar drug delivery [33].

The particles that are internalized by macrophages are delivered to lysosomes, where they are exposed to degradation by acidic pH (~4.550) and hydrolytic enzymes. Particles phagocytosed are then carried onwards by proximal transportation through the mucociliary escalator to the oropharynx or to the lymphatic system. Macrophage avoidance strategies involve designing particles under 200 nm (under the efficient phagocytic uptake threshold), polyethylene glycol (PEG) surface-coating to form stealth surfaces and apoptotic cell surface-mimicking phosphatidylserine-coating [34,35].

Ironically, in the pulmonary tuberculosis case, alveolar macrophages targeting is a welcome treatment goal instead of a barrier due to the presence and multiplication of Mycobacterium tuberculosis in these cells. The so-called Trojan horse approach actively creates particles of the 1-5 m size to use AM phagocytosis as a means of delivering intracellular drugs - making the defense mechanism of the lung a therapeutic option [11].

3.3 Enzymatic and Metabolic Barriers

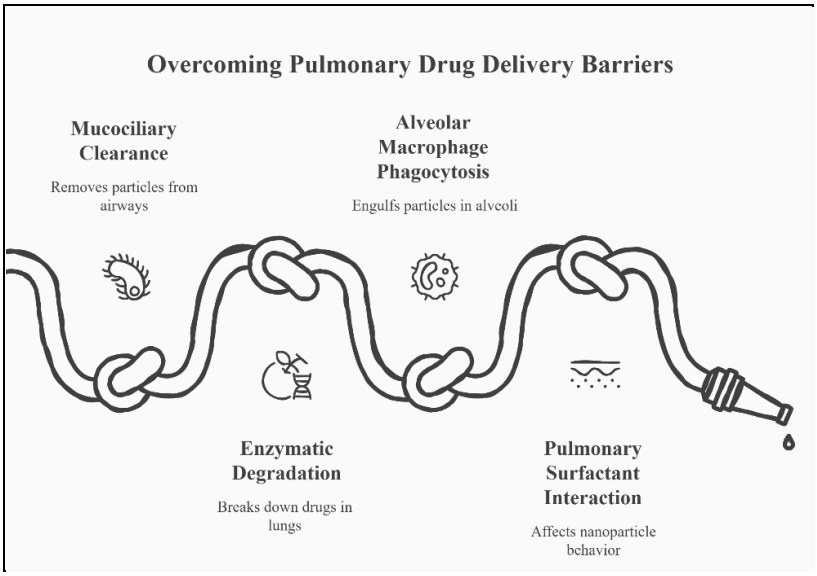
The lung contains a large variety of metabolic enzymes that may have a strong impact on the bioavailability of drugs inhaled. Oxidative metabolism of inhaled compounds is catalyzed by Phase I enzymes, which include cytochrome P450 isoforms (CYP1A1, CYP1B1, CYP2B6, CYP3A4/5) that are mainly expressed in Club cells, ciliated epithelium and alveolar macrophages. The lung also expresses phase II conjugation enzymes (glutathione S-transferases, UDP-glucuronosyltransferases, sulfotransferases) that collectively mediate biotransformation that can reduce the bioavailability of inhaled peptides, proteins and prodrugs [36].

Proteases are a significant hurdle to inhaled peptide and protein therapeutics. The constitutive proteins of the bronchial and alveolar epithelium and in the ALF are neutral endopeptidase (NEP), angiotensin-converting enzyme (ACE), dipeptidyl peptidase IV (DPPIV), and other

serine and cysteine proteins. Protease inhibitors co-administration, encapsulation of biologic payloads into polymeric nanoparticles or lipid nanoparticles, and PEGylation are some formulation strategies used to protect biologic payloads against enzymatic degradation in the lung microenvironment [37].

3.4 Immunological Barriers

In addition to macrophage phagocytosis, the lung has an elaborate immunological barrier system. Airway surface liquid secretory immunoglobulin A (sIgA) opsonizes inhaled antigens. The adaptive immune responses to inhaled particles are coordinated in the bronchial submucosa by bronchus-associated lymphoid tissue (BALT), which is composed of organized lymphoid aggregates. The dendritic cells spread across the airway epithelium sample breathe in the antigens and transmit traffic to the regional lymph nodes to trigger T-cell responses. When protective against pathogens, these immunological barriers also may dampen the effect of inhaled biologics and nucleic acid therapeutics, inducing immune responses that decrease therapeutic persistence [38].



4. Aerosol science and particle characteristics

4.1 Key Aerosol Parameters

Aerodynamic characteristics of inhaled particles are dictated by a combination of key parameters that, together, define how they will be deposited regionally in the respiratory tract. The most clinically significant value is the aerodynamic diameter (da), which is the diameter of a unit-density sphere of the same gravitational settling velocity as the particle itself, regardless of its true geometric form or density [39]. This parameter allows predicting the trajectory of the particles through the airways by the forces of inertia, gravity and diffusion.

Mass Median Aerodynamic Diameter (MMAD) is the aerodynamic diameter at which half of the aerosol mass is made up of particles smaller and half of the aerosol mass is made up of particles larger. It is the main measure of pharmaceutical characterization, and the Geometric Standard Deviation (GSD) is a measure of polydispersity of the aerosol distribution; a GSD of less than 2.5 indicates acceptable monodispersity to inhale therapeutically [40]. A regulatory and clinical measure of inhaler performance, the fraction of emitted dose and aerodynamic diameter less than 5 µm (Fine Particle Fraction (FPF)) is the expected fraction of aerosols that can penetrate the oropharynx and be deposited in the conducting and respiratory airways [41].

Fine Particle Dose (FPD) = FPF x Emitted Dose, give absolute measure of mass of drug of therapeutic relevance. The active particle size range of most inhaled therapeutics is the respirable fraction, which is the particles with a da 1 5 µm (bronchial targeting) or 1 3 µm (alveolar targeting). Pharmacopoeial guidelines (USP <601>, Ph) require characterization of these parameters by cascade impaction (Next Generation Impactor, NGI; Andersen Cascade Impactor, ACI). Eur. 2.9.18) [42].

4.2 Physico-chemical Properties of Particles

In addition to aerodynamic diameter, the density, shape, surface energy, hygroscopicity, and electrostatic charge of particles play a role in the outcomes of aerosol behavior and deposition. Porous particles engineered with PLGA, albumin, or lipid matrices have large geometric diameters (>5 µm) and small MMAD (1-3 mm) due to proportionality between aerodynamic and geometric diameter and multiplied density. This method, such as large porous particles (LPPs), allows deep lung deposition and escape macrophage phagocytosis (which is effective with dense particles in the 1-5 m geometric range) [43,44].

Hygroscopicity is a characteristic of a particle to take in water vapor in the humid airway (relative humidity 99.5% in the alveoli). During inhalation, hygroscopic particles increase in diameter in transit, a phenomenon which can be exploited therapeutically with excipient-enhanced growth (EEG) strategies - in which mannitol and sodium chloride-containing submicrometer particles increase to the respirable range in the warm, humid airways, enhancing lower airway deposition with reduced oropharyngeal losses [45]. Wall deposition (one of the loss mechanisms) or

particle-epithelium adhesion can be enhanced by the triboelectric charge on dry powder inhaler (DPI) particles, which is generated by triboelectric charging during processing and turbulence inside the device, and neutralizing the charge through neutralizers in formulation or device design prevents unwanted effects of charge [46].

Particle Size (MMAD)	Primary Deposition Site	Dominant Mechanism	Clinical Relevance
>10 µm	Oropharynx / Trachea	Inertial Impaction	Oral candidiasis (steroids); reduce using spacers.
5–10 µm	Large bronchi / Trachea	Inertial Impaction	Central airway diseases (acute bronchitis)
1–5 µm	Bronchioles to Alveoli	Sedimentation + Impaction	Asthma, COPD, TB — primary therapeutic window
0.5–1 µm	deep alveolar region	Sedimentation + Diffusion	Deep lung, systemic absorption, biologics
<0.5 µm	Alveoli (risk of exhalation)	Brownian Diffusion	Ultra-small nanoparticles; high loss by exhalation.

Table 1: Relationship between aerosol particle size, deposition site, dominant mechanism, and clinical application.

5. Mechanisms of particle deposition in the respiratory tract

The five major physical processes that control aerosol particle deposition in the lung include: inertial impaction, gravitational sedimentation, Brownian diffusion, interception and electrostatic precipitation. The proportion of mechanisms is dependent on the aerodynamic diameter of the particles, density, shape, and the local airflow conditions of the respiratory tract. Knowledge of these mechanisms is the mechanistic keystone of pulmonary formulation science.

5.1 Inertial Impaction

The most important deposition mechanism of particles with aerodynamic diameters larger than 5 µm is inertial impaction, which is the main determinant of deposition in the oropharyngeal and tracheobronchial regions [10,47]. This process is propelled by the fact that the high-momentum particles are not able to keep up with the rapid change in airstream direction at the bifurcations of the airways.

When there is a curvature of the airstream, a particle that has enough inertia preserves its path and hits the wall of the airway. Impaction efficiency is measured as the Stokes number (Stk) and it is defined as: Stk = 0.500d12U 9ηD/ 2D, where 0.500d12U = particle density, d1 is aerodynamic diameter, U is the mean flow velocity, 9ηD = air viscosity, and D airway diameter. High Stokes numbers (Stk > 0.5) predict impaction. In line with this, high inspiratory flow rates, which raise U, bring impaction to more peripheral airways- why DPIs, which demand high inspiratory flow rates to deagglomerate powder, deposit higher levels of drug in central airways at higher flow rates [48]. Impaction losses in the oropharynx, glottis and tracheal bifurcation are significantly increased by turbulent flow, which is common in these areas, usually contributing 50-80% of dose loss with unspacer pMDIs [49].

5.2 Gravitational Sedimentation

Gravitational sedimentation is the most common mode of particle deposition when the aerodynamic diameter of the particle is in the range 0.58 µm to 8 µm and when the airflow velocity is low and the particle residence time is long (i.e. small bronchioles, respiratory bronchioles and alveolar ducts). According to Stokes, the settling velocity (v_t) is: $v_t = \rho_p d^2 g / (18\eta)$, g being the gravitational acceleration. Deposition through sedimentation is more likely to occur when the size, density and time to settle of the particle are large.

The critical clinical implication of this mechanism is that the breath-hold after inhalation is a significant increase in residence time in the respiratory zone, facilitating the sedimentation of 1-5 µm particles in the alveolar zone. It has been demonstrated that a breath-hold of 510 seconds after inhalation increases total lung deposition up to 10 percent in case of medium-size particles [51]. Tachypnea (rapid breathing rate), on the other hand, decreases alveolar residence time, and compromises deposition caused by sedimentation, which is critical in critically ill patients with a high breathing rate [52].

5.3 Brownian Diffusion

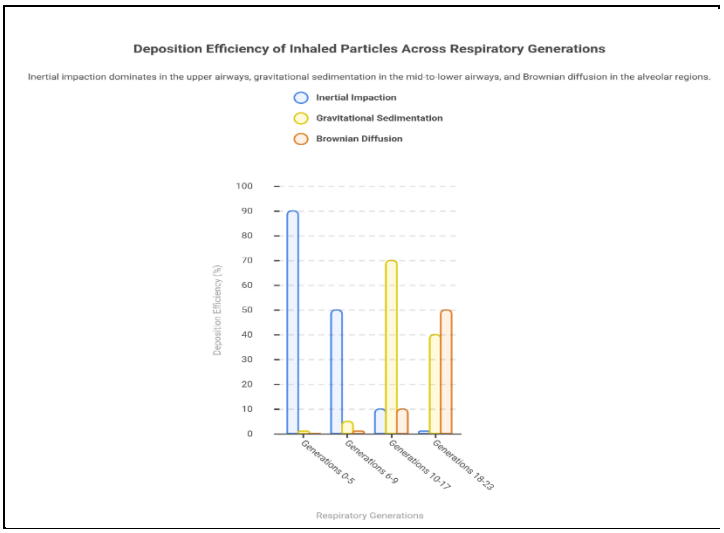
The preponderant deposition process in ultrafine particles with aerodynamic diameters less than 0.5 µm (500 nm) is brownian diffusion which increases in importance as the size of the particle drops down to nanometer dimensions [53]. These particles can be affected by the airstreams by random bombardment (Brownian motion) which results in random displacement of the particles and the ultimate deposition on the wall. The Stokes-Einstein equation is used to characterize the diffusion coefficient D: D = kT / (3pi eta d), where k is the constant of Boltzmann, T is the absolute temperature, and d is the diameter of the particles.

Although diffusion-mediated deposition is most effective in the alveolar region when the particle is smaller than 0.5 µm, the total deposition efficiency (the so-called diffusion-impaction valley) is lowest at about 300 500 nm, at which both diffusion and impaction are not very efficient. This low

deposition efficiency implies that a large proportion of nanoparticles in this size regime is exhaled without deposition, and their therapeutic utility is limited unless it is designed as nanoparticle-in-microparticle (nano-in-micro) composite systems that deposits in the alveoli due to the aerodynamic diameter of the composite and releases nanoparticles upon dissolution [54].

5.4 Interception and Electrostatic Precipitation

Interception is a deposition process suitable with fibrous particles (e.g., asbestos fibers, engineered nanofibers). The center of mass of a particle can travel with the airstream but the long physical length of the particle causes its surface to contact the airway wall as it approaches bifurcations. The ratio of the length of the particle to the airway diameter is known as interception parameter. Electrostatic precipitation is a process where charged particles are pulled towards oppositely charged airway surfaces or the epithelium is interacted with by image-force. Triboelectric charging during aerosolization in DPI formulation may lead to preferential deposition of charged particles in the upper airways, leading to less peripheral lung deposition [55].



Mechanism	Particle Size	Airway Region	Key Governing Parameter	Clinical Implication
Inertial Impaction	>5 µm	Oropharynx, large bronchi	Stokes number, velocity of the flow.	Slow with spacer, decrease breathing.
Gravitational Sedimentation	0.5–8 µm	Bronchioles, alveolar ducts	Settling velocity, breath-hold time	Breath-hold 5–10s post-inhalation
Brownian Diffusion	<0.5 µm	Alveolar region	Diffusion coefficient (size-dependent)	Nano-in-micro composite systems
Interception	Fibers (any size)	Bifurcations	Measurement of fiber length / airway diameter	Applicable to engineered nanofibers
Electrostatic Precipitation	Charged particles	All regions	Surface charge, image force	Cancellation of charges in DPIs

Table 2: Summary of primary aerosol deposition mechanisms, governing parameters, and clinical implications.

6. Patient and breathing pattern factors influencing deposition

6.1 Flow rate and pattern of breathing in inspiration

IFR is probably the most significant patient-specific variable that determines the inhaled drug deposition. In DPIs, IFR is required to be sufficient (minimum of 30-60 L/min depending on devices resistance) to create sufficient turbulent energy in the inhaler to deagglomerate powder into respirable particle. Excessively high an IFR (greater than 90 L/min), in turn, causes greater inertial impact on the oropharynx and upper airways and decreases peripheral lung delivery [56]. A low IFR (approximately 30 L/min) is preferred in pMDIs to reduce inertial impaction at the oropharynx, but actuation synchronization with inhalation is the main issue with the pMDI technique [57].

Tidal volume, inhalation time, pause time (breath-hold) and the ratio of inhalation-to-exhalation time (I:E ratio) each vary the amount of time spent in residence in different airway regions and thus affects sedimentation and diffusion-mediated deposition. It has been consistently shown in studies conducted with gamma scintigraphy that a 10-second post-inhalation breath-hold was significantly better than no breath-hold in total and peripheral lung deposition, especially with 1 5 mm particles [58].

6.2 Age-Related Differences

The lungs of children are highly differentiated concerning anatomy, physiology and the place of aerosol deposition.

Infants and young children possess smaller airway diameters (relatively greater resistance), smaller tidal volumes (~68 mL/kg), increased breathing rates (3040 breaths/min in neonates), and poor coordination to use an inhaler. These aspects cause impaction losses to move more to the central airways, decrease alveolar penetration efficiency, and require the use of spacers, valved holding chambers, and nebulizers to achieve effective delivery of drugs [59]. Geriatric patients have unique problems: because of the decrease of FEV1, air trapping, loss of elastic recoil, and decrease in ciliary beat frequency, mucociliary clearance is compromised and alters aerosol distribution patterns, which raises the risk of central deposition and airway mucus build-up [60].

6.3 Disease-State Alterations

The pulmonary disease significantly changes the geometry, compliance, and the distribution of ventilation in the lung directly affecting the patterns of drug deposition. Bronchoconstriction in asthma causes changes in airway caliber to accelerate airflow velocity in the impacted areas, and to redistribute impaction losses to more central airways, leading to the development of hot-spots depositions in central airways, and decreased peripheral drug delivery [61]. Emphysematous damage of the alveolar-capillary network, air trapping and heterogeneous ventilation in COPD results in areas of low aerosol penetration- a major hurdle of delivering drugs to diseased tissue. Patients with advanced COPD can have a severely impaired IFR, restricting their use of resistance-dependent DPI devices [62]. Pharmacokinetic modelling research has demonstrated that patients with severe COPD might need to take significantly more inhaled doses than healthy individuals to get the same drug concentration in lung tissue [63].

7. Regional drug deposition and deep lung targeting strategies

7.1 Oropharyngeal Region

The main area of impaction loss of inhaled aerosols is the oropharyngeal area, which includes the oral cavity, pharynx, larynx, and glottis. The high inertia and turbulent flows caused by the complicated three-dimensional geometry ensure that particles with MMAD >10 μm are almost entirely deposited in this region. The clinical implications of oropharyngeal deposition of drugs on inhaled corticosteroids (ICS) are that local deposition of drugs leads to candidiasis, dysphonia, and systemic cortisol suppression after secondary GI absorption. Spacer devices on pMDIs slow down aerosol velocity and permit the propellant to evaporate, changing the MMAD of the plume at device exit (~35 μm) to significantly less (<5 μm) by the time it gets to the oropharynx- radically lowering oropharyngeal impaction and increasing the effectiveness of the lung deposition process (<20 to >50) [64,65].

7.2 Tracheobronchial Region

The tracheobronchial (TB) segment, which extends between the trachea and the end-bronchioles, is the main pathway of therapeutic intervention in such conditions as asthma, COPD, and acute bronchitis. Short- and long-acting beta-2 agonists (SABAs/LABAs), long-acting anticholinergic agents (LAMAs), and inhaled corticosteroids are drugs that are deposited here and have their pharmacological effects on bronchial smooth muscle, goblet cells and inflammatory effector cells. Extrafine ICS formulations (MMAD 1.1-1.5 1μm) (e.g., HFA-beclomethasone) are much more highly deposited at the periphery (small airways, generation 10-16) than traditional formulations, which is especially important in small airways disease and severe asthma [66,67].

7.3 Alveolar/Deep Lung Targeting

Systemic drug delivery targets the alveolar region (generations 1723); and conditions that mainly impact the gas-exchange surface, including pulmonary fibrosis, alveolar proteinosis, and pulmonary hypertension. To obtain consistent deep lung deposition, MMAD values of 1-3 um, FPF of 60 and above, slow inspiratory flow (less than 30 L/min) and a post-inhalation breath-hold are needed. Large porous particles (LPPs) that have MMAD <3 μm because of low density (<0.4 g/cm 3) and with geometric diameters greater than 5 μm represent a novel strategy in particle engineering to deliver to the deep lung, avoiding oropharyngeal impaction and phagocytosis by alveolar macrophages [68].

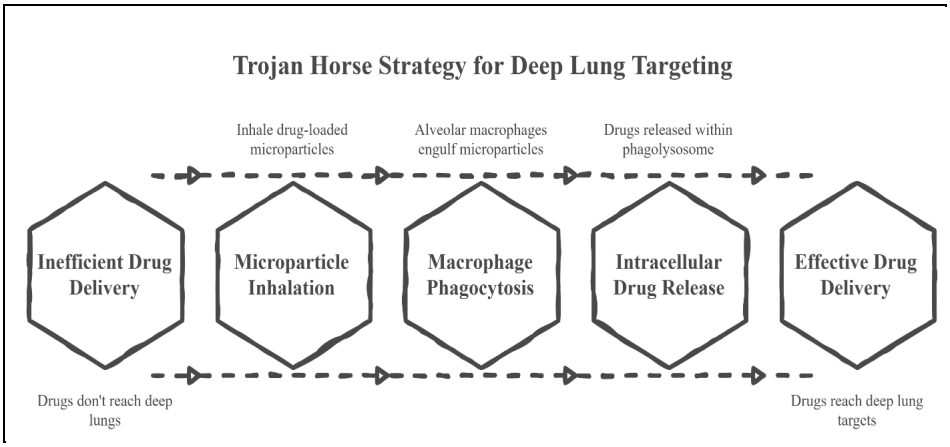
7.4 Deep Lung Targeting for Pulmonary Tuberculosis

Mycobacterium tuberculosis (Mtb) causes pulmonary tuberculosis (PTB) that infects an estimated one-fourth of the world population and is one of the major causes of infectious mortality on the planet. The pathophysiology of PTB is unique in that the alveolar macrophage is the main location of bacterial habitat and replication, as well as the therapeutic focus in direct delivery of the anti-TB drug [11,69]. When deposited in the alveolar space due to breathing in aerosolized respiratory droplets, Mtb is quickly phagocytosed by AMs. In macrophage phagolysosomes, Mtb resists lysosomal degradation by inhibiting the maturation and acidification of phagosomes, creating a safe intracellular niche that is inaccessible to systemically delivered antibiotics at therapeutic levels [70].

The use of inhaled drug delivery systems as an anti-TB treatment based on attacking AMs exploits the phagocytic appetite of the macrophage towards particles in the 15 -5 - m aerodynamic size, the so-called Trojan horse, principle to deliver anti-TB drugs (rifampicin, isoniazid, pyrazinamide, ethambutol) directly to the intracellular PLGA microparticles loaded with drugs, liposomes, solid lipid nanoparticles, and chitosan-based systems developed in the form of inhalable dry powds (MMAD 1-5 ug) have shown to be superior in macrophage uptake and intracellular bactericidal activity in vitro and in preclinical models relative to free drug solutions [73,74].

Active targeting can be achieved using mannose, a ligand to the mannose receptor (CD206) overexpressed on AMs, which results in a substantial increase in AM internalization of nanoparticles. Solid lipid nanoparticles that are covered with mannose and loaded with rifampicin have demonstrated 3-fold increased macrophage uptake compared to non-targeted preparations [75]. The elegant scalability of such formulations to inhalable microparticles of MMAD 2-4 -mm afforded by spray-drying of drug-nanoparticle composites into inhalable microparticles offers

a means to scale-up such formulations into DPI-compatible dry powders, bypassing the stability constraints of aqueous nanosuspensions to nebulization [76]. There are no approved inhaled anti-TB formulations, although clinical translation is progressing with the maturing of formulation science and regulatory frameworks [77].



8. Computational and in vitro modeling of lung deposition

8.1 In Vitro Methods

Cascade impaction is the pharmacopoeially standardized technique of determining the aerodynamic particle size distribution (APSD) of aerosol drug delivery systems in vitro. The Next Generation Impactor (NGI, 8 stages, cut-off diameters 0.2414.1 μm at 30 L/min) and the Andersen Cascade Impactor (ACI, 8 stages) impaction collect aerosols on impaction plates covered with suitable collection medium, allowing calculating MMAD, GSD, FPF, and Fine Particle Dose [78]. They are not a copy of anatomical geometry or physiological dynamics but standardized, reproducible aerodynamic data on which regulatory comparisons are made. Physiologically relevant extrathoracic impaction data are also available using realistic mouth-throat (MT) models such as the Alberta Idealized Throat (AIT) and patient-specific upper airway casts based on CT images that are anatomically accurate [79]. Twin liquid impingers (TLI) and dual impinger systems are simplified low-cost screening systems based on early formulation development. Combination of simulated breaths (to reproduce realistic waveforms of inhalation) and cascade impactors has a significant beneficial effect on the physiological relevance of in vitro characterization and predictive power of IVIVC models [80].

8.2 Computational Fluid Dynamics (CFD) Modeling

Computational fluid dynamics (CFD) has become an effective in silico method to predict airflow and particle transport/deposition in respiratory geometries that are anatomically realistic. CFD models are numerical solutions to fluid flow (Navier-Stokes equations) plus Lagrangian particle tracking or Eulerian-Eulerian multiphase particle transport. The oropharynx and large bronchi complex transitional and turbulent flows involved in impaction losses are captured using turbulence modeling (k-ε, k-ω SST, Large Eddy Simulation) [81,82].

Patient-specific CFD models, with reconstructs of high-resolution CT images, allow prediction of the individualized deposition patterns and can quantify the impact of disease severity (e.g., COPD-induced airway remodeling) on the distribution of drugs. CFD studies have shown that the pattern of deposition of severe COPD patients is significantly different than in healthy individuals at the same IFR, with proximal displacement of deposition as a result of airway constriction and non-uniform ventilation [83]. The use of in vitro impactor data is being more and more combined with CFD modeling to develop IVIVC relationships, and optimize formulation development, without the need to use expensive clinical scintigraphic studies [84,85].

8.3 In Vitro–In Vivo Correlation (IVIVC)

Developing strong IVIVC of inhaled products is a major scientific and regulatory issue. In contrast to oral dosage routes, IVIVC relationships are highly developed, the interplay of the aerosol physics, patient physiology, and airway geometry in pulmonary delivery forms a multi-variable system that is challenging to simplify to simple relationships. The best in vivo deposition data of radiolabeled aerosols in human subjects are found in gamma scintigraphy (2D) and SPECT-CT (3D) imaging, as compared to in vitro and in silico predictions [86,87]. New digital and AI-aided tools, which incorporate machine learning and CFD results, are promising to enhance the accuracy of IVIVC prediction in diverse patient groups [88].

9. Implications for formulation and device design

9.1 Particle Engineering for Optimal Deposition

The science of particle engineering has progressed to a high level whereby it is now possible to precisely control MMAD, FPF, density, surface morphology and drug-release kinetics of inhalable formulations. The workhorse technology in DPI powder manufacture is spray drying, which provides control of particle size, morphology, and composition at a scalable, continuous process [89]. The high-end spray drying conditions may give rise to particles in custom morphology dimpled, corrugated, porous or toroidal, with superior aerodynamics (high FPF, low cohesion) relative to classical smooth spheres. Supercritical fluid technologies (e.g., SEDS Solution Enhanced Dispersion by Supercritical Fluids) generate crystalline or

amorphous particles of extreme homogeneity, which are especially useful in the poorly soluble drugs that require a specified aerodynamics [90].

The therapeutic nanoparticles (50200 nm) are encased in porous microparticle matrices (MMAD 150 mm) of nanoparticle-in-microparticle (nano-in-micro) composite systems that consists of rapidly dissolving carriers (mannitol, leucine, lactose). When the nanoparticles are deposited in the alveoli, they are dissolved in the ALF, and nanoparticles are released that penetrate the mucus layer, avoiding the action of macrophages and allowing a long-term delivery of drugs into cells. This architecture integrates both aerodynamic potential of microparticles and biological potential of nanoparticles- a strategic duality that is at the heart of next generation pulmonary nanomedicine [91,92].

9.2 Device Selection Based on Physiological Principles

The choice of device to use in pulmonary drug delivery cannot be separated of the lung physiology and patient specific considerations as discussed in this chapter. High-velocity aerosol plumes (approximately 30 m/s at actuation) produced by pressurized metered-dose inhalers (pMDIs) must be slowed down to avoid oropharyngeal impaction, and this is done by spacer devices or soft-mist technology. The use of hydrofluoroalkane (HFA) propellants has facilitated extrafine pMDI formulations (MMAD = 1.13 μm) that deposition of peripheral lung is better than the old CFC formulations [93]. Dry powder inhalers (DPIs) are patient-controlled and need patient-generated IFR to be deagglomerated; they are therefore very patient- and disease-dependent. Passive DPIs (Turbuhaler, Diskus, NEXThaler) completely depend on patient IFR, which restricts their application in patients with grossly disabled lung function [94].

Nebulizers are devices that transform the solution or suspensions of drugs into aerosol droplets by using compressed gas (jet nebulizer), ultrasonic vibration, or mesh vibration. They do not mandate patient coordination or IFR, and are applicable to acutely ill patients, mechanically ventilated patients, pediatric patients, and geriatric patients. Vibrating mesh nebulizers (VMNs) are high fine particle fractions (FPF of order 70%) and low drug waste with narrow droplet size distributions, the state-of-the-art in nebulized delivery. Smart inhaler systems-incorporating electronic control of inhalation method, dose timing and patient compliance through Bluetooth-linked sensors are a potential potent intervention to help reduce the discrepancy between pharmacologically optimal delivery and actual patient performance [95].

9.3 Excipient Considerations

Inhalable formulations made of excipients need to meet high safety, regulatory and functional requirements. Lactose monohydrate is the most frequently used carrier of DPIs, gives flowability, blending, and dosing consistency, and carrier particles (50 200 μm) settle in the oropharynx once the drug micronized particles are released [96]. Leucine and trileucine are used as surface-active dispersibility enhancers -coating particle surfaces to decrease inter-particle cohesion and enhance FPF without biological activity. The DPPC-mimicking phospholipids are used as biocompatible surface modifiers as well as lipid nanocarrier systems. Tracing amounts of magnesium stearate (0.05-0.5%) cause a radical decrease in cohesion of DPI preparations, preferential coating of micronized drug particles, enhancing dose emission homogeneity [97].

Device Type	Aerosol Generation Mechanism	Optimal IFR	Patient Requirement	Key Advantage
pMDI	Propellant expansion	30 L/min	Coordination required	Portable, compact, HFA extrafine option
pMDI + Spacer	Reduction of propellant + spacer velocity	30 L/min	Low coordination	Reduced oropharyngeal deposition
DPI (Passive)	Patient-generated turbulence	40–90 L/min	Adequate IFR required	Propellant-free, breath-actuated
DPI (Active)	Built-in motor/energy source	30 L/min	Minimal effort	IFR-independent, high FPF
Jet Nebulizer	Venturi effect of compressed gas.	Passive breathing	Minimal effort	High concentrations, aqueous solutions
Vibrating Mesh Nebulizer	Vibrating mesh apertures	Passive breathing	Minimal effort	Large FPF, small residual volume
Soft Mist Inhaler (SMI)	Mechanical spring energy	~15–30 L/min	Low coordination	Low aerosol velocity, high lung deposition

Table 3: Comparison of the key types of inhalation devices in terms of aerosol generation, patient needs, and benefits of the therapy.

10. Conclusion and future perspectives

The chapter has outlined the continuum of mechanistic links between the structural and the cellular physiology of the lung and the physics of the aerosol deposition and the principles of design of pulmonary formulations. The exceptional anatomical design of the respiratory system, with its branching through 23 generations, supported by a huge alveolar surface and an extremely thin diffusion barrier, offers an impressive entry point both to local and systemic drug delivery. But the same architecture, combined with an advanced system of physiological

defenses, provides formidable obstacles that require mechanistically-inspired development and device policies.

Inertial impaction, gravitational sedimentation and Brownian diffusion are the three main deposition mechanisms that dominate over different aerodynamic size ranges of particles and regions of the airways, which offers the key to a rational approach to drug deposition to desired respiratory locations. Novelties in particle engineering, including large porous particles, nano-in-micro composite systems, and hygroscopic excipient-enhanced growth platforms have greatly broadened the scope of deposition profiles achievable. At the same time, predictive gaps in the bench characterization and the clinical outcomes are being bridged by computational fluid dynamics modeling and physiologically realistic in vitro techniques.

An example of the translational relevance of mechanistically based pulmonary drug delivery: in the case of pulmonary tuberculosis, deep lung targeting has the potential to revolutionize anti-TB therapy by utilizing the intracellular Mycobacterium tuberculosis niche in the alveolar macrophage as a Trojan horse: formulation scientists can deliver the therapeutic agent directly to this niche, potentially changing the therapeutic landscape for drug-resistant TB.

Further innovations in pulmonary drug delivery are defined by the development of artificial intelligence-controlled aerosol optimization, personalized inhaler technology in response to real-time spirometric measurements, 4D-printed airway models of ultra-patient-specific CFD, and bioinspired nanocarrier surfaces to circumvent the mucus-surfactant-macrophage gauntlet of the alveolar micro The interplay of lung biology, materials science, aerosol physics, and digital health technologies hold promise of a new age of accuracy in pulmonary medicine a place where dose, device, and deposition are optimized, not in an average patient, but in the individual

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