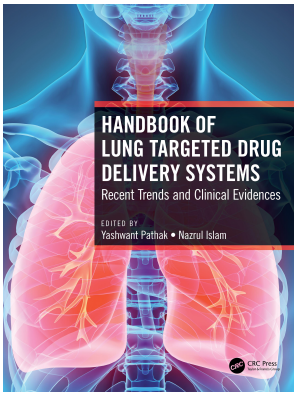

Handbook of Lung Targeted Drug Delivery Systems Recent Trends and Clinical Evidences

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Understanding the Pharmacokinetics and Pharmacodynamics of Lung and Lung Drug Delivery

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Understanding the Pharmacokinetics and Pharmacodynamics of Lung and Lung Drug Delivery

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5.1 Introduction

The propensity of a drug to reach its target and elicit an effect is partly dependent on drug formulation and route of drug administration. Furthermore, the time course for the movement of a drug through and out of the body (pharmacokinetics) and the biochemical and physiological effects of the drug at the target site (pharmacodynamics) are key determinants during the process of drug development. Therefore, understanding the pharmacokinetics (PK) and pharmacodynamics (PD) of a drug is essential. Drugs can sometimes be formulated to aid delivery to specific tissues or organs, and in their review, Dawidczyk, Russell, and Searson (1), highlight the relevance of understanding the PK and PD of drug delivery.

Over the last few decades there have been studies that have explored using the lungs as a means of drug delivery. The lungs or pulmonary route is non-invasive and can be used in the administration of drugs for both local and systemic effects. This route can be used to deliver drugs to patients with chronic obstructive pulmonary diseases (COPD) such as asthma. Also, due to its high permeability and large absorptive surface area, the lungs are ideal for drugs intended for systemic effects. The epithelium of the alveoli has been found to be an absorption site for a number of therapeutic agents (2, 3). Furthermore, the pulmonary route has an advantage over enteral routes of drug administrations because of minimal first-pass metabolism.

In this chapter, we delve into the PK and PD of the lung and lung drug delivery with emphasis on recent trends and clinical evidence.

5.2 Pharmacokinetics of the Lung and Lung Drug Delivery

5.2.1 Absorption of Drugs in the Lungs

Drug delivery to the lungs may have two main purposes: local or systemic effects. For drugs administered via the lungs or pulmonary route for systemic effects, drugs have to be absorbed into the bloodstream across a first barrier: the alveolar blood (air–blood) barrier. The alveolar blood barrier is made up of an epithelial cell, basement membrane, and endothelial cell. While this anatomical arrangement facilitates movement of gases or volatile liquids across the lungs, it can be a major barrier to other large molecules. Before gases or volatile liquids are absorbed into systemic circulation, they must move across epithelial lining fluid. The epithelial lining fluid is usually at the corners of the alveoli and also has a layer of surfactant. The surfactant is made up of phospholipids such as phosphatidylcholine and phosphatidylglycerol. The surfactant also contains key apoproteins (4). Functions of the surfactant are diverse, two of which include maintaining fluid homeostasis in the alveoli and eliciting a number of defense mechanisms. A number of studies have suggested that the surfactant may impair diffusion of molecules (drugs) out of the alveoli (5, 6).

There are a number of mechanisms by which drugs are known to be absorbed from the lungs. It has been hypothesized that drug absorption occurs via transcytosis (adsorptive or receptor mediated), through large transitory pores in the epithelium or paracellular transport between bi-junctions or tri-junctions (7). It is noteworthy that often the high bioavailability of drugs administered into lungs may be due to the lungs' large absorptive surface area, thin diffusion layer, and relatively slow elimination (7).

There are conflicting results on the effect of pathophysiological changes (e.g. inflammation) on drug absorption from the lungs. Some have reported that permeability of the lungs is increased during inflammation (8, 9). Some researchers have demonstrated that absorption is not affected, while others suggest a decrease in absorption (10, 11). Those who have reported that absorption may not be affected have explained this as restitution after epithelial injury (10, 11).

5.2.2 Elimination of Drugs in the Lungs

Elimination of xenobiotics from the body occurs via metabolism and excretion. Metabolism refers to biochemical transformation of xenobiotics catalyzed by specialized enzymes usually located in the liver, intestines, and lungs. Generally, metabolism converts lipophilic xenobiotics into more hydrophilic products that facilitate their excretion from the body.

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Xenobiotic metabolism may involve different biotransformation reactions that lead to the generation of water soluble and sometimes reactive metabolites (Phase I reactions). Phase I reactions may be followed by conjugation of metabolites with endogenous molecules such as glucuronic acid, acetate, sulfate, and glutathione (Phase II reactions). Phase I reactions may be oxidation reactions catalyzed by monooxygenase enzymes, i.e. cytochrome P450 (CYP) monooxygenases and flavin monooxygenases (FMN). Phase I reactions could also be reductive reactions catalyzed by CYP reductases.

CYP enzymes are responsible for oxidative metabolism of xenobiotics such as drugs, environmental pollutants, and carcinogens. CYP enzymes also metabolize endogenous compounds such as hormones. In humans, the CYP enzyme system is made up of about 57 isoforms that show differences in catalytic activity. CYPs act by using one atom of molecular oxygen to oxidize xenobiotics. The CYPs usually require NADPH-cytochrome P450 reductase to donate electrons for the reduction of the second oxygen, and this yields water. Functionality of the NADPH-cytochrome P450 reductase is relevant for xenobiotic oxidation (12).

Metabolism of xenobiotics in the lungs differs significantly from what pertains in the liver and intestines. Expression levels of enzymes in the lungs are generally low, and the patterns of drug-metabolizing enzymes differ. In the lungs, CYP3A5, CYP2B6, CYP1B1, and CYP1A1 and CYP2E1 appear to be the most common CYP enzymes (13–17). The most abundant CYP enzyme in the liver, CYP3A4, has a relatively low expression in the lungs. The isoform CYP3A5 is by far the most important CYP enzyme in pulmonary tissue (18–20). Data is scanty on the role of Phase II enzymes in the lungs (21). It is noteworthy, however, that the expression and catalytic activity of sulphotransferase enzymes in the lungs appears to be about the same in the liver. Also, peptidase activity has been found to be high in the lung, as found elsewhere in the body (22). As already indicated, activity and level of expression of xenobiotic metabolizing enzymes in the lung is low, and this may account for disparate data reported in the literature.

Drug-metabolizing potential of the lungs is generally lower than that of the liver, and there is little evidence to suggest that the lungs play a major role in systemic clearance of xenobiotics. Xenobiotics after administration into the lungs have near complete bioavailability because of the low metabolic activity. Nonetheless, some drugs (salmeterol, theophylline, etc.) still undergo some extent of metabolism in the lungs (23–27). There is the likelihood of formation of drug metabolites in the lungs, hence, in the process of drug development there is the need to assess risk of metabolic interactions and toxicity. Metabolism of drugs in the lungs could also aid the activation of certain prodrugs. For example, beclomethasone dipropionate is metabolized by esterases to 17-beclamethasone monopropionate, an active metabolite (28).

The lungs also have the capacity to remove secretions and foreign agents that are deposited in the airway. There are ciliated cells that move mucus and any foreign agent out of the lungs in a proximal direction (29). At the end, the mucus and foreign agents are expectorated and/or swallowed. This process is termed *mucociliary clearance* (30–32). Inhaled drugs that may contain insoluble particles (diameter > 6 mm) are eliminated from the airway via mucociliary clearance (33, 34). Drugs administered into the lungs that have particle sizes with diameter less than 6 mm can move across the mucus layer and enter the bronchial epithelium (35). Additionally, drugs administered into the lungs that have small particle sizes may be deposited in the alveoli and eventually dissolve in them (37,35).

The human anatomy also makes possible mucociliary clearance occurring from the peripheral toward the central airways (36). Mucociliary clearance can be affected by age and airway disease (41, 38, 44). Studies have shown that pharmacotherapy can be used to improve mucociliary clearance in patients with COPD (39, 47, 40, 49).

Drugs administered into the lungs can also undergo alveolar clearance aided by macrophages (42). Drugs that dissolve in the alveoli may be phagocytosed by alveolar macrophages (43–45). To improve bioavailability via the pulmonary route, drugs are now being designed to escape alveolar clearance (55, 35, 43). Current pharmacological research suggests that alveoli macrophages may play beneficial roles in the management of diseases such as leishmaniasis and tuberculosis (46 ,44).

5.3 Pharmacodynamics of Lung Drug Delivery: Recent Trends and Clinical Evidence

5.3.1 Inhaled Antibiotics

Research into delivery of antibiotics into the lungs is still at the early stage. At present, a number of studies have focused on inhalers formulated into dried powders that deliver antibiotics directly into airways where there may be infectious microorganisms. Some commercially available inhaled antibiotics are shown in Table 5.1.

TABLE 5.1

Current Commercially Available Inhaled Antibiotics

Antibiotic	Indication	Approving Agency	Reference(s)
Aztreonam (inhalation solution)	To improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa* infection aged ≥ 7 years	US FDA	(45)
Tobramycin (inhalation solution and powder)	Management of cystic fibrosis patients with *Pseudomonas aeruginosa* infection aged ≥ 6 years	US FDA	(46)
Colistimethate (dry powder for inhalation)	Management of chronic pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged ≥ 6 years	European Medicines Agency	(47)

US FDA – United States Food and Drug Administration

TABLE 5.2

Inhaled Pulmonary Aerosols Undergoing Clinical Trials

Drug	Phase	Type	Potential Clinical Use	Company	References
Amikacin (Arikace™)	Phase I | II	Liposomal formulation for nebulization	Cystic fibrosis	Transave Inc.	(57)
Amikacin (BAY41–6551)	Phase III	Solution for inhalation	Pneumonia	Bayer	(58)
Aztreonam	Approved for marketing	Lyophilized drug for nebulization	Cystic fibrosis	Gilead Sciences	(59)
Ciprofloxacin	Phase III	Dry powder for inhalation	Pseudomonas infection	Bayer	(60)
Levofloxacin	Phase III	Solution for inhalation	Cystic fibrosis	Mpex Pharmaceuticals	(61)
Tobramycin	Phase III	Dry powder for inhalation	Cystic fibrosis	Novartis	(62)

Delivery of antibiotics with inhalers into the lungs could result in high drug concentrations at the infection site. This will eventually decrease the risk of systemic side effects. By comparison, the use of oral or intravenous antibiotics often leads to low drug concentration in the lungs. Inhaled aerosols of antibiotics have been shown to have significant clinical benefit in the management of pulmonary infections (53-55). Additionally, several clinical trials of inhalation antibiotics are ongoing; examples of a few are listed in Table 5.2.

5.3.2 Hormones Administered through the Pulmonary Route

5.3.2.1 Inhaled Insulins

The use of exogenous insulin has greatly improved diabetes mellitus management. Despite this, pharmacotherapy with exogenous insulin remains suboptimal in many people with diabetes mellitus. Additionally, available insulins administered parenterally have metabolic actions that are delayed and with prolonged period of effect. The aforementioned challenges could lead to postprandial hyperglycemia and late postprandial hypoglycemia. Scientists have investigated other possible routes for insulin administration. Among these other routes, lung delivery of insulins has shown promise.

Available insulin preparations on the market are usually administered via parenteral routes. However, the lungs provide an alternative for administration of some polypeptides such as insulin. The lung is well vascularized, has a large surface area, good solute exchange, and an alveolar epithelium that can facilitate systemic delivery of insulin. A number of clinical trials have shown the possibility of insulin therapy via lung delivery.

Inhalable insulin is usually formulated into a powder and delivered to the lungs with an inhaler. This approach is considered as a paradigm shift in insulin therapy, as it differs in diverse ways from the traditional. Earlier work with inhalable insulin concluded that although this formulation appears to be equally effective, it is not superior to injected insulin (56–61). Additionally, inhalable insulin may not be cost effective (62).

Two rapid-acting insulins administered by inhalation, Exubera and Afrezza (Technosphere® Inhaled Insulin), have been an innovation milestone in the search for alternative routes of insulin administration. Inhaled insulin most likely would have advantages for diabetic patients because some of these patients have needle phobia and also have challenges with correctly administering insulin via the parenteral route. It is noteworthy, however, that in 2007, Exubera was withdrawn from the market. This withdrawal was as a result of poor sales and difficulty in handling inhalers by some patients (63).

In a study to assess the efficacy of a newly developed inhaled insulin among 25 patients with Type 1 diabetes mellitus, the baseline-corrected glucose infusion rate (GIR) after administration of 8 U of Technosphere® rose faster and declined sooner than in patients who received 10 U of subcutaneous insulin lispro (64). Peak GIR after 8 U of Technosphere® Inhaled Insulin was reached 30 min after administration, whereas subcutaneous administration of insulin lispro lead to a GIR peak of approximately 150 min. In the same study, time to 50% of maximal effect (T50% C_{max}) was 19 min for Technosphere® Inhaled Insulin and 50 min for insulin lispro. After 2 hours, Technosphere® Inhaled Insulin had delivered 60% of the total glucose lowering effect compared to 33% for insulin lispro. The GIR for Technosphere® Inhaled Insulin returned to baseline at approximately 3 hours, whiles that of insulin lispro was 5 hours (64).

In another study among 12 patients with Type 1 diabetes, peak GIR was achieved at 53 min with Technosphere® Inhaled Insulin administered using the Gen2 inhaler compared with 108 min for insulin lispro (65).

Additionally, inhaled insulin was used to manage subcutaneous insulin resistance syndrome, a rare condition that occurs as a result of rapid degradation of insulin in subcutaneous tissue (66). Data from "The Medical Letter on Drugs and Therapeutics" that compared inhaled and conventional insulin treatments showed that glycemic control as assessed by mean decrease in hemoglobin A1c from baseline to end point did not differ significantly (67). Furthermore, adverse events associated with inhaled insulin appear to be comparable to subcutaneous administration, although cough may occur with the former, which tends to decrease with continued use (64).

5.3.2.2 Inhaled Growth Hormone

Since the advent of growth hormone replacement therapy among children in the 1950s (68), use of injections has been the only route of administration. Growth hormone administration by injection is associated with non-compliance and early termination of treatment (69–73). Despite advances in drug formulation and delivery methods, there have been few alternatives to the administration of human growth hormone aside from parenteral routes. Since compliance with injections

is a significant challenge with drug delivery among children, the development of an inhaled formulation as an alternative to daily injections is imperative.

Currently, drug delivery via aerosol technology has improved with the use of drugs that have larger particle size, low densities and a tendency to agglomerate. The aforementioned improvements tend to increase efficiency of deep lung delivery and also improve systemic absorption. Application of this has enabled development of somatropin inhalation powder (SIP), an inhalation formulation of human growth hormone.

Walvoord and colleagues in 2009 reported that inhaled SIP administered for 7 days to growth hormone deficient children was well tolerated and resulted in a dose-dependent increase in the blood levels of insulin-like growth factor 1 (IGF-I) and growth hormone. Of the expected drug bioavailability based on previous adult data, SIP was found to be only 50% (73). The limiting factor in the development of SIP has been its bioavailability data. Future studies are thus required to improve the low bioavailability of SIP.

5.3.3 Inhaled Corticosteroids

The effects of corticosteroids are mediated via the glucocorticoid receptor. Generally, glucocorticoid receptors are ubiquitous in the body, hence, corticosteroids may act on these receptors in several tissues. There are two known glucocorticoid receptors: Type I and Type II. Most ligands appear to bind to the Type II receptor. The therapeutic and adverse effects of inhaled corticosteroids are mediated by the Type II receptor (72, 73). Stimulation of gene transcription by corticosteroids is known to be associated with several adverse effects, whereas repression of transcription factors, such as activator protein-1 and nuclear factor-B, appear to lead to the relevant anti-inflammatory effects of corticosteroids (72, 73).

Receptor binding affinities of corticosteroids are usually estimated in comparison with standard dexamethasone which has an affinity of 100. Mometasone furoate is reported to have the highest affinity of 2300, followed by fluticasone propionate (1800) and beclomethasone monopropionate (1345) (75). The new corticosteroid ciclesonide, which has an active metabolite desciclesonide, also shows a high receptor binding affinity of 1200 (76, 77). Reports suggest that receptor binding affinity differences among drugs can be compensated for by administering dose equivalents (78).

In a recent systematic review, Halpin and colleagues concluded that there is no evidence that suggests that the use of inhaled corticosteroids may lead to adverse or beneficial outcomes in acute respiratory infections due to coronavirus (79). They further suggested that randomized controlled trials are needed to assess the benefits of inhaled corticosteroids in the management of coronavirus disease 2019 (COVID-19) in patients with or without chronic respiratory disease (79).

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