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Review Article

Influence of Particle Size and Particle Deposition of Inhaled Medication in Lung Disease: A Comrehensive Review

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ABSTRACT

Drug particles less than 5 µm have the greatest probability of deposition in the lung, whereas those less than 2 µm tend to be concentrated in the alveoli. A large proportion of particles within the 2-5 ***µm*** range are present in the dose released from the inhaled drug, providing a relatively even distribution across the lungs. The efficient need for inhaled therapy highly depends on the essence of the method of drug delivery and the patient's ability to correctly use the system. A large range of inhaler products, each with positive and negative aspects, are on the market. It facilitates the administration of a lower dose; there is a quicker onset of action and less severe side effects. The deposition of the inhaled drug in the lung is dependent on particle size, inhalation technique and the type of inhaler device. Importance of particle size distribution and Particle aerodynamic diameter, Influence of environmental humidity on particle size Particle deposition in the airways, Methods to identify drug deposition in lungs, Physiological factors which affect the therapeutic efficacy of pulmonary delivery drugs. The nano and micro size particles is a mainstay of treatment for a variety of pulmonary diseases because they provide a platform to deliver drugs directly reliably and inexpensively to the disease site, thus allowing for a minimum amount of drug to be used and minimize side effects.

Background

A non-invasive, rapid, and efficient approach to administering therapeutic agents locally and systemically is the pulmonary route of administration. On the other side, since the lungs have a large surface area available for absorption and ample vasculature, inhalation often has a great opportunity for systemic transmission.[1] The delivery of a drug to its target site might result in a fast onset of action, which is often desired. Compared to oral or parenteral administration, smaller dosages can be given locally, minimizing the risk of potent side effects and lowering treatment expenditures.[2,3] When a drug is poorly absorbed orally (e.g., sodium cromoglicate)[4] or rapidly metabolized orally (e.g. isoprenaline), the pulmonary route is also effective.[5] Although the lung has considerable metabolic potential, avoiding first-pass (presystemic) metabolism in the liver may be preferable.[2]

Compared to the liver and gastrointestinal tract, drug-metabolizing enzymes are smaller in the lungs. These characteristics generate conditions well suited to the successful absorption of drugs, providing a possible route for delivering systemic drugs.[6,7] Pulmonary drug delivery, however, is a difficult administration route. Next the efficacy of inhalation therapy depends on the site of the drug's deposition in the lung. Inhaled drug deposition is a complex process dependent on the lungs' anatomy and physiology, the drug's physicochemical characteristics, the design and characteristics of the formulation, and the type of delivery device used for administration.[8] The movement and deposition of particles in the lungs are highly affected by the airway geometry along the

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respiratory tract.[9] In the alveolar zone, the main site of absorption, only particles of a particular size (usually 5 µm) and shape can deposit.[10]

Anatomy and Physiology of Lungs

The lung is the organ of outward breathing, where oxygen and carbon dioxide are exchanged between blood cells and inhaled air. The design of the aviation pathways also efficiently prevents the entrance of foreign airborne particles, including bacteria, and speeds up their evacuation.[11]

It is possible to consider the respiratory tract as containing the conducting (central) regions (trachea, bronchi, bronchioles, terminal, and respiratory bronchioles) and the respiratory (peripheral regions (respiratory and alveolar bronchioles), although there is no definite demarcation between them (Fig. 1). The nose, throat, pharynx, and larynx form up the upper respiratory system, whereas the trachea, bronchi, bronchioles, and alveolar regions make up the lower respiratory tract. The airways will be specified by a symmetrical design in which each airway splits into two identical divisions or generations. The trachea (generation 0) splits into two main bronchi (generation 1). The right bronchus is larger and leaves the trachea at a lower angle than the left, making it more likely to accept inhaled particles. Further branching of the airways eventually led to the formation of terminal bronchioles. These are divided into respiratory bronchioles that interact with alveolar ducts that lead to alveolar sacs and alveolar sacs that communicate with respiratory bronchioles (generation 2, 3). These contain approximately $2 \times 1^8 - 6 \times 1^8$ alveoli, producing a surface area of 100 m^2 to 140 m^2 in an adult male.[12,13]

The blood barrier between the alveolar space and the pulmonary capillaries is exceedingly thin to allow for fast gas exchange.[14] The alveoli are mucus-extracted and have a much flatter epithelium, 0.1-0.5 µm thick, simple squamous form. A floor-active component that consists of phospholipids, called lung surfactant, is coated with the alveolar floor; its location is later stated.[15,16] Conducting airways are lined in ciliated epithelial cells. Insoluble particles deposited on the walls of the airways in this area capture the mucus, which is then carried up from the lungs by the beating cilia to the throat and swallowed.[10,17]

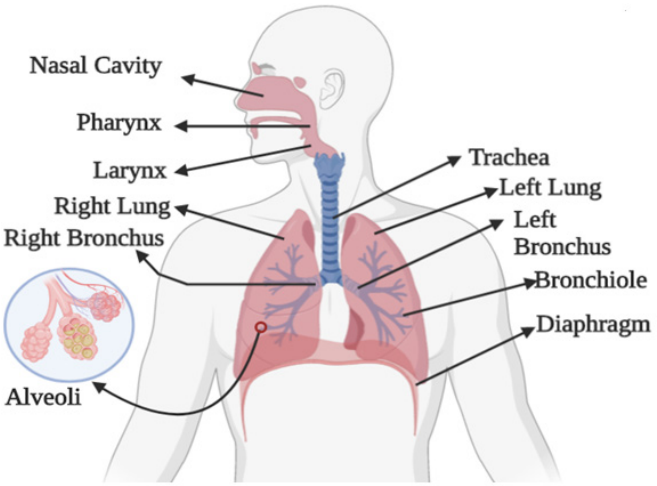

Fig. 1: Human Respiratory System

Absorption of Particles in Respiratory Tract

Small molecule medications and several therapeutic peptides and proteins are naturally permeable to the pulmonary membrane. The broad barrier to the absorption of inhaled drugs is the epithelium of the lung. In the trachea, it is dense (50–60 µm), but in the alveoli, its thickness decreases to 0.2 µm.[18] When moving distally from the trachea, bronchi, and bronchioles to the alveoli, cell types and shape change is significant. Macromolecules are more sensitive to the lungs than any other bodily entrance site.[19] A few peptides have demonstrated very high bioavailability through the pulmonary route, especially those chemically altered to inhibit peptidase enzymes. If they are strongly cationic, small molecules can show prolonged absorption.[20] Whereas rapid molecular absorption in the lungs has a variety of medicinal applications, there are times when slowing the absorption rate of inhaled small molecules is necessary, either to keep them working locally in the lungs or to regulate their absorption throughout the body. Very insoluble Molecules that slowly dissolve from an inhaled particle might reside in the lungs for hours or even days.[21]

The drug absorption rate and quantity differ over the length of the respiratory tract. For example, different areas of each region (about 2 m^2 conducting airways but about 140 m^2 alveolar surfaces) are influenced by absorption in different regions.[22.23]

The airways and alveolar areas have variable epithelial thickness and cell populations. A mucus gel covers the airway epithelium, while a surfactant layer coats the alveolar surface.[24] Drug clearance from the trachea and bronchi is mainly mediated by ciliated cells and mucus, while macrophages largely handle clearance from the deep lung.[22.25] In conjunction with mucus, the ciliated cells form a significant route for drug clearance from the trachea and bronchi, while macrophages are critical for deep lung clearance.[26] The amount of drug deposited and diffused inside the lungs was determines by an aerosol's overall therapeutic efficacy. These processes are a physical barrier to aerosolized drug delivery to the airways. A complete explanation of the role of each physiological zone about ultimate pharmaceutical absorption needs a solid understanding of lung anatomy and physiology.[27,28] Pneumocytes line the surface of the alveoli in two types: type I pneumocytes, which are thin squamous cells that form an important part of the capillary gas exchange barrier, and type II pneumocytes, which are bigger cuboidal cells that generate lung surfactant and are more diffuse than type I cells.[29] Alveolar (phagocytic) macrophages scavenge and transport particulate matter to

the lymph or mucociliary escalator, accounting for around 3% of the alveolar region's cells.[30]

Larger particles (5-10 µm) are deposited in the oropharyngeal area and larynx because of impaction. Particles of a diameter of 1 to 5 µm are normally seen in the tracheobronchial tract. In the alveoli and narrow conducting airways, gravitational sedimentation deposits particles with a diameter of 0.1–1 µm. Particles smaller than 0.1 µm are not deposited and are ejected during exhalation (greater than 0.1 µm are deposited and expelled).[31] Fig. 2 shows particle size-dependent deposition in various parts of the respiratory tract. To investigate the science of bronchodilator particle size effects, the research has already assessed regional airway drug deposition with the simultaneous calculation of clinical response. The system uses various particle sizes to transmit the target effect or cells to inhaled lung regions.

Mechanisms of Drug Absorption from the Lungs

The lung contains many of the absorption processes involved in other routes of administration that occur in organs. In general, paracellular or transcellular absorption of inhaled drugs may be possible. Paracellular absorption occurs via close junctions, claudine, and occludine integral proteins that stretch between lung epithelial cells in the paracellular space.[32] Research findings have also shown that apical to basal trans-epithelial electrical resistance, which shows the degree of cell tightness, decreases from the tracheal area to the distal airways until the alveolar region increases again. Therefore, paracellular absorption in the distal bronchioles is most likely to occur. Several hydrophilic drugs with relatively small molecular weights, such as insulin (Mol. Wt.: 5808 Da), have been documented to be absorbed into the lungs through paracellular transport.[22] A few other methods can improve the paracellular transport of drugs, for example by reversibly decreasing the tightness of paracellular junctions by administering compounds such as chitosan, allowing larger molecules to move across.[33]

Transcellular transport, in which the medication must diffuse into the cells to be absorbed, forms a major part of drug absorption through the lungs.[32] Transcellular transport, in which the medication must diffuse into the cells to be absorbed, forms a major part of drug absorption through the lungs.[34] Transcellular transmission frequently requires transporter molecules that are expressed on the cell membrane surface. In relation to intestine, liver, and kidney transporters, there is a scarcity of information about lung transporters.[35] Most of the other transporter express studies were done in vitro, which means that the degree of expression or distribution of transporters in vivo may not be accurately described. Furthermore, nothing is known about the extent to which such transporters play a role in the absorption kinetics of several drugs.

The solute carrier and ATP binding cassette transporters are two major transporters found in lung cells.[36] Via organic cation transporters and organic anion transporters, the solute carrier can transport organic cationic or anionic molecules. They can either enhance or impede the absorption of the drugs, depending on the location of expression of such receptors, either on the apical side at the lumen of the airway or on the basolateral side facing the endothelium of the blood capillaries. For such transporters, an immense diversity of substrates makes these receptors an important problem to consider during dosing calculations. Vesicular transport, which involves the creation of invaginations in the cellular plasma membrane that later separate into individual vesicles that engulf the particles within, is another potential absorption mechanism.[37-39] Depending on the particle size, vesicular transport can be mediated by either caveolin- or clathrin-. Caveolin-mediated transport usually includes particles of less than 120 nm in size, while clathrins transport larger particles of 150-200 nm in size.[37]

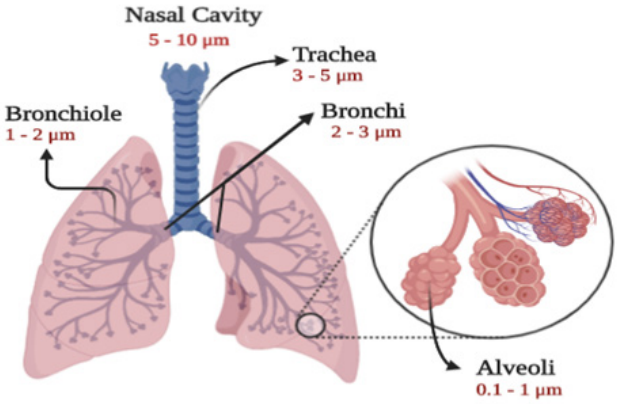

Fig. 2: Absorption of Particles from Respiratory Tract

Lung Surfactant

Pulmonary surfactant, a lipoprotein complex composed of 90 percent lipid and 10 percent protein synthesized, secreted, and recycled by type II epithelial cells in the alveoli, lines the pulmonary airways. In minimizing surface tension and being host protection against inhaled pathogens and particles, the surfactant film of the lung plays a dual role.[40,41] Alveoli are stabilized against collapse by reducing the alveolar surface tension at the air-liquid interface, thereby maintaining a wide surface area for gas exchange.[42] The surfactant also enables oxygen penetration into the blood and through the lung surface lining. It would be extremely difficult to breathe without the lung surfactant, as oxygen diffusion through the lung surface lining would be hampered.[43,44] Lung surfactants also experience anti-inflammatory and antioxidant effects. In addition, pulmonary surfactants allow the movement of accumulated particles to the bronchial tree's upper airways. However, interactions have been identified between the lung surfactant phospholipids and inhaled drugs.[45] Lung surfactant has been shown to increase

the solubility of steroidal drugs (glucocorticosteroids), which have affected their residence time in the lung, with anti-inflammatory and antioxidant impact.[46] Other studies have shown that certain antibiotics can impair pulmonary surfactant function.[47] These reactions between the antibiotic and the lung surfactant should also be closely examined before inhalation antibiotics are administered.[48] Furthermore, potential interactions between deposited nanoparticles and lung surfactants can affect the role of biophysical surfactants, the metabolism of surfactants and the clearance of particles, or trigger toxicity caused by particles.[3,49] It is reported that in the presence of a sufficient amount of aerosolized insoluble particles, the activity of the lung surfactant is decreased (e.g., polymer microparticles).[50] This can disrupt the surfactant's physiological function, including the retardation of particle clearance from burdened lungs. Lung surfactants can allow large molecules to accumulate, such as protein therapeutics, which may increase alveolar macrophages' intake and digestion.[51,52] They become enveloped by a lung surfactant monolayer as aerosol particles lodge in the lung. These cell - derived particles are quickly digested and then removed from the alveolar zone by macrophages.[53] The certain new studies indicate that the diffusion of the medication out of the alveoli could be hindered by the lung surfactant. The addition of exogenous surfactant into the inhaled mixture expands the distribution further into the lung lumen of drug particles.[54]

Pulmonary Disease

A wide variety of persistent pulmonary conditions have been implicated in lung diseases such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, extreme progressive pulmonary hypertension, pulmonary tuberculosis, bacterial and fungal pulmonary infections, asthma, lung cancer, idiopathic pulmonary fibrosis (IPF), and multiple interstitial pulmonary diseases.[55] Such diseases are therefore chronic and sometimes lethal; it takes longer to treat them. Any of them are not totally healed and no treatments have been found to be effective in completely recovering lung functions. The IPF that is commonly known is idiopathic pulmonary fibrosis, which makes up 45% of IPF patients. The frequency of IPF and COPD, irrespective of sensitivity to common environmental risk factors, rises with age.[56,57] It is currently estimated that about 300 million and 210 million people worldwide suffer from common diseases such as asthma, IPF and COPD, respectively.[58,59] Be that as it may, pulmonary tuberculosis remains the top irresistible executioner around the world, with 10 million individuals becoming sick with TB in 2018 causing over 3 million deaths.[60] Conventional pharmacotherapy for chronic lung disorders can be broken into a few categories according to clinical agent types. A variety of antibodies, genetic compounds, peptides, and chemical drugs have been treated for persistent lung diseases (e.g., siRNA, miRNA, and shRNA).[61-63]

Drug Delivery to the Pulmonary System

Drug distribution to the lung system was performed by encapsulation of the drug to be administered in microparticles with a size range between 0.5 and 10 microns, ideally between 2 and 5 microns, formed by a drug-releasing substance with a pH greater than 6.4.[74-76] In a desired embodiment, the drug distribution mechanism is based on the development of microparticles that are stable at a pH of 6.4 or less and unstable at pH of greater than 6.4, or which are stable at both acidic and basic pH, but which are unstable at pH between about 6.4 and 8. Many types of components can also be used, include biodegradable natural and synthetic polymers, such as proteins, polymers of mixed poly (hydroxy acids), alginate, and amino acids (proteinoids). The microparticles were changed in another embodiment only after reaching the targeted cells to effect targeting to particular cell types

Table 1: Targeted Formulations with size particles

Sr no	*Drug*	*Disease*	*Formulation*	*Targeted site*	*Particle size*	*Reference*
1	Anticholinergic drug	COPD	Pressurized MDI	Pulmonary	0.8 to 5 µm	[64]
2	Ciprofloxacin	cystic fibrosis and COPD	DPI	Pulmonary	3.2 to 3.4 µm	[65]
3	Paclitaxel	lung cancer	DPI	Pulmonary	2 to 4 µm	[66]
4	Sodium cromoglycate	Asthma or COPD	DPI	Pulmonary	<5 µm	[4]
5	Dehydroepian-drosterone	Asthma or COPD	Nebulizer	Pulmonary	<5 µm	[67]
6	Tilorone and Pirfenidone	IPF	Ultrasonic nebulizer	Pulmonary	<5 µm	[68]
7	Paclitaxel	lung cancer, COPD	Nebulization (Microsprayer)	Pulmonary	4 to 6 nm	[69]
8	Tobramycin	Cystic fibrosis	DPI	Pulmonary	<5 µm	[70]
9	Tacrolimus	Lung transplant rejection	DPI	Pulmonary	140 nm	[71]
10	Budesonide	Local anti-inflammatory	DPI	Pulmonary	1 to 5 nm	[72]
11	Ciprofloxacin hydrochloride and gatifloxacin hydrochloride	Respiratory infections	DPI	Pulmonary	<5 µm	[73]

Table 2: Different In-Vivo Study of Pirfenidone with systemic and targeted dose

Subjects	*Systemic dose (Oral)*	*Targeted dose (Pulmonary)*	*Targeted Route*	*Reference*
Male C57B1/6 Mice (6-8 Week)	1197 mg/day	Efficacy Dose 10µg/kg Higher Dose- 50 µg/kg	Intra-tracheal	[83]
Male Sprague Dawley Rates	200 mg/(kg.day)	20 mg/(kg.day)	Inhalation	[84]
Male Wistar Rates	25-800 mg/(kg.day)	50 mg/(kg.day)	Endo-tracheally	[85]
Male Sprague Dawley Rates	160 mg/kg	300 µg/rate 30-1000 µg/kg	Intra-tracheal	[86]
Normal healthy volunteers, Smokers (higher risk for intolerance), and Patients with IPF	801 mg	25, 50, 100 mg (nebulizer dose)	Inhalation	[87]

Table 3: Marketed drug dose Differences of Systemic Dose and Targeted Dose

Drug	*Oral (Systemic) Dose*	*Inhalable (Targeted) Dose*
Salbutamol	4 mg/day	100 µg/day
Beclomethasone diprop.	8 mg/day	250 µg BD
Fluticasone Propionate	5 mg QD	5 µg QD
Voriconazole	400 mg BD	40 mg BD
Terbutaline Sulfate	15 mg/ day	0.5 mg / dose
Dapsone	100 mg BD	50-500 µg/day
Tacrolimus	2-4 mg/day	200 µg/dose
Sildenafil	60-300 mg/day	5 µg / day
Itraconazole	200 mg BD	10 mg, 20 mg/day
Ethionamide	250 mg /day	2 µg/day

BD- Two times in a day, QD- Four times in a day

and to effect release. Ultrafine particles may have greater toxic respiratory effects than fine or coarse particles in urban air, epidemiological reports have shown.[3,77] To investigate the science of bronchodilator particle size effects, the research has already assessed regional airway drug deposition with simultaneous calculation of clinical response. To use the various particle sizes to transmit the desired impact or cells to inhale lung regions.

Pharmacokinetics of Inhaled Drugs

The inhaled mode of administration generates high local concentrations in the lungs and relatively low levels of systemic absorption when dosages with a high therapeutic ratio are delivered. The pharmacokinetic testing of drug absorption from of the lungs offers a reliable and reproducible method of evaluating the various delivery mechanisms of inhalers, and some determining the bioequivalence of generic drug formulations. To determine the effects of the inhalation technique on drug delivery in vivo, measures of drug absorption from the lungs may also be applied. For example with salbutamol administered through a large quantity spacer, lung bioavailability is shown to have changed by factors such as the number of actuated puffs, inhalation-actuation delay and washing procedure.[78,79] Differences between dry powder reservoir and pressurised metered-dose aerosol

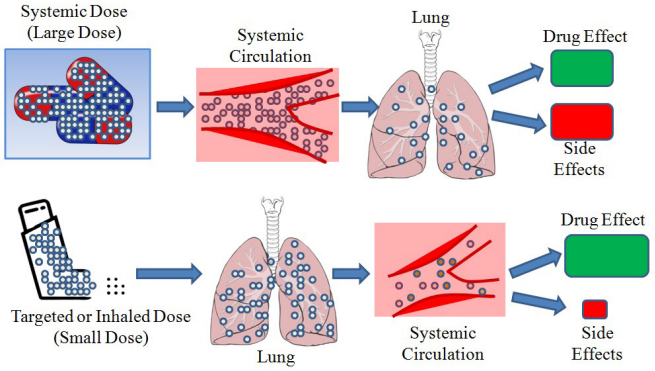

Fig 3: Importance of Particle Size with Route of Administration

systems in drug delivery to the lungs directly translate into commensurate differences in clinical effectiveness for both inhaled corticosteroids and b2-adrenoceptor agonists for delivery.[80] Pharmacokinetic assessment appears to have a defined purpose in the measurement of drug delivery to the lungs, and it provides useful information that is comparable to other methods such as radiolabelled deposition. Research into the pharmacokinetics of proven and novel drugs and delivery mechanisms over the next decade is anticipated with keen interest and, ideally, will provide a clearer understanding of how to improve the benefit-risk ratio for inhaled drugs.

Distribution of Particulate Size and Aerodynamic Diameter

The physicochemical characteristics of the drug like the formulation, the delivery/releasing method, and the patient are the four primary factors that influence drug particle deposition in the airways.[81,82] The use of inhaled therapy has a few advantages over systemic (oral or intravenous) administration. As in the targeted inhaled dose (Fig. 3), the drug dose is requiring less as compared to conventional oral dose. Targeted dose with smaller particle size has improved and more drug effect with less side effect. Systemic larger dose is travel less to lung and give larger side effect. As in targeted inhaled smaller dose is goes into lung in higher amount and less in systemic circulation. Particles will distribute in lung as per its size and density. It facilitates the administration of a lower dose; there is a quicker onset of action and less systemic side effects. The deposition in the lung of the

inhaled substance depends on the size of the particles, the technique of inhalation, and the form of inhaler device. The patient's inhaler procedure using the system is an integral part of the deposition of the drug inside the lung. For the most efficient delivery of inhaled medications, the right inhaler technique is crucial.

The most essential physical feature of an aerosol for inhalation is its particle size. The particle size of aerosol measurement is carried out by the aerodynamic diameter of the aerosol (da), which is the physical diameter of an airborne unit of density with a velocity equal to that of the particle in consideration. It is used to standardize the particle size of an aerosol.[88,89] When the scale is log-normally distributed, the geometric standard deviation (σg) is used to indicate the size distribution. For approximately aerodynamic diameter (da) for spherical particles,

$$d_a = d_p \cdot \sqrt{\rho / \rho_0} \quad \ldots (1)$$

Where dp is the physical diameter, ρ is the particle density and ρ^0 is unit density (i.e., 1 g cm^{-3}). When dp is the mass median diameter, da is termed the mass median aerodynamic diameter.[90] Porous particles are effectively transported to and accumulated in the lungs with large physical diameters on the order of 20 µm. Because of the porous or hollow nature of their structure, their low density means such particles have a limited aerodynamic diameter and are therefore brought deep into the lungs in the inspired air. Furthermore, large particles are less susceptible to aggregation than smaller ones, providing advantages of composition, and the particles are too heavy to be removed by alveolar macrophages from the airways.[91,92]

Influence of Environmental Humidity on Particle Size

As a particle enters the respiratory system, the shift in relative humidity from baseline to high (99 %) causes condensation of water on the particle surface, which continues until the vapour pressure of water reaches that of the surrounding environment.[93-96]

Particle Deposition in the Airways

The delivery by inhalation of therapeutic compounds provides a promising and efficient alternative to existing invasive techniques. The size and density of inhaled particles in various regions of the respiratory tract are primary factors in determining their efficiency of deposition.[97] The application of an inhaled therapy agent within the lung has a significant impact on the efficacy of that treatment. In addition, it is important to distinguish the impact of the delivery mechanism from the pharmacological activity for precise evaluation during the drug development process.[98]

The effectiveness of a therapeutic aerosol depends on its ability to penetrate and be retained in the respiratory tract. Aerosols need a size smaller than approximately 5 µm or 6 µm to penetrate to the peripheral (respiratory) areas, with less than 2 µm being preferable for alveolar deposition.[86,99] In addition to the environmental changes in the previously mentioned size and the hetero disperse nature of inhalation aerosol size distributions, literature values for 'respirable' size differ and must be considered. In the upper respiratory tract, larger particles or droplets are deposited and are quickly removed by the mucociliary clearance process from the lung.[100,101] As a result, systemic absorption of the drug becomes available and can potentially cause adverse effects. A sufficiently large corticosteroid aerosol can be accumulated in the mouth and throat, risk causing adverse effects, including oral candidiasis. The size of the aerosolized drug may be particularly significant in treating specific disorders where penetration to the peripheral airways is desirable, such as the treatment and prevention of Pneumocystis carinii pneumonia alveolar infection.

For particulate deposition in the lung, three mechanisms are mainly responsible: impact, gravitational sedimentation, and diffusion (Fig. 4(a) and 4(b)).[102,103]

Inertial impaction

The airstream changes direction in the mouth, or where a bifurcation happens in the respiratory tract.[104] Instead of following the shifting airstream, particles within the airstream, having sufficiently high momentum, can impact on the airway walls. For large particles with a diameter greater than 5 µm and especially greater than 10 µm, the major method for deposition in the nose, mouth, throat, larynx, and major conducting airways is this mechanism particularly significant and prevalent in the upper airways.

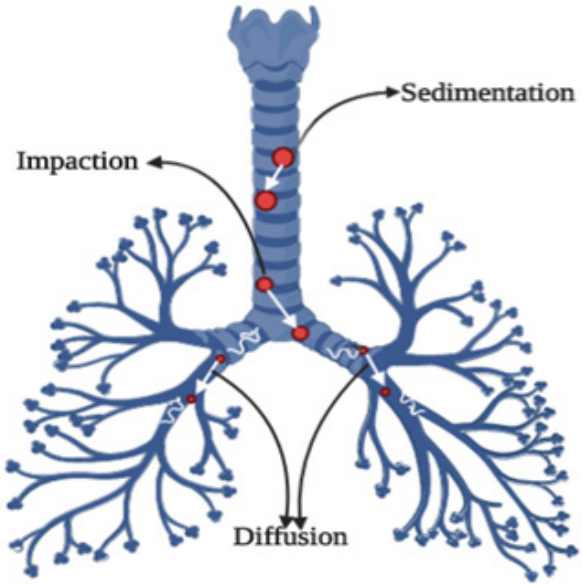

Fig. 4(a): Mechanisms for Particles Deposition in Lung

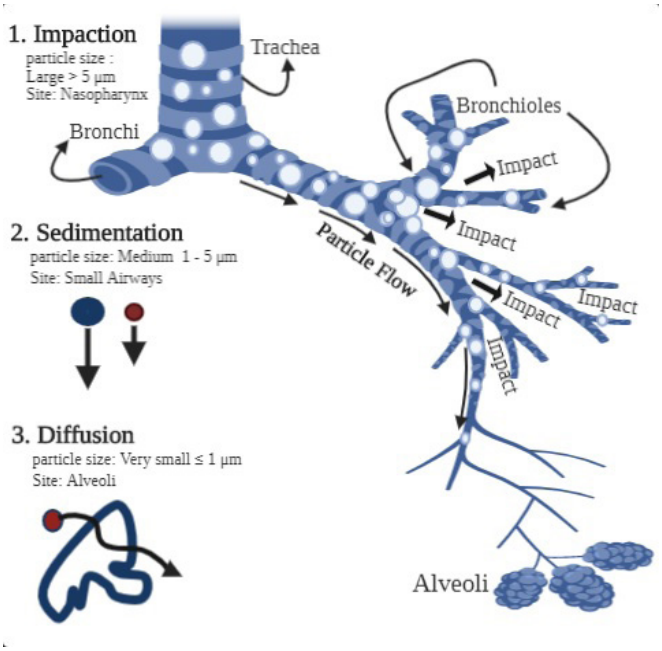

Fig. 4(b): Mechanisms for particle Flow and Deposition

The airstream velocity decreases as the conducting airways are further divided, and the impact becomes a less prominent deposition process.[13,102,105] The probability of impaction is proportional to

$$\frac{\text{Vt V}Sin\theta}{\text{gr}} \quad ...(2)$$

Where θ is the change in the direction of the airways, r is the airway's radius, V is the airstream velocity and Vt is the terminal settling velocity.[106]

Gravitational Sedimentation

Gravitational sedimentation refers to particle settlement under gravity action, which occurs predominantly in narrow airways and alveolar cavities where there is a small distance to be filled by the particles before reaching the walls. A particle settling under gravity will achieve a constant terminal settling velocity (Vt) from Stokes' law:[107]

$$Vt = \frac{\rho g d2}{18\eta} \quad ...(3)$$

Where ρ is the particle density, g is the gravitational constant, d is the particle diameter, and η is the air viscosity. As a result, the size and density of an inhaled particle and its residence duration in the airways affect gravitational sedimentation. Sedimentation is an important deposition mechanism for particles in size range from 0.5 µm to 3 µm, in the small airways and alveoli, for particles that have escaped deposition by impaction.[65.67] Deposition by sedimentation in the airways and alveoli increases with increasing particle size and increasing particle residence time. Larger particles are primarily deposited by inertial impact and smaller particles by Brownian diffusion mechanism.[101]

In the lower bronchial airways and the alveolar zone, where airflow is slower, particle deposition via sedimentation occurs. Particles with a diameter of 0.5-5 µm were that avoided impact in the upper airways and are deposited in the lower tracheobronchial and alveolar areas by deposition and impaction. Deposition in the trachea-bronchial area is significantly more likely if the aerosol particle size is between 3 and 5 µm.[64,86] If the particles are smaller than 3 µm in size, substantial deposition in the alveolar region could be expected. Particle sedimentation is governed by the (higher) gravitational force working more dominantly on the particles than the (lower) dragging force exerted by the airflow.[85,102] With an increase in particle size and a reduction in flow rate, the rate of sedimentation deposition increases. For particles of a size greater than 0.5 µm, this mechanism is particularly important. The probability of deposition in cylindrical airways by sedimentation [P(S)] is calculated as:[102]

$$P(S) = 1 - e\frac{4gC\rho d2LCos\theta}{9\pi\mu Rv} \quad ...(4)$$

Where g is the acceleration due to gravity, C is the Cunningham slip angle correction factor, Φ is the angle relative to gravity, ρ is the density of the particle, L is the tube length, d is the radius of the particle, μ is the viscosity of fluid, and R is the radius of the airways.

Brownian Diffusion

Diffusion is the main mechanism of deposition caused by Brownian motion for particles less than 0.5 µm in size. With decreasing particle size and airflow rate, this motion increases and thus becomes an essential mechanism in the lower airways and alveolar region for particle deposition. Here, particles travel through the streamline from high to low concentration and deposit through interaction with the airway wall. The geometric rather than aerodynamic scale of the particles govern this process.[102,104,108] When they collide with air molecules, nanoparticles deposit through diffusion due to the displacement. The probability of deposition in the cylindrical airways by diffusion [p(D)] is calculated as:[78]

$$P(D) = \sqrt{2KTC/3\pi\eta d/R} \quad ...(5)$$

$$Dif = \frac{k.T}{3\pi.\eta.d} \quad ...(6)$$

Where k is the Boltzmann constant, R is the airway diameter, η is the gas viscosity, T is the absolute temperature, and d is the particle diameter.[109] There are several barriers to optimizing pulmonary drug delivery deposition. The physical features of a particle, including size and density, together with the airflow in the lung, decide its final place of deposition. The airflow varies both spatially and temporally and is determined by the geometry of the lung, the mechanical properties (compliance and

resistance) of the lung tissue, and the driving pressures produced by the diaphragm and intercostal muscles within the lung.[80,83] The problem lies in the fact that it is very hard to test these effects in vivo, and that these factors will change all lung diseases will change these factors. In addition, it is difficult to determinate the distribution of particle deposition in a non-invasive way. Subsequently, the deposition mechanisms' causes and consequences are covered under real conditions. This has contributed to a restricted understanding of different parameters' impact in clinical conditions on the deposition and distribution of particles.[79]

Nuclear medical imaging has been the most commonly used experimental method for measuring regional particle deposition. A radionuclide contrast agent is inhaled into the lung, and the radiation released from such a agent is imaged to enable its local concentration to be measured. [69] This allows for regional deposition measurement; however, spatial resolution is insufficient to associate deposition with precise airway positions.[68] And thus, there is limited scope for investigating the fundamental drug deposition mechanisms using this process. A lack of experimental evidence has facilitated an emphasis on deposition computer simulation. Although this has proven to be effective in many instances, to accurately simulate particle deposition, both in healthy and diseased states, a thorough knowledge of airway geometry and pressure/flow inputs is needed.

Methods to Identify Drug Deposition in Lungs

It is necessary to calculate any variance in pulmonary deposition because the accurate calculation of the quantity of the drug to enter the lung makes it possible to check the dosage and the ability to link the dose to clinical effect. Responsive and accurate methods are needed to analyze therapeutic strategies in depth. A range of proven non-imaging and imaging methods may examine inhaled drug deposition.

Non-imaging or Pharmacokinetic Methods

The approaches that do not require imaging include the pharmacokinetic methods of charcoal-block and urinary excretion. Both pharmacokinetics (PK) measurement techniques will allow the relative pulmonary bioavailability of an inhaled medication to be quantified. The method of charcoal blocking uses the ingestion of charcoal to obstruct any systemic absorption through the gastrointestinal route, thus quantifying pulmonary bioavailability. By comparing 'area under the curve' data across various regimens, the urinary excretion method estimates systemic transmission, so it is useful to measure relative pulmonary bioavailability. Several research groups have used both PK data and lung imaging to measure deposition, and PK methods provide similar results to lung imaging data for total lung deposition. PK approaches have the advantage of not having a radiation dose over lung imaging methods, so it would seem like there is little need to go to an imaging system to test lung deposition. The key drawbacks of the PK data are that these methods may not be appropriate for all medicinal products and the lack of knowledge these methods provide about the regional deposition of the inhaled medicinal product inside the lung in vivo may be relevant concerning the clinical effect. Any drug formulation that can be radiolabelled adequately can be carried out through imaging studies. A recent workshop on the role of PK methods in establishing bioequivalence for inhaled drugs has reinforced the existing consensus opinion that the lack of reliable information on regional inhaled drug deposition is the limitation of the PK methods.

Imaging Methods

Two-dimensional Gamma Scintigraphy

The 2D planar approach has been employed in most research using scintigraphy to assess drug deposition. The lungs are photographed using one or more, gamma camera detector heads after inhalation of a radiolabelled aerosol to obtain a static view of the pattern of inhaled deposition. The standard procedure is for the study volunteer to stand, sit, or lie between two static gamma camera heads for an acceptable amount of time to obtain a simultaneous anterior and posterior image. The anterior and posterior images are then merged to generate a geometric median image. That image must then be corrected for background activity, radioactive decay, and imaging effects through various tissue densities, also known as tissue attenuation correction.[108]

Single Photon Emission Computed Tomography (SPECT)

Except that the gamma camera system is set up to rotate around the patient/volunteer, gathering 360° data, SPECT uses similar concepts to 2D, planar imagery. Increased details on regional deposition and clearance are the main benefit of SPECT. The amount of time needed to obtain a SPECT study is longer than for 2D planar scintigraphy with acquisition times of 10-20 min, and when using a radiolabel that is easily cleared from the lung, this can trigger problems. In SPECT studies such as ^{99m}TC-DTPA or ^{99m}Tc-colloid, slowly cleared radiolabels are favored for this purpose.[108,110] Application of SPECT has to clinical trials in drug deposition, ventilation and perfusion defect evaluation, and other applications such as epithelial permeability analysis.

High-Resolution Computed Tomography (HRCT)

For the diagnosis and longitudinal evaluation of lung disease, data obtained from CT is very useful, but there has also been a rise in interest in using such data to understand inhaled drug deposition better. Detailed central airway anatomy, regional ventilation, and texture

assessment of the lung, in health and in the presence of lung disease have been studied using HRCT data. To measure disease incidence and therapeutic action, CT density is also used. HRCT data can be used to produce central airway models for the mathematical modeling of aerosol deposition and has been used to demonstrate regional deposition, including deposition inequalities between left and right lungs, and to simulate broad edge points. The significance of human anatomical variation, even in the healthy population, and the impact on aerosol deposition are increasingly recognized.[108,111] It can be seen that the inclusion of HRCT data is very helpful, but it has the apparent disadvantage of having a higher radiation dose than that used for SPECT imaging. For this purpose, a changed protocol is used conservatively and frequently to keep the radiation exposure to a minimum.

Positron emission Tomography (PET)

PET requires various scanners and uses a radiolabelling method that is distinct from that used in SPECT or 2D planar gamma scintigraphy. PET is often paired with CT (PET/CT) in modern scanners. Computer analysis will then create three-dimensional representations of a radiolabel-emitting positron. Some unique examples for inhaled drugs such as ^{124}Insulin and ^{125}Insulin, PET integrates the radiolabel into the formulation being tested and uses positron-emitters such as ^{11}C, ^{18}F. Although the resolution is higher than SPECT (4-6 mm), the images created are identical to those made using SPECT. However, the use of PET for inhaled deposition studies has some important logistical problems, most notably the cost, the complicated methods of radiolabelling, and the need to have a cyclotron on site within a short distance from the research centre.[108,112] PET-CT enables the evaluation of high spatial resolution aerosol deposition, 3D ventilation, and perfusion data, and provides new insight into cellular inflammatory cell activity. However, the high cost, the difficulty of image analysis and the relatively few centres that can solve the technical problems surrounding using positron emitters as radio labels are opposed to PET.[112]

Factors Influencing the Therapeutic Efficacy of Drugs Delivered by the Pulmonary Route

As shown in Fig. 5, many factors influence respiratory deposition and others explained below.

Airway Geometry

The lung deposition of aerosol droplets/particles is strongly affected by the airway design in the respiratory tree. Every bifurcation, branching and decrease in the lumen diameter of the airways in the respiratory tract encourages the probability of particle deposition by impact and reduces the therapeutic effect of the fraction of particles available.[113,114] The structure of the pharynx and larynx affect the airflow in the trachea and bronchi. At bifurcations in the upper respiratory zone, the sudden decrease in the downwards diameter contributes to the generation of turbulent airflow that increases the deposition of particles in the upper airways.[115,116]

Inhalation Mode

The inhalation mode greatly affects the degree and area of the respiratory structure's particle deposition. In the peripheral alveolar area of the lung, nose breathing increases the probability of deposition of fine particles (about 10 µm) since larger particles are preserved in the nose and pharynx. In comparison, mouth breathing increases the chances of deposition of coarse particles (about 10 µm) with in the upper tracheobronchial region.[117,118] The time between inspiration and exhalation is increased by holding the breath, which encourages particle sedimentation at the periphery of the lung.[119]

Airflow Rate

The regional deposition of aerosol droplets/Particles in the respiratory tract is significantly influenced by the change in the inspiratory airflow rate. By improving aerosol deposition in the oropharynx region and upper airways, rapid and turbulent airflow decreases the residence time of the particles in the airways, while slow inhalation contributes to deposition in the lower peripheral airways.[120,121] Furthermore, the lower deposition proportion of fine particles is followed by an increase in the airflow rate and vice versa. At a very slow airflow rate, the inhalation of an aerosol reduces the probability of particle/droplet effects, reducing aerosol particles deposition in the upper respiratory tract and by sedimentation and diffusion,

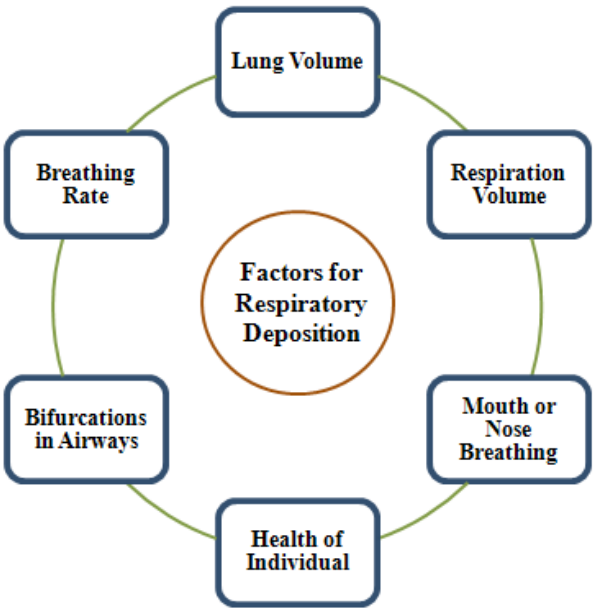

Fig. 5: Factors Influencing Respiratory Deposition

targets the lower airways.[122] Finally, increasing the number of tidal particles (the volume of air displaced between natural inspiration and expiration when there is no extra effort) increases the accumulation of aerosol particles in the lower bronchial and alveolar regions. These are all the key reasons why patients are advised to breathe slowly and deeply and hold their breath when inhaling a substance.[123]

Mechanism of Particle Clearance

The particles are either eliminated from the lungs after inhalation of aerosol particles through the lungs, absorbed into the blood / lymphatic circulation or degraded by drug metabolism.[124] The various clearance mechanisms used to remove foreign particles in different regions of the respiratory tract are reviewed under the parts.

Muco-ciliary Clearance (MCC)

MCC represents an essential protective mechanism for eliminating the respiratory tract of insoluble inhaled particles and serves as a possible physical obstacle for drug penetration. In healthy subjects, most of the accumulated particles in the trachea-bronchial region of the respiratory tract are removed within 24 hours of inhalation. In contrast to the lower airways, MCC is predominant in the upper airways.[125,126]

Mechanical Clearance

The removal of inhaled particles from the upper airways is aided by nose blowing, sneezing, coughing, and swallowing. This process occurs in the wider airways immediately after the deposition of particles. Coughing is automatically caused when a particle about ≥10 μm in size is inhaled. A high airflow rate is required for efficient cough clearance, and as this is only available in the upper airways, it is only in this area that it is successful. The cough becomes the main clearance method in respiratory illness conditions such as bronchitis, asthma or pneumonia where MCC becomes affected. Therefore, for the optimal drug effect, it is necessary to maintain aerosols at sizes of ≤10 μm.[127,128]

Enzymatic Degradation

Many inhaled drugs are substrates for the CYP450 enzymes found in the lung epithelia, despite the amount of degrading enzymes in the lungs being much less than that in the liver.[129] Certain isoforms such as CYP2S and CYP2F have been recognized as lung-specific.[130] Moreover, metabolic enzymes such as esterases and peptidases from Phase II are also expressed in the lungs. The concentrations of these enzymes vary greatly between the various types of cells lining the lung regions.[131]

Alveolar Macrophages

The effectiveness of inhaled treatment can be severely restricted by the housekeeping role of alveolar macrophages.[10,132] If another inhaled drug substance has low solubility and the particles stay in the alveoli for sufficient time, macrophages may be washed, decreasing the amount of medicinal product available for a therapeutic effect. The key obstacle to achieving controlled drug release is in the alveoli remains clearance by alveolar macrophages. Most of the substances used only to prepare particles are rigid and have all the physicochemical characteristics that make them an ideal target for macrophage absorption that can sustain the release of a drug for the long term.[133,134]

Lung Receptors

Most of the inhaled medications interact with pulmonary cell-expressed unique receptors. Pulmonary delivery performance can be increased by targeting individual cells with a low risk of systemic side effects. Therefore, understanding the numerous cellular receptors in the lungs provides the potential for pulmonary therapy to be more successful. The β-adrenergic receptors, muscarinic receptors, histamine receptors (H1 and H2), glucocorticoid receptors, leukotriene 1 receptors and prostacycline receptors are the most important receptor groups, none of which are uniformly distributed in the lungs.[11] Most β-adrenergic receptors, certain bronchi, and the terminal bronchioles, are found in the epithelium of the alveolar walls. β2-Adrenergic receptor agonists are medicines that function on the β2-adrenergic receptor, inducing smooth muscle relaxation and dilation of bronchial passages (salbutamol (albuterol), terbutaline and isoprenaline).[135] In the submucosal glands and lung lymph nodes, the smooth muscles of the airways, bronchi, and alveolar regions have a higher density of M3 receptors, although they make up a lesser fraction. Methacholine acts to contract the smooth muscles through M3 receptors.[136] The H1 and H3 receptors are both predominantly located in the human respiratory tract's bronchial smooth muscle. These receptors contribute to the mediation of increased vascular permeability and smooth muscle contraction in the respiratory tract.[137] Many novel receptors have now been identified as potential targets for developing novel therapies for lung disease, including orphan receptors.[138]

Disease States

Bronchial obstruction and narrowing of airways occur in respiratory disorders due to the accumulation of mucus and inflammation. Cystic fibrosis is a genetic condition in which dense mucus is formed in large amounts by the epithelial cells of the lungs, decreasing the lumen diameter in all airways.[71] Chronic bronchitis is associated with severe mucus generation, thickening of the alveolar wall, and small bronchi occlusion.[72] Asthma is a chronic inflammatory condition due to constriction of the bronchial airways in response to a stimulus marked by airflow obstruction (pollutants, allergens, or exercise). A thickened mucus layer and subepithelial fibrosis can also result in this constriction in turn.[4] These all-disease situations modify the geometry of the airways, resulting in