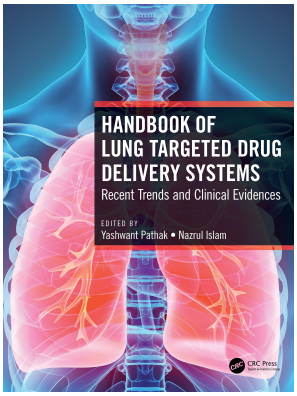

Handbook of Lung Targeted Drug Delivery Systems Recent Trends and Clinical Evidences

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Transepithelial Route of Drug Delivery through the Pulmonary System

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Transepithelial Route of Drug Delivery through the Pulmonary System

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4.1 Introduction

The pulmonary route is one of the non-invasive routes of drug delivery to achieve both systemic and local effects through inhalation. It has been used to deliver drugs targeting different tissues and organs, such as CNS, the heart, etc. A wide variety of drugs can be delivered through this route because of the presence of a different type of epithelia that enables ease of absorption; lungs are a highly perfused organ, hence more degree of absorption is seen, especially at the alveolar site, and this also permits distribution to different organs via a pulmonary vein.

The inhalation route of delivery has gained importance in recent years, since various chronic diseases are not targetable if treated by various conventional routes because of biological barriers like the blood–brain barrier, or other factors for example limiting bioavailiability of the drug while the pulmonary drug delivery can improve the systemic concentration. Also, it provides low side effects with high efficacy. Chronic diseases like asthma and chronic obstructive pulmonary diseases are targeted mainly by the inhalational route because of their ability to provide systemic delivery of a drug. It also helps in overcoming local side effects, like pulmonary alleviation, and pulmonary inflammation and constriction.

However, despite high absorption and various other advantages of targeting the lungs, there are various barriers that reduce drug motility inside the respiratory tract. These barriers can be physiological, mechanical, due to drug properties, etc. Pulmonary clearance is the major drawback seen in this type of delivery system. Such problems can be overcome by selecting the appropriate system, such as dry powders or metered-dose inhalers. Nowadays nano-drug delivery systems are being explored, including liposomal systems and inhaled solid nanoparticles. Many formulations are being developed, including inhalable insulin, which has been extensively used by the pharmaceutical industry (1).

4.2 Macrostructure of Lungs

Lungs are responsible for the exchange of gases that distributes oxygenated blood to various parts of the body, since the lung is a highly perfused organ, it can have a vascular supply which allows it to be a site of interest for transmission of various drugs for targeted delivery of a drug. The respiratory epithelium is lined by mucociliary lining, which plays a vital role in mucociliary clearance (2).

The respiratory tree is broadly differentiated into:

1. Airways
2. Blood circulation

This defines the air passage into the lungs. There are two types of zones found in the respiratory tree:

a. Conducting zone
b. Respiratory zone

The conducting portion is composed of trachea, bronchi, bronchioles, larynx, pharynx, sinuses, and nasal cavity. This zone starts from the nose or mouth and bifurcates 17 times until it reaches the respiratory or gas exchange zone. Every part has a varying epithelial lining, for example, from the nasal cavity to bronchi are pseudostratified columnar ciliated epithelium, and bronchioles are lined by ciliated columnar epithelium. From the larynx to the periphery the branching increases dichotomously. There are two daughter bronchi for each parent bronchiole. As branching increases, the cross-section area increases exponentially with the decrease in the diameter of the passage. The conducting part terminates at the bronchioles, which mark the beginning of the acinus that is the beginning of the respiratory part, which includes the alveolar region.

The primary function of this zone is to transport the gas from the nose/mouth to the gas exchange zone. If the air inspired is cool and dry, and absorbed in the same condition, it can drop the core body temperature, and the expiration of humidified air can cause unnecessary loss of water from the body. Hence, this is another role of the conducting zone. Proper humidification of inhaled air by this zone plays an important role in maintaining respiratory health, since inhalation of dry air can cause damage, such as (3)

- Cilia destruction
- Disorganization of columnar and cuboidal epithelia

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- Disorganization of the basement membrane
- Cellular degeneration
- Mucosal ulceration

Furthermore, hyper-humidification of inspired air can lead to water intoxication and bronchoconstriction, which can also cause serious damage to the conducting passage. These factors can lead to impaired drug delivery and also affect mucociliary clearance. Hyper humidification can also be a reason for an infectious condition.

The conducting tract can be divided into two parts:

- Extrapulmonary air conduits, which define the outer part of the lungs starting from the nose, pharynx, and larynx. The trachea is the bridge between the larynx and primary bronchi. It is covered with 16–20 hyaline rings which are the cartilage rings to support the trachea.
- Intrapulmonary air conduits begin from intralobular bronchi to terminal bronchioles which are surrounded by cartilage surrounded by cylindrical musculature airway tubes.

a. Respiratory or gas exchange zone
This is composed of distal to terminal bronchioles which are part of the conducting zone but contribute to the respiratory zone, alveoli and alveoli, and alveolar sacs, which are lined with a thin, simple squamous epithelial lining. This zone is suitable for a gaseous exchange due to its physiological characteristics, like the presence of a thin diffusive layer and alveolar ducts that have a significantly high surface area of about 102 m^2, hence providing more area for gas diffusion through this zone.

The outer epithelia of alveoli contain the following cells, Type 1 pneumocyte cells line the alveolar walls which are surrounded by the capillaries, surfactants secreting cells secreting dipalmitoylphosphatidylcholine. Type 2 pneumocyte cells are found in between the type 1 cells, they are high in phospholipid which is the precursor to surfactant production which plays an important role in maintaining alveolar surface tension to prevent collapse.

The blood–air barrier is formed with alveolar epithelial cells and vessels with a thin basement membrane (0.1–0.5 micro m) contributing efficient gaseous exchange from lungs' alveoli to blood. This promotes drug delivery through pulmonary nasal epithelia

b. Blood circulation
Lungs are highly perfused organs and are supplied by two different circulatory systems: pulmonary and respiratory. The pulmonary circulation conditions the inspired air and provides nutrients to the same, and the bronchial circulation is a part of systemic circulation which receives a low cardiac output of about 1%, mainly supply from the trachea to terminal bronchioles. Pulmonary circulation is under high cardiac output and covers the alveoli to obtain an effective gaseous exchange. The anastomosis can be seen in the medium-sized bronchi–bronchioles region.

4.3 Drug Targeting: Anatomical Sites

As is clear from the above discussion, the major absorption takes place from the alveolar region due to its physiology, hence drug delivery should be fashioned in such a way that it ensures the delivery of the promised dose to the alveoli that enables drug delivery to deep in the lungs. Due to the physiology of the conducting zone, there is no such absorption seen from that region, whereas non-respiratory bronchioles exhibit poor drug absorption ability and hence are not preferred as a site to target drugs. Many factors play an important role in drug delivery to the respiratory region which can greatly be affected by various factors as mentioned in Table 4.1, including the pathophysiology of the lungs and the type of dosage form used; for example, the metered dosage form delivers 20% of the dose to the alveolar region, while spacers and patient parameters like actuation can lead to the delivery of more than 20% of the dose to the target site. Drug deposition and cilia clearance are major factors affecting the drug flow in the lungs. These factors can be termed as anatomical barriers that resistat the drug to the target site (4).

4.3.1 Anatomical Barriers to Drug Flow

Inhaled air contains certain pollutants which are treated as a foreign bodies by the body, in response to which various cells like mucus-secreting cells, macrophage, and lymphocyte, produce a certain immunological response which can be

TABLE 4.1

Factors Affecting Pulmonary Drug Delivery

Factors Affecting Pulmonary Drug Delivery		
Drug-related Factors	**Formulation-related Factors**	
Lipophilicity	**Physicochemical properties**	**Dosage form**
Polymorphism	pH and mucosal irritation	Aerosolised form
Chemical nature	Viscosity	Metered dosage form
Molecular weight		
pKa and partition coefficient	Toxicity	Dry Powder dosage form
Dissolution and solubility		

considered as barriers to the drug flow. There can be many such factors, as follows:

- Epithelial lining – The epithelia of conducting airways is primarily formed of goblet cells, mucus-forming cells which allow the formation of a protective layer over the surface of conducting tubes and hence forms a barrier to gaseous absorption. Also, the presence of cilia causes clearance of the tract which acts as a major barrier in drug flow towards the absorption site.
- Endothelia – Pulmonary endothelial lining is primarily formed of capillary endothelium; the alveolar endothelial contain organelle free domains contributing as a barrier to gaseous absorption. The presence of a high number of endocytotic vesicles makes them when there is an increase in hydrostatic pressure.
- Alveolar macrophages – The presence of macrophages in the alveolar region restricts entry of any foreign particle into the systemic circulation which is further cleared by fluid lining and mucociliary clearance.
- Interstitium and basement membrane – The interstitium membrane is the space between two cells which generally contains cells like monocytes, leukocytes, fibroblasts, etc. The major function of this layer is to form a tight junction between two cells which are further drained of interstitial fluids present in the basement membrane, forming a barrier to gaseous exchange.
- Epithelial fluid lining – As seen in gastric mucosa, respiratory epithelia contain a fluid lining which wets the drug, allowing efficient absorption. The major composition of the mucin layer is phospholipid and protein which needs to be cleared with time, hence, it increases the ciliary beats and mucociliary clearance.
- Surfactant – The surfactants help increase surface area by reducing surface tension. Hence, in the lungs, they help prevent collapse and increase effective surface area for gaseous exchange. They are produced by pneumocyte type II cells in the alveolar region and also have bacteriostatic bacteriocidal action. As drug delivery is considered, this may increase the absorption of certain drugs and reduce the same for others, depending upon the physicochemical properties of the drug and the surfactant.
- Mucociliary clearance and drug retention time. The upper respiratory tract is lined by cilia which does not adhere to the airway epithelia by mucus secretion. The ciliary movement, also called ciliary beating, causes upward movement of mucus. The drug particles are foreign particles, in response to which mucus is secreted. This mucociliary layer reduces in thickness in the peripheral region; this enhances drug deposition in the central respiratory tract. Drug absorption enhances retention time.

Pulmonary retention of drugs is affected by the physicochemical property of the drugs, their particle size, and solubility; more lipophilic drugs have a higher retainability in the lungs. Hepatic enzymes like CYP1A1 and CYP2EA have metabolizing capacity and reduce retention time. Various xenobiotic compounds like serotonin by phase 1 and 2 enzymes are located in epithelial cells. The CYP enzymes are largely present in Clara and alveolar type 2 cells. Due to high perfusion and high cardiac rate, the pulmonary metabolism is very high. In the tracheobronchial region, the perfusion rate is low, hence there is more equilibrium and higher retention (5).

Lungs' histology varies from nasal to terminal bronchioles and alveolar regions. The airways consist of many barriers, as discussed, which interfere with drug delivery and absorption. Major drug absorption is seen in the alveolar region, which contributes to the barrier in absorption. Due to this, a different route of absorption is seen via the pulmonary route as shown in Figure 4.1. The process of absorption depends upon drug properties like pKa, lipophilicity, and the partition coefficient of the drug. Membrane properties also affect the absorption; the dissolution process is necessary before absorption which requires an adequate amount of fluid for the wetting of the drug particle (6). Absorption can happen by passive diffusion of particles, that is, direct absorption of particles through the membrane without any requirement of energy. Mostly lipophilic drugs having a particle size less than 50 Da can absorb through this mechanism. The bigger particles are absorbed through carrier-mediated transport where membrane-bound proteins are present which helps in translocating the particles. This can be facilitated diffusion in which no energy is required; it can be seen for the larger size hydrophobic particles and small-sized hydrophilic drugs. Active transport of drugs can be seen for the particles which are large—mostly for the hydrophilic particle. In lungs, alveoli, which are highly perfused, are the absorption site of drugs. Also, the presence of surfactants reduces the surface tension, thereby reducing the particle size and enhancing particle absorption.

The major mechanisms of drug delivery are as follows:

- **Passive diffusion**

  It is in the process of absorption where the flow of components is seen in the direction of the concentration

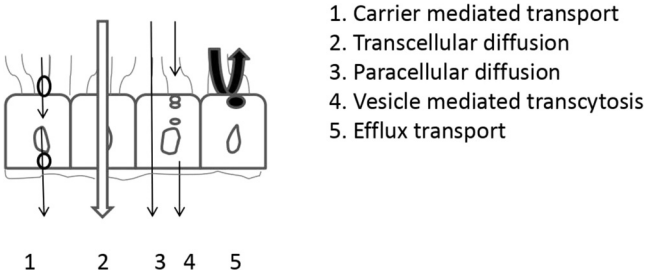
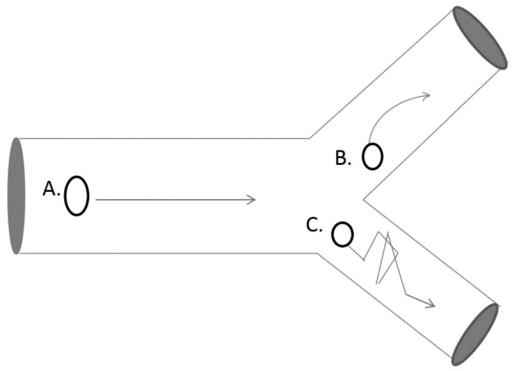


FIGURE 4.1 Mechanisms Involved in Drug Absorption



A. Impaction
B. Sedimenation
C. Diffusion

FIGURE 4.2 Mechanism of Drug Deposition

gradient. Lipophilic component absorption takes place by membrane diffusion, as the partition coefficient absorption increases. Whereas the hydrophilic compounds move through intercellular junction pores and are absorbed through passive diffusion. The absorption of hydrophilic components is inversely related to their molecular weight. Most of the exogenous molecules with molecular weight less than 40 kDa are absorbed through air spaces present between tight junctions.

- **Efflux and transporter-mediated absorption**

  Transport mediators like PEPT2, which is a high-affinity peptide transporter, are present in various sites of pulmonary epithelia, especially in the apical region of the trachea, type II cells, etc. Receptor-mediated or endocytotic movement of molecules like albumin and immunoglobulin is possible through the alveolar region.

  Efflux proteins, like MDR1-P-glycoprotein (P-GP), are associated with multiple drug resistance.
- **Vesicle-mediated transport**

  In the lungs' epithelia, many non-coated vesicles called caveolae are present. Their main role may be to transport the drug molecule. Vesicle-mediated transport is said to be a minor pathway for the transport of materials like protein across the alveolar epithelium, where the air–blood barrier plays an important restricting factor.
- **Non-specific particle trapping**

Nanoparticles with particle size less than 100 nm are taken up by alveolar cell type 1 by endocytosis. To reach circulatory system circulation, they are drained into the lymphatic system.

4.4 Drug Deposition: Mechanism

Particles given through the pulmonary route are very fine and pre-aerosolized, with a fine radius. This enables particles to travel along the pathway and reach the absorption site, that is the alveoli. The respiratory tree gets narrow as we move towards the periphery; the radius of bronchioles reduces, increasing the pressure of air, thereby increasing the velocity. With an increase in surface area, the particles are more exposed to the walls of the airway. This phenomenon imparts resistance to the flow by allowing particles to stick to the walls. This is called drug deposition. Drug deposition starts in the device itself and the remaining fraction occurs in the respiratory system, either in the conducting airways or in the alveoli region. This in turn increases the residence time, which promotes drug deposition by various mechanisms, either by inertial impaction sedimentation or diffusion as shown in Figure 4.2. Inertial impaction occurs predominantly in the extrathoracic airways and in the tracheobronchial tree, where the airflow velocity is high and rapid changes in airflow direction occur. For small-sized particles, sedimentation occurs, and diffusional transport can be seen for an ultrafine particle which shows Brownian motion.

4.4.1 Physiological Factors Affecting Deposition

1. Mode of inhalation

   The method of inhalation by a patient strongly influences the degree and extent of molecular throat deposition, which will be swallowed and contributes to a non-therapeutic dose. Irrespective of the mode of drug delivery, this factor plays a crucial role in drug deposition, since it will indirectly explain the therapeutic dose available which will ultimately reach the targeted site of action.

   Drug deposition in mouth and throat can lead to insufficient drug efficacy and can vary amongst the population. Factors like proper breathing time and inspirational frequency can increase lung deposition, which can be done by using devices like pMDI which increases the velocity of aerosolized particles, hence can reach up to deeper portions of the lungs ultimately increasing lungs deposition.

   Thus the criteria for selecting the mode of drug delivery should be based on the fact that more drug deposition is seen in the respiratory zone and less in the conducting zone.
2. Oropharyngeal deposition

   As discussed earlier, lungs have a complex histology where there is a high level of physiological variability and this factor plays a major role in influencing drug deposition. Since the pathophysiological conditions vary from one person to another, the therapeutic dose also varies. The particle size is modulated in such a way

that it can reach up to the respiratory zone easily since the conducting airways are narrower and can restrict the particle flow. We will see how the diseased state affects the deposition within the lungs in the following section.

4.4.1.1 Effect of Diseased State on Drug Deposition

Diseases can be infectious or obstructive when we talk about a pulmonary diseased state. In the case of obstructive diseases like chronic pulmonary obstructive diseases, the movement of a drug to the absorption site becomes negligible. Obstructive diseases either increase the pulmonary ciliary clearance, due to which the drug gets cleared off the lungs as seen in COPD, or the bronchiole epithelial thickens with hypersecretions of mucus, in the case of diseases like chronic bronchitis. In the case of emphysema, the destruction of alveolar walls result in permanent enlargement of the gas exchange zone. The obstruction causes deposition of particles on the bronchial airways. Infectious diseases like bacterial exposure are commonly seen in the upper respiratory tract;

Insufficient inhalation ability is observed in the case of zygomycosis, a pseudomonas infection which interferes with tidal volume

Pulmonary clearance

Drug retention time is explained by the anatomical and physiological condition of airways, which is directly influenced by the drug clearance rate, which can be explained as the time taken by the airways to completely clear the deposited particles from their surface. This is of great importance as chronic immune responses can be undone and also resist the entry of foreign particles. But despite this, it also interferes with drug absorption and therapeutic efficacy of the drug, whch influences the dose.

4.5 Levels of Clearance

- Mucociliary clearance
  The epithelia of the conducting airway are composed of a "clearance escalator" which is composed of ciliated epithelial, and goblet or mucus-producing cells are responsible for the upward beating. This allows the removal of the deposited particle in the range of 24 hours.
  In turn, the dosage form has to be selected in such a way that particles reach the target site before depositing on the edges of the conducting airway (7). This can be done by ensuring the aerodynamic nature of the particle and use of an efficient dosage form which can minimize the retention time and accelerate the particle movement.
- Phagocytosis or alveolar macrophage clearance
  This has been discussed in this chapter. Alveoli are composed of cells like macrophages which ensure that entry of any particle which can lead to the induction of systemic immune response is restricted. Phagocytosis is one of the mechanisms which restricts the movement of particles until the alveolar region and particles are engulfed by macrophages. This type of clearance can be called *alveolar macrophage clearance*. The dosing regimen can again be affected by the clearance of the drug in the alveolar region.
- Alveolar and epithelial absorption
  Lungs have a large surface area with a high surface to volume ratio and good airway epithelial permeability which are some of the prerequisites for the absorption of particles, hence drug particles can be absorbed when deposited and also can be cleared rapidly by mucociliary clearance from the epithelial lining. Hence, different approaches have to be followed to reduce absorption at the non-targeted regions of airways by identifying the physio-chemical nature of the drug as well as the targeted site. For example, rapid absorption can be seen in the case of hydrophobic molecules with less molecular weight; if they have to reach the deeper airways for their absorption, they must be treated in such a way that they can resist absorption in the upper airways by altering their physicochemical properties.
- Metabolic degradation
  Lungs secrete various enzymes, either through the epithelial endothelial layer that is a membrane-associated enzyme or from the alveolar region, such as alveolar macrophages which will affect enzymatic degradation of the drug. This can directly affect the drug dose, which can influence the therapeutic activity of the drug (8).

4.5.1 The Mechanism to Overcome Pulmonary Clearance

Various methods are being adapted to overcome clearance of deposited aerosolized particles, like the controlled release dosage form where particles are deposited and the release is controlled by the use of novel mechanisms; in this, we can control the amount of drug release and the targeted delivery of the drug (9). Pulmonary clearance is affected by various factors, which are shown in Figure 4.3 and these factors can be altered in order to alter the pulmonary drug delivery. Summary of all the methods adapted to avoid pulmonary clearance are mentioned in Table 4.2.

1. Mucociliary clearance

The major amount of drug clearance is seen by mucociliary clearance, hence it is present in the maximum area of conducting airways, which are the primary contact surfaces for the drug. Mucociliary clearance is one of the host defensive mechanisms which protects against foreign particles inhaled with air, hence drug particles are cleared by this mechanism.

The upward beating of cilia along with mucus produced by mucus-secreting cells efficiently removes the particles and creates a pathogen-free environment. This is called a mucociliary escalator, which can be avoided using various mechanisms.

- Mechanisms to avoid mucociliary escalator
  Particle residence time or particle deposition time plays an important role in drug release. It can be increased to about a day or more by altering the aerodynamic

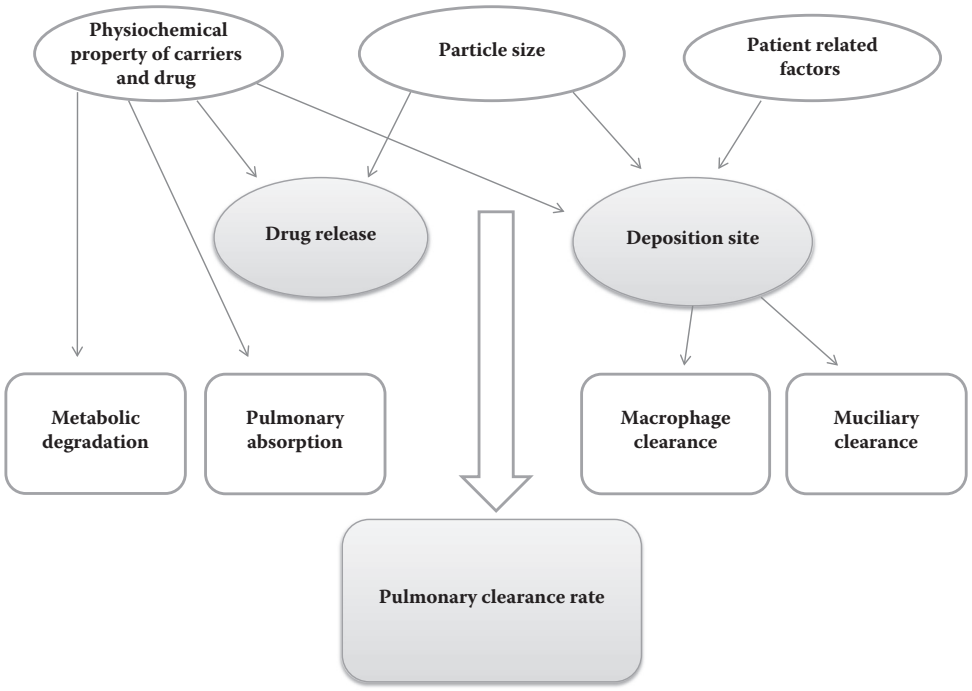


FIGURE 4.3 Factors Affecting Pulmonary Clearance

TABLE 4.2

Summary of Types of Pulmonary Clearance with the Mechanisms to Avoid Them

Pulmonary Clearance	Mechanisms to Avoid Pulmonary Clearance
Mucociliary clearance	Aerodynamic property
	Polymers like chitosan, hyaluronan
Rapid drug absorption	Drug structure modifications
	Microencapsulation
Macrophage clearance	Particle size
	Stealth characterstics

property of a drug particle. It ensures negligible deposition in the conducting airways, hence more drugs can reach the deeper airways for absorption. Aerodynamic diameter (d_a) is the diameter of a particle with a density of 1 g/cm^3 and its settling velocity is the same as that of a nanosphere with some arbitrary density. Deposition mechanisms are defined by the aerodynamic diameter and flow dynamics of the inhaled particle; by altering these we can achieve suitable particle flow according to our requirement.

Physical mechanisms of deposition are explained in the previous segment, which includes Brownian motion, particle sedimentation, inertial force causing particle impaction, and electrostatic deposition. Particle deposition and flow mechanisms of particles are directly dependent on d_a. For example, particles with $d_a > 0.5$ micrometers will be deposited by gravity, while particles with $d_a < 0.5$ are exhaled since their time of interaction with the lung lumen is less and the retention time is low. This can be altered by increasing breath-holding which will increase the retention of particles, hence the diffusion pattern is changed for the ultrafine particles.

Particles of more than 5 micrometers are deposited in the proximal lung regions like larynx, mouth, etc. For them, impaction is the major mechanism for deposition. Particles of size range varying from 1–5 micrometers are said to be optimal for efficient drug delivery to the alveolar region of the lungs. They are least deposited in the upper region of the pulmonary tract; mucociliary clearance does not interfere with this size range of particles. Also they are generally used for the aerosol delivery of a drug; for instance, terbutaline is used by the asthmatic patient as a bronchodilator where particle size ranges from 1.8 to 2 micrometers.

- Avoiding extracellular barriers
  The airways are covered with airway surface liquid (ASL) which functions as a primary defense mechanism. ASL is composed of two types of fluids. One is the preciliary liquid layer (PCL), the water layer. The other is the mucus layer formed by goblet cells over epithelia

on top of PCL. These two are found to be associated with cilia; the upward flow of cilia causes the flow of the fluid lining. This is termed *mucociliary clearance* because it resists any retention of drug particles or any foreign material on the epithelia. Hence, it can be avoided by increasing the diffusion rate of particles through the mucociliary lining.

Despite comprising highly complex biochemistry, mucus shows one additional property of mucoadhesion. The particles adhere to the mucus surface through the forces of interaction, like hydrophobic interactions, Van der Waals forces of attraction and surface characteristics, providing effective mucus absorption. Diffusion takes place as a polymer chain diffuses into the mucus membrane. As retention of particles increases on the mucus surface, diffusion also increases, which will increase the absorption of drugs, thus improving their bioavailability.

Increased contact time or mucoadhesion can be achieved by the use of polymers comprised of hydrophobic domains, like hyaluronan, chitosan, mucin, tween 80, etc. Physiochemical properties of the formulations can also affect the mucoadhesion, including particle size, molecular weight, concentration density, chemical structure, etc. Agents like S-carboxy methylcystein, a mucolytic agent, break the glycoproteins present in mucus and weaken the mucus membrane allowing easy passage of particles. Other mechanisms include the use of polymers like lecithin; when linked to the dosage form, they increase the particle internalization through the membrane.

2. Rapid drug absorption

The small sized particles which have high chances for rapid absorption through airways, reducing the pulmonary local concentration, increases dosing hence reducing patient compliance. Mechanisms discussed further can be adapted to avoid the rapid absorption of the drug.

- Modification in drug structure
  Chemical modifications can allow retention of the drug molecule by different mechanisms such as extended drug release. These modifications should not alter the therapeutic value of the drug. The overall motive behind this idea is to increase the retention time on pulmonary epithelia. Such an alteration can cause variations, including increasing hydrophobicity, which can increase drug retention on the tissues, and thus increases the local effect inside the pulmonary airway system.

  Another approach can be the addition of a positive charge on the lipophilic drug molecule, increasing its molecule binding capacity. Such approaches can increase the therapeutic affinity of the drug.
- Microencapsulation
  Controlled drug release can be achieved by controlling or extending the diffusion rate. Extending the release can be done by using polymers, which work as a carrier or vehicle promoting slow diffusion of the drug. The major step is the selection of carrier, which will influence important parameters like which site to target, the release pattern of drug, diffusion rate, tissue binding capacity retention time, etc. Dosage form-related factors are also influenced by the choice of the vehicle incuding shelf life, stability, toxicity, etc.

  Various examples of the controlled release dosage form are liposomes, microparticles, and PEGylation.

3. Macrophage clearance

As discussed in the previous section of this chapter, macrophage phagocytosis is the process in which macrophages engulf the foreign particles as an immune response. Macrophage clearance can be avoided by changing some physical factors of the dosage form, like particle shape and particle size (10).

- Particle size
  Particles are developed in such a way that they can invade deeper airways without any resistance provided by mucociliary escalator and thus deposition. This is done by altering a particle's aerodynamics, hence particles having an aerodynamic diameter in the range of 0.5–1 micrometers reached the deeper airways with negligible deposition. But particles with this diameter are more attacked by macrophages, so it is a challenge to develop a formulation that can invade with the least deposition and also can avoid macrophage clearance.

  Large porous particles (LLPs) offer one approach with particles having a geometric diameter of more than 5 micrometers, but their aerodynamic diameter is less than 5 micrometers. This is because of their low density; they show better flowability as compared to conventional forms. Due to their large size, they can avoid macrophages. They can deposit homogenously on the cell surface and show no toxicity.

  Geometric diameter plays an important role when we talk about avoiding macrophages. Another approach is reducing geometric diameter to nanometers; this way they can remain on the surface and can resist ciliary as well as macrophage clearance. These nanoparticles, NPs, can extend drug release, hence can be used for controlled drug release. They offer advantages over conventional dosage forms, but some disadvantages restrict their use. For example, their minute size makes them easy to expel from lungs before they reach deeper airways—this can be avoided by forced inhalation—or they can be incorporated in microparticles and hence can be delivered efficiently.

  Low-density micron-scale particles, such as Trojan particles, are produced by using polymer-like polystyrene, hence polystyrene nanoparticles (PS-NP), are assembled into hollow micron-scale particles while spray drying. Trojan microparticles are formed during spray drying; assembly is driven by van der Waals forces. These low-density hollow particles offer good flowability and dispersibility characteristics, and as they are delivered to deeper airways they are able to produce sustained/controlled drug release.

- Stealth characteristics
  This is one of the promising ways of avoiding macrophage clearance. This can be altered by attaching or coating the main therapeutic ingredient with a material that provides stealthiness to the agent. Altering stealth characteristics can provide controlled drug delivery in the pulmonary airway.

  Agents like PEG can increase the circulatory time in the airway and also reduce the clearance. Microparticles are coated with this material, which increases their circulatory time.

  Other ingredients like hyaluronic acid, known for their mucoadhesive properties, are used in many pulmonary therapeutics. Also, they can be used for the controlled delivery of drugs.
- Drug release within or from macrophages
  When the drug-loaded vehicles undergo phagocytosis, macrophages act as a reservoir for the drug release. This can serve in maintaining the dose inside the body which helps to reduce dosing frequency and also improves patient compliance. Some of the recent approaches to increasing drug retention inside the lungs are to use of nanocarriers coated with specific ligands that have an affinity towards MR or mannose receptors which are found on macrophages. Mannose acts as an indicator between self and non-self as they are not present at the terminal ending of mammalian glycoproteins but are present on the surface of pathogenic glycoproteins. This promotes receptor-based cellular uptake of various mannosylated formulations like liposomes coated with specific ligands with an affinity for MRs. Mannose derivatives include O-palmitoyl mannan (OPM) and p-aminophenylmannopyranoside (PAM).

4.6 Airway Cells, Pulmonary Circulation, and Receptors: Importance and Function

4.6.1 Airway Cells

Drug absorption is observed in the respiratory region, which is marked by a thinner epithelial, responsible for the diffusion of gases and drug delivery. The alveolar region is a site of interest for pharmaceutical scientists seeking to provide sufficient therapeutic effect. Hence, a detailed study of the alveolar region is necessary. The alveolar region is composed of two types of cells, alveolar type 1 cells (AT1) and alveolar type 2 cells (AT2) as discussed in the earlier portion of this chapter. AT1 covers over 95% of the area, whereas AT2 cells are more numerous, in the ratio of 2:1 (AT2:AT1).

AT1 is highly water permeable and is responsible for the transport of macromolecules because of the presence of a high number of vesicles and caveolae, thus reduce cell thickening (11). AT2 cells are responsible for the secretion of surfactants, and are also responsible for the recycling of the same. They either proliferate into more AT2 cells or differentiate into AT1 cells. They are embedded in the alveolar epithelia in such a way that they form a highly tight layer, preventing leakage.

4.6.2 Airway Receptors

Understanding of pulmonary receptors is of great importance as it increases the targeted delivery efficacy. Pulmonary epithelia comprise of many membrane-bound receptors especially in the smooth muscle and epithelia of airways. Pulmonary epithelia are composed of parasympathetic receptors which can be of two types, adrenergic and muscarinic receptors; both are G protein-coupled receptors and are targeted to relax the smooth muscle, which can cause bronchodilation.

Amongst all the most commonly explored receptors are adrenergic beta 2 receptors, BAR. They are most prominently present on alveolar cells of both AT1 and AT2 cells. beta1 adrenergic receptors are majorly present on alveolar epithelia. Beta 2 adrenergic receptors can be seen on the mast cell, epithelia, and endothelia. Targeted delivery of beta-receptor agonists can result in a response like the relaxation of smooth muscle bronchodilation and hence are used in COPD. Overexposure results in resistance, which can cause sensitization of receptors against agonistic action. All the actions are summarized in Figure 4.4.

Activation of G-protein coupled receptors seems to have more therapeutic use because of their higher specificity for COPD than asthma. A subtype of the muscarinic receptor, M_3, can lead to the release of acetylcholine, causing bronchoconstriction by smooth muscle constriction, which is contradictory to the beta 2 receptor bronchodilation action (12).

4.6.3 Effect of Blood Circulation on Drug Delivery

Bronchial blood circulation can play a major role in clearing out foreign particulate material, balancing the temperature of the pulmonary environment as an immunological precursor which is due to the presence of various cells like mast cells, lymphocytes, etc.

In the human lungs, the pulmonary artery carries blood from the right ventricle, and then deoxygenated blood is carried to the lungs, where gaseous exchange takes place in the alveolar region and the oxygenated blood is carried by pulmonary vein to the left atrium, where oxygenated blood is then pumped to the different parts of the body.

Different pathophysiological conditions can result in physiological changes like an increase in mucosal vasculature and dilation of arteries. This condition can be seen in COPD, where dilation results in edema and bronchial constriction. Such physiological changes interfere with various factors like drug delivery, therapeutic dose; lung hyperinflation can result in constriction of blood vessels like an arterial vessel. Drug absorption is affected by blood flow; more blood flow results in high absorption. However, if the drug is intended for local systemic effect, due to high mucociliary clearance, high blood flow can result in certain adverse effects (13).

Pulmonary airways are lined by two major cells which are responsible for secretions found in pulmonary airways: serous and mucous cells. They are found beneath the epithelial lining of bronchial airways which are responsible for immunological and anti-microbial activity that is by certain secretions like anti-microbial peptide, lysozyme, and antibody-like IgA. Types of secretions with their secretory cells are listed in Table 4.3.

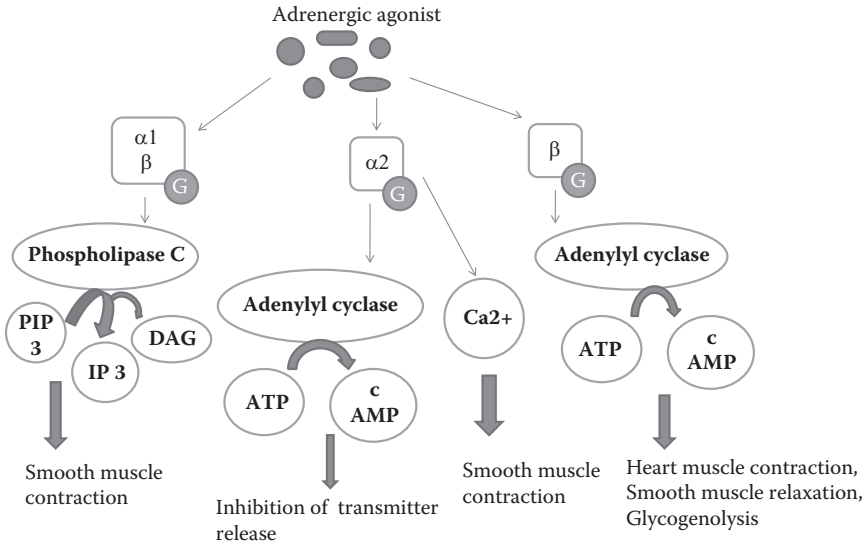


FIGURE 4.4 Adrenergic Receptor Mechanism of Action

TABLE 4.3

Various Types of Secretory Cells and their Secretions Found in the Pulmonary Airway

Mucous Cell	Serous Cell
• Mucin • Anti-microbial peptide	• Mucin • Lysozyme • Proteoglycan • IgA • Lactoferrin • Anti-microbial peptide • Albumin

The extent of mucus secretion depends on the patient's pathological condition and disease state if any. Mucus is secreted by the interference of muscarinic receptors (M_{1-3}), which is cholinergic stimulation. Cholinergic innervations can also result in the synthesis of macromolecules like albumin and epithelial changes by interfering with active ion transport and passive water efflux.

Drug delivery is significantly affected by mucus production. If a drug is hydrophilic, then molecules eventually undergo dissolution and absorption as soon as they come in contact with the mucus membrane. Whereas, if the drug molecules have different properties, then drug particles will show low dissolution and absorption.

4.7 Pulmonary Drug Delivery: Dissolution, Metabolism, Absorption, and Clearance

4.7.1 Pulmonary Dissolution

Particles are dissolved as they enter the body before absorption in the lungs. This process is enhanced by the presence of fluid lining the airways (14). The airways are lined by bi-phasic-phospholipid and mucus lining in the bronchi-bronchioles region and by surfactants in the alveolar region. They both affect the dissolution in their own ways. The process is affected by the physicochemical properties of drugs and their solubility in fluid. Drugs are restrained by mucus, and dissolution is enhanced at the alveolar region by the presence of surfactants.

4.7.2 Pulmonary Absorption

The process of absorption depends upon drug properties like pKa, lipophilicity, and the partition coefficient. Membrane properties also affect the absorption; the dissolution process is necessary before absorption, which requires an adequate amount of fluid for the wetting of the drug particle. Absorption can happen by passive diffusion of particles, that is, direct absorption of particles through the membrane without any requirement of energy. Mostly lipophilic drugs having a particle size less than 50 Da can absorb through this mechanism. The bigger particle is absorbed through carrier-mediated transport where membrane-bound proteins are present which helps in translocating the particles. This can be facilitated diffusion in which no energy is required, it can be seen for the larger size hydrophobic particles and small-sized hydrophilic drug. Active transport of drugs can be seen for the particles, which are large, mostly for the hydrophilic particle. In lungs, alveoli are the absorption site of drugs because they are highly perfused. Also, the presence of surfactants reduces the surface

tension, thereby reducing the particle size and enhancing particle absorption.

4.7.3 Mucociliary Clearance

The upper respiratory tract is lined by cilia which does not adhere to the airway epithelia by mucus secretion. The ciliary movement, also called ciliary beating, causes the upward movement movement of mucus. The drug particle is the foreign particles in response to which mucus is secreted. This mucociliary layer reduces in thickness in the peripheral region this enhances drug deposition in the central respiratory tract. Drug absorption enhances retention time. The alveolar region is lined by lymph nodes and cells like macrophages cause phagocytic clearance of the drug by macrophage clearance. This process is slow, and since they are highly perfused, the absorption is carried out more quickly.

4.7.4 Pulmonary Retention

Pulmonary retention of drugs is affected by the physicochemical properties of the drugs, such as their particle size and solubility. More lipophilic drugs have a high retainability in the lungs. Hepatic enzymes like CYP1A1 and CYP2EA have metabolizing capacity and reduce retention time. Various xenobiotic compounds like serotonin are located in epithelial cells. The CYP enzymes are significantly present in Clara and alveolar type 2 cells. Due to high perfusion and high cardiac rate the pulmonary metabolism is very high. In the tracheobronchial region, the perfusion rate is low, hence, more equilibrium and high retention.

4.8 Affect of Lung Physiology and Pathophysiology on Drug Absorption

Many factors like high altitude pulmonary edema, deep breathing, hyperventilation, etc. can cause variation in breathing patterns from one person to another by the expansion of alveolar epithelia, as well as increased permeability of transcellular pores across a membrane; smokers have increased permeability of the blood–brain barrier which can cause increased uptake of a molecule.

A pathophysiological condition which causes bronchoconstriction can affect the absorption capacity of lungs, like COPD or cystic fibrosis in which hypersecretion of epithelia causes airways constriction. They play a large role in the selection of drug delivery mechanisms. The main motive is to target the site where high absorption is found with the desired local effect. Hence, pathophysiological factors play an important role in the delivery of drugs to target sites where it can overcome the effect of the blood–air barrier with a high degree of absorption.

To get the desired therapeutic effect, sometimes overlooked is multiple drug therapy where one drug targets the primary disorder and the other reduces the resistance interfering with the action of the primary drug. For example, vasoconstrictors are taken up by the patient with bronchodilators where vasoconstrictors constrict the blood vessel reducing their vasicular uptake and increasing the pulmonary drug concentration.

4.8.1 Pharmacokinetics of Nasal Drug Delivery

Drug absorption through the intranasal route is expressed in the terms of absolute absorption, or Ae. Ae can be expressed by the following equation

$$Ae = \frac{(AUC)i.\ n(Dose)i.\ v}{(AUC)i.\ v(Dose)i.\ n}$$

where (AUC)in is the area under the curve by intranasal administration, and (AUC)iv is the area under the curve by intravenous; (dose)in and (dose)iv are the intranasal and intravenous doses respectively.

The other way of calculating absolute availability is through urinary excretion data before intranasal and intravenous drug delivery that is expressed by unmetabolized drug excreted in the urine form, or Au^{∞}.

$$Ae = \frac{(A\infty)i.\ n(Dose)i.\ v}{(A\infty)i.\ v(Dose)i.\ n}$$

Absolute absorption through urinary data collection can be applicable only when the fraction of drug absorbed and excreted in urine is the same as in intranasal delivery.

4.8.2 Pharmacokinetic Processes of Oral, Intravenous, and Inhalation Administration

Oral drugs first interact with the gastrointerstitial tract where they are absorbed into systemic circulation after reaching the liver through the portal vein. Here, the drug-release kinetics are influenced by dissolution and solubility in the gastrointestinal environment. Here, the first-pass metabolism takes place, which decreases bioavailability through hepatic clearance.

After that, the drug reaches the intestinal environment where drug crosses the mucosa through membrane permeability transporter affinity and drug solubility and other physicochemical properties. When a drug is taken via an intravenous route, the drug can resist the gastrointestinal absorption and hepatic clearance (15).

To have high pulmonary clearance but low systemic bioavailability, the drug should have a low systemic affinity. Also, the systemic clearance should be high to increase pulmonary retention or selectivity.

Pulmonary retention may also be increased by the high protein binding affinity of drugs which reduces free drug concentration in plasma. In turn, this reduces bioavailability.

The PK or airway selectivity is the approach by which efficient delivery in the pulmonary targeted delivery is seen. Airway selectivity can be optimized by varying particle size, charge, etc.

4.9 Pulmonary Drug Delivery: Different Molecular Size

4.9.1 Smaller Molecules Used to Deliver Drugs through the Pulmonary Route

The systemically acting molecules, when given via inhalation, can show a high rate of systemic absorption. They can be

classified based on the molecule's size; particles with a molecular weight less then 1000 Da are said to be small molecules. The bigger molecules are proteins, peptides, and vaccines.

Drugs with smaller weight are being widely used in conventional form, due to their lower molecular weight, and their pharmacokinetic and bioavailability parameters. Inhalation is being widely used for drugs given by inhalation, due to rapid absorption.

As lungs provide absorption for both lipid-soluble and water-soluble drugs by the cellular membrane and aqueous porin channels respectively, smaller molecules are easily absorbed through pulmonary epithelia. Various example of nano peptide molecules given as drugs via pulmonary transepithelial route include treprostinil.

This has an antiplatelet and vasodilatory action when given either by a systemic route or by pulmonary inhalation. Treprostinil is given by subcutaneous infusion because it is less cumbersome and does not require a central catheter for its application. Even though the drug has a higher half-life, it has to be administered by subcutaneous infusion, and it causes complications like infection at the site of action. It also causes discomfort because of the needle-based delivery of the drug. For this reason it is given via the pulmonary route.

4.9.2 Large Microporous Molecules

Large porous molecules have been used to treat many pulmonary diseases. The major problem in pulmonary drug delivery is ciliary clearance. The molecules having a mean geometric radius range between 1 and 5 microns will have high, deep pulmonary retention. Deep pulmonary retention reduces clearance with high systemic effect and to increase the retention molecules have to remain in the above range.

Microspheres are the type of delivery system in which the drug is uniformly distributed in the polymer matrix. Microspheres can be macro- (3 micro m), meso- (1–3 micro m), and nanoporous (200–500 nm). Porosity provides pulmonary retention, hence, macroporous microspheres have sustainable action. Aerodynamic radius is affected by the diameter range of the particle.

These large, highly porous molecules tend to resist accumulation. The molecules in the presence of alveolar macrophages undergo phagocytosis.

4.9.3 Pulmonary Delivery of Large Peptides and High Molecular Weight Drugs

Drugs like insulin and low molecular weight heparins are used extensively by the patients with lifelong persisting diseases, hence much research has been done to make the delivery system non-invasive. Pulmonary delivery provides a scope for lower invasiveness, so this route is explored for such drugs.

4.9.3.1 Insulin

Inhalable insulin is short-acting insulin for patients with diabetes type I or II. In the case of diabetes I, a combination of long-acting insulin with inhalable insulin is recommended. The recombinant human insulin is given by a thumb-size inhaler with a powder of fumaryl diketopiperazine. The microparticles are then absorbed into the circulation as soon as they come in contact with the lung's surface. The sudden absorption of insulin makes them fast-acting. This is known as *technosphere technology*. By this, the rotating dose of 2.5 micro g of insulin can be taken before every meal. Many disadvantages of the inhalable insulin include decreased diffusing lung capacity for carbon monoxide as compared to subcutaneous delivery of insulin. This route is not convenient for all patients, such as those who smoke or those with diabetes ketoacidosis.

4.9.3.2 Low Molecular Weight Heparins (LMWH)

These drugs come under the category of blood thinners, given in conditions like deep venous thrombosis or DVT. The nature of low molecular weight heparins is anionic, hence when given by the oral route it causes inadequate absorption through the gastric mucus membrane and even through the pulmonary route. LMWH carry an anionic charge because of the presence of carboxylic acid and sulfate groups at the glucosaminoglycan region.

Using drug delivery carriers like dendrimers, which have a positive charge, can create an overall non-ionic environment, causing ease to absorption by the pulmonary route.

4.10 Nanocarriers in Pulmonary Delivery of Drugs

- Liposomal delivery system
  The liposomal nanocarriers can be utilized in aerosol as they are highly aqueous compatible. For this reason, the retention seen in hydrophobic compounds is not seen in drug–liposomal complexes, hence reduced toxicity is another advantage of this system. It can be used to deliver drugs via the intracellular route, so they are good carriers if the drug needs to be delivered to the alveolar macrophages. They are advantageous because they can provide action for systemic as well as local irritation.

  Another factor that makes liposomes a great tool for drug delivery is the depot effect. This is the effect in which carriers mimic the immune system by sustained release of an antibody. Aerosols equipped with jet nebulizers are used to deliver liposomal formulations for treating many respiratory problems. Alveofact was the first liposomal formulation given via the pulmonary route, to treat diseases like respiratory distress syndrome (RDS). These formulations are given in liquid form through aerosols.
- Solid lipid nanoparticle in pulmonary delivery
  They contain solid lipids which remain solid at room temperature, water, and a surfactant. These SLNs are being used widely because they provide a sustain and controlled release pattern when given through the pulmonary route. When compared to other polymer-based nanoparticles, these physiological lipid-based nanoparticles show low pulmonary tolerability and high toxicological properties (16–25). They are generally given as

dry powder by aerosol. A few of the examples of SLN-based drug delivery are isoniazid and rifampicin, given with controlled and sustained delivery for treatment of tuberculosis through the pulmonary route.

- Dendrimer based pulmonary delivery
  These are nanoparticles which have a star-shaped structure. They are highly branched macromolecules. They are characterized by layers between each cascade point known as generations. The structure can be divided into three portions: inner central core, inner branches, and outer core. Their high branching and entrapping efficiency are used in delivering drugs of varying molecular weights and hydrophilic entities by host–guest interaction, and hydrophobic entities by covalent bonding. The major advantage provided by their structure is that they provide wide scope for functionality, increasing the chances of structural modification of by conjugation of different drugs and functional groups which amplifies the functionality. They have a higher surface to molecular functional group ratio. Hence, they are widely used as a vector in gene and drug delivery. Several disadvantages of dendrimers can be high toxicity, short half-life, and low aqueous solubility. The dendrimer form is generally used in gene delivery to the pulmonary region.
- Micelle
  These are the colloidal system, liquid crystal nanodispersion containing small particles ranging from 10–400 nm in diameter. The system contains a vesicle, in which the drug can be entrapped and delivered in higher concentrations greater than their water solubility. The other advantage offered by this system is that it can be modified based on the requirement; the outer shell of the micelles can be modified with certain functional groups.

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