Chapter 2
Pulmonary Drug Metabolism, Clearance, and Absorption

Bo Olsson, Eva Bondesson, Lars Borgström, Staffan Edsbäcker, Stefan Eirefelt, Katarina Ekelund, Lena Gustavsson, and Tove Hegelund-Myrbäck

Abstract Delivering therapeutic agents to the lungs requires a deep understanding of the kinetics and dynamics of drugs in this biologically and physiologically complex system. In this chapter these concepts are discussed and include drug dissolution rates in the airways, physical clearance mechanisms of the mucociliary escalator and cough, alveolar macrophage clearance, pulmonary metabolism, and pulmonary absorption. Finally, these aspects are considered together with drug and formulation aspects as determinants of duration of effects of inhaled products. The mechanisms of elimination of drug activity in the lungs by the various clearance processes described here are important factors to consider both in the development of new drugs and in understanding the relative merits of existing therapies.

Keywords Airway selectivity • Lung absorption • Lung metabolism • Lung retention • Mucociliary clearance • Prodrugs • Pulmonary drug dissolution • Pulmonary drug transporters • Soft drugs

2.1 Introduction

There are essentially three major benefits that may be attained by delivering medication to the lungs via the inhaled route: rapid onset of action, high local concentration by delivery directly to the airways (and hence high therapeutic ratio and increased selectivity), and needle-free systemic delivery of drugs with poor oral bioavailability. If any of these benefits can be achieved and are of therapeutic importance, inhalation will be a reasonable delivery route. These benefits are dependent
Bo Olsson et al. on the mode and rate of elimination of the delivered drug from the lungs by the various clearance mechanisms, which are the subject of this chapter.

An inhaled drug substance may be eliminated from the lung by mucociliary or cough clearance to the gastrointestinal tract, by passive or active absorption into the capillary blood network, or by metabolism in the mucus or lung tissue (Fig. 2.1). These mechanisms may act in parallel and are responsible for the disposition and dissipation of the initially high local drug concentration in the lungs over time. Hence, these mechanisms have an important role, e.g., in determining the drug’s duration of action in the lungs and the airway selectivity of the inhaled drug. Since elimination by absorption and metabolism, and pharmacodynamic activity require the drug to be in solution, dissolution kinetics may be an important factor in this context.

2.2 Dissolution

Once the drug aerosol has been deposited onto the lung surface, the immediate fate of the drug depends on its physical state. A free, solubilized drug will rapidly diffuse into the epithelial lining fluid and become available for absorption, while a drug deposited as particulate material has to be dissolved prior to absorption and may be subject to clearance by other mechanisms such as mucociliary or cough clearance (see below).

The physicochemical properties of inhaled drugs vary considerably, from very hydrophilic to very hydrophobic (log P from −2 for the β₂-agonist salbutamol
[albuterol] sulfate and 5 for the corticosteroid fluticasone propionate, where P is the octanol:water partition coefficient) with low aqueous solubility from submicrogram per milliliter (0.1 µg/mL fluticasone propionate) to that of hundreds of milligram per milliliter (250 mg/mL for salbutamol sulfate). For compounds with high aqueous solubility, dissolution is not considered to impact the lung clearance rate, and no or only small differences in pharmacokinetics are expected for different types of formulations unless the regional deposition is substantially different and/or absorption is altered by excipients. The very poorly soluble compounds show fairly rapid onset of absorption followed by sustained absorption over time, which is thought to be dissolution limited. For micronized lipophilic drugs, time of peak concentration has been suggested to correlate with intrinsic solubility [151].

Assuming diffusion-controlled dissolution, the rate of dissolution is proportional to the drug’s solubility, the concentration of the drug in the surrounding liquid film and the area of the solid–liquid interface. The solubility of a drug depends on the compound, the formulation and physical form of the drug, as well as on the composition of the dissolving media in the lung the epithelial lining fluid. The composition of this fluid is mainly water (96%), salts, phospholipids, proteins, and mucins with a pH about 6.6 in healthy individuals [7, 44], while the surface-lining layer in the alveoli is composed of a thin layer of alveolar surfactant (phospholipids and proteins). The lipids and proteins in the lining fluid will increase the wetting, the solubility, and hence the dissolution rate of poorly soluble drugs [115, 166]. Generally, the solubility, and hence dissolution rate, is higher for a less thermodynamically stable material (crystalline polymorph or amorphous form) than that of a molecular high-order crystalline state. The concentration in the liquid film surrounding an amorphous particle may thus become supersaturated, which can promote crystallization into a more stable material unless the rate of disappearance of the solute from the surrounding liquid is sufficiently rapid. The particle surface properties can, therefore, change with time, potentially affecting both the solubility and the surface area. An example was presented by Freiwald et al. [47], where amorphous beclomethasone dipropionate (BDP) particles delivered by hydrofluoroalkane (HFA)-propelled aerosols re-crystallized in contact with bronchial fluid in vitro as shown by scanning electron microscopy images.

The total liquid volume available for dissolution in the human lung is approximately 10–30 mL. Considering that a clinically relevant dose of fluticasone propionate, as an example of a poorly soluble drug, would require a volume in excess of 1 L for complete dissolution in a stationary system, the liquid volume in the lung is small. The thickness of the lining fluid varies from about 5–10 µm in the conducting airways and gradually decreases distally to about 0.01–0.08 µm in the alveoli (although in pooled areas it may be several microns thick) [38, 107]. A drug particle deposited in the conducting airways can thus be immersed in the lining fluid while the lining fluid film may be much thinner than the diameter of a deposited drug particle in the alveoli. Consequently, the area of the solid liquid interface between the particles and the fluid is proportional to particle surface area in the conducting airways but limited by the thickness of the fluid in the alveoli. This suggests that particles deposited in the upper airways could dissolve more rapidly than particles deposited in the alveoli. However, other factors such as greater solubility, larger
total interfacial surface area, and/or more rapid absorption in the periphery could arguably lead to the opposite.

Assessing dissolution in the lungs is very complex as each of the governing parameters will be different in the different regions of the lungs, leading to several different dissolution processes occurring in parallel. By contrast, dissolution in the gastrointestinal tract can be described as a continuous process over a sequence of tanks with different properties [170].

Dissolution in the lungs has not been as systematically explored as dissolution in the gastrointestinal tract; rather the knowledge is derived from a number of diverse studies investigating in vitro dissolution models in the environmental and drug research area. Hence, there are presently no established in vivo predictive in vitro dissolution models for pulmonary formulations, in contrast to the standardized dissolution test methods available for oral solid dosage forms [51]. The lack of standardized methods may also be linked to the fact that there are no controlled release products for inhalation on the market, although the field has been intensely researched for decades. Still, in attempts to identify dissolution methods to characterize inhaled drugs, several dissolution models have been investigated, for a review see Salama et al. [127]. Most models use large liquid volumes in which the powder is immersed [30, 138], but models mimicking the air–liquid surface have also been published [24]. In these models, samples of well-defined aerodynamic particle size distributions can be prepared by deposition of the aerosol in a cascade impactor, but the mass of drug per surface area presently needs to be far higher than in the in vivo situation for analytical reasons. As a consequence, an important aspect of in vivo relevance is lost. Even though the dissolution models are fairly simple compared to the physiological complexity of the lungs, there is evidence suggesting correlations between in vitro dissolution and in vivo exposure and efficacy, especially in the field of modified-release formulations. An example is the correlation between therapeutic effect duration in an in vivo bronchoconstriction animal model and in vitro dissolution profiles presented for salbutamol sulfate controlled-release formulations [123].

In conclusion, there is no reason to doubt that the dissolution rate of formulations or compounds may affect the rate and mode of clearance from the lungs, and therefore influence the pharmacodynamic properties of a drug. As a result of the difficulty in accounting for all the confounding factors, direct evidence is scarce, which limits our ability to predict how variations in formulation that affect solubility and/or dissolution will affect the pharmacokinetic and pharmacodynamic properties of a product.

2.3 Mucociliary and Cough Clearance

Mucociliary clearance is of fundamental importance for the removal of secretions and foreign particles that have been deposited in the airways. The overall principle of the system is simple: the ciliated cells in the epithelium transport the mucus together with any deposited particles in a proximal direction and eventually the mucus is expectorated or swallowed. Inhaled aerosolized drug deposited in the lung will either
penetrate the mucus, dissolve, and become absorbed or follow the mucus and eventually become swallowed (Fig. 2.2). After deposition in the airways, the vast majority of insoluble particles larger than about 6 μm in geometric diameter is eliminated from the airways by mucociliary clearance [140]. Smaller particles are able to penetrate the mucus and enter the bronchial epithelium. The smaller the particles, the faster they reach the epithelium and thus escape mucociliary clearance. Small particles will be preferably deposited in the alveolar part of the lungs and will be dissolved or retained for substantially longer periods of time in the lung than larger insoluble particles that are more proximally deposited.

The mucus is produced by secretory (goblet) cells within the epithelium and by submucosal glands. Traditionally, the fluid is considered to consist of two phases [90]: the watery periciliary sol phase in which the cilia can beat without too high resistance, and the gel phase overlying the sol phase that contains mucins and other glycoproteins. The rapid strokes of the cilia bring them in contact with the gel, thereby propelling it in the proximal direction (Fig. 2.2) [145, 146]. In the lungs of healthy individuals, the production of mucus reaches about 10–20 mL/day [152]; in patients with chronic bronchitis 10 times these volumes may be produced.

![Figure 2.2](image.png)

**Fig. 2.2** Mucociliary clearance competing with particle dissolution and absorption. Particles deposited on the mucus layer will gradually dissolve and diffuse toward the cell layer where the drug substance eventually may get absorbed. Particles of slowly dissolving compounds will be partly cleared by ciliary action thus reducing the amount absorbed (reprinted with permission from [34]).
Mucociliary clearance of insoluble particles has been studied extensively in vivo. The mucociliary transport of such particles can be examined by direct observation through a bronchoscope, by radiography or by external monitoring of radiolabeled particles. It is fair to assume that total lung deposition does not differ to a clinically meaningful degree between healthy volunteers and patients for any of the common inhalation products on the market. However, the regional distribution of the total lung dose is likely to differ substantially between a healthy individual and a patient suffering from asthma or chronic obstructive pulmonary disease (COPD). In asthma, and also in COPD, the cross-sectional area of the airways will be smaller and thus an inhaled aerosol is more prone to impact in the more proximal parts of the lung [147]. The more central deposition of inhaled drug in constrained lungs means that any mechanism that clears the central lungs of drug into a site from which it is not systemically available (e.g., mucociliary clearance) could explain a reduced systemic exposure in patients – on the condition that the rate of absorption is sufficiently slow compared with the rate of clearance.

Mucus velocity increases from the peripheral toward the central airways [46], as is expected from the anatomical arrangement. In healthy individuals, the mucus moves upward at a rate of about 1 mm/min in the small peripheral airways but can be as quick as 20 mm/min in the trachea [164]. The rate of mucociliary clearance decreases with age in healthy individuals and can also be affected by airway disease. Patients with acute asthma have markedly reduced clearance [94]. Mucociliary clearance is also reduced in patients with chronic obstructive lung disease [19, 163] and is reduced by smoking [49, 83]. β-Agonists are known to improve pathologically reduced mucociliary function in patients with asthma [111] or chronic bronchitis [124]. The long-acting β-agonist formoterol is a powerful ciliary stimulant [86] that has been shown to increase mucociliary clearance by 46% after 6 days of treatment in patients with chronic bronchitis [93]. Inhaled corticosteroids do not appear to affect directly mucociliary clearance [32, 125], and the improved mucociliary clearance observed with inhaled corticosteroids in asthma patients is thus most likely a result of their anti-inflammatory properties [1, 94].

When mucociliary clearance is decreased, cough becomes increasingly important for the removal of secretions from the airways. A considerably larger proportion, around 60%, of centrally deposited particles were shown to be eliminated by coughing in patients with chronic obstructive lung disease compared with healthy individuals, where the value was around 8% [117]. Total clearance was similar in the two groups.

2.4 Clearance by Alveolar Macrophages

Slowly dissolving drug deposited in the alveolar region will tend to be phagocytozed by alveolar macrophages, which slowly dispose of particles either by transporting them along the alveolar surface to the mucociliary escalator, or by translocation to tracheobronchial lymph or by internal enzymatic degradation.
Phagocytosis appears optimal for particles of 1.5–3 µm in size [102]. This size discriminating property of the macrophages has been a basis for controlled-release formulations of inhaled drugs [35]. Large porous particles will reach also the alveoli because of their relatively small aerodynamic size but clearance by alveolar macrophages is reduced as a result of their large geometric diameter.

2.5 Pulmonary Drug Metabolism

The body’s primary detoxification enzymes, the cytochrome P450 (CYP) families, show the highest expression levels in hepatocytes and enterocytes but are also expressed in the lungs and other organs, providing a line of defense against ingested or inhaled xenobiotics. There are 57 active human CYP genes divided into families and subfamilies mainly based on sequence (Cytochrome P450 Homepage, http://drnelson.utmem.edu/cytochromeP450.html). The human drug metabolizing enzymes belong to the families CYP1, CYP2, and CYP3. These enzymes catalyze an oxidation reaction in which a functional group is introduced to the molecule, serving as a site of conjugation, increasing hydrophilicity, and thereby facilitating elimination [106]. After this initial phase I conversion, the compound is excreted or conjugated to an endogenous group by a phase II enzyme. This serves to further increase hydrophilicity, e.g., through acetylation, methylation, sulfation, or conjugation with glucuronic acid, glutathione, or amino acids [106]. Even though detoxification and facilitation of excretion is the primary scope of CYP biotransformations, sometimes an activation of a compound can occur. Reactive or toxic metabolites, which could potentially harm the tissue, may be formed.

In the lungs, several CYP isoforms are expressed as well as other biotransformation enzymes such as sulfotransferases (SULT), UDP glucuronosyl transferases (UGT), glutathione S-transferases (GST), esterases, peptidases, cyclo-oxygenases, flavine mono-oxygenases (FMO) [69, 109, 169]. The wide range of biotransformation enzymes enables metabolism of a broad spectrum of chemically different substrates. Local metabolism of several inhaled compounds, pharmaceutical drugs as well as tobacco-smoke components, pollutants, and toxicants have been demonstrated in lung tissue [73, 101]. Table 2.1 gives an overview of the expression of metabolic enzymes detected in the lungs.

Metabolism in lungs differs substantially from the intestinal–hepatic metabolism. The expression levels of enzymes are generally lower and the expression patterns of drug-metabolizing enzymes differ. In the lungs, CYP1B1, CYP2B6, CYP2E1, CYP2J2, CYP3A5, and CYP1A1 (the latter being highly induced in smokers) appear to be the most common CYP enzymes (Table 2.1), whereas the major CYP enzymes in human liver are CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 [31, 69, 119, 134, 171]. The most abundant liver CYP enzyme, CYP3A4, is expressed to a lower degree in pulmonary tissue and evidence points toward it only being expressed in 20% of the individuals tested, whereas the isoform CYP3A5 is considered more important in lung tissue [3].
There is less information available regarding the phase II enzymes compared with the CYPs. However, the expression and metabolic activity of SULT enzymes appear to be about the same in the lungs and in the liver, whereas epoxide hydrolase and esterases show an intermediate metabolic activity. The UGT enzyme activities appear to be low in human lungs. Somers et al. [137] estimated the metabolic activity of different enzymes in the lungs compared with those in the liver and showed that CYP enzymes displayed between 1 and 10% of the activity in the liver, epoxide hydrolase and esterases around 20% and SULT enzymes a similar activity in lungs, and for some isoforms, substantially higher than that in the liver [137]. Peptidase activity is high in the lung, as found elsewhere in the body [109].

Pulmonary tissue consists of several cell types with different expression patterns of metabolizing enzymes. In combination with low expression levels of certain enzymes, this results in technical and methodological challenges when studying lung metabolism, which may be one reason for the disparate results on enzyme expression levels that are reported in the literature (Table 2.1). Low expression levels of mRNA can be detected using polymerase chain reaction (PCR) techniques, giving an indication that a functional enzyme could be active in some cell types in the tissue, even though metabolic activity has not been demonstrated. In addition to these challenges, there are substantial differences between human and the most common laboratory animals in the expression pattern of biotransformation enzymes, which further complicates investigations and data interpretation.

The drug-metabolizing capacity of the lungs is in general substantially lower than that of the liver, and there is little evidence of a major contribution to systemic clearance. Many small molecules have near complete bioavailability via lung absorption as a consequence of low metabolic activity and relatively rapid absorption [12, 107, 128, 154, 155]. Still, several drugs, such as budesonide, ciclesonide, salmeterol, fluticasone propionate, and theophylline are substrates to enzymes present in the lungs [21, 57, 99, 112, 156]. Since formation of local metabolites cannot be excluded, and are sometimes anticipated, studies are conducted during drug development to screen for lung metabolism and assess the risks for metabolic interactions and toxicity, e.g., by incubating candidate drugs with lung subcellular fractions. However, local metabolism in the lungs can be taken advantage of, as several of the drugs listed above demonstrate. One example is the use of prodrugs where the administered form of the drug is activated in situ by metabolic enzymes. Ciclesonide, e.g., is metabolized into its active form by esterases in the lungs and further reversibly conjugated to fatty acids [99]. The prodrug beclomethasone dipropionate (BDP) is metabolized to the more potent 17-beclamethasone monopropionate (BMP) by esterases in the lungs [167]. For budesonide, the conjugation to fatty acids in the lungs results in the formation of a compound that has a substantially lower elimination rate. This reversible biotransformation contributes to the prolonged lung retention and duration of effect observed with this compound [156, 158]. The concept of “soft drugs” is another approach where differences in metabolic stability between the lungs (stable, to retain efficacy) and in circulating blood (labile, to minimize side effects) are the target properties.
<table>
<thead>
<tr>
<th>Isoform</th>
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<th>Protein expression</th>
<th>Metabolic activity</th>
<th>Comment</th>
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<td>Only in smokers, decrease to normal levels within 2 months after cessation of smoking</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>CYP2J2</td>
<td>Yes</td>
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<td>CYP3A4</td>
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<td>(Yes)</td>
<td></td>
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<tr>
<td>UGT</td>
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<td>Yes</td>
<td>(Yes)</td>
<td>Varied expression among isoforms</td>
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<td>GST</td>
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<td></td>
<td>Yes</td>
<td>High metabolic capacity</td>
</tr>
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<td>Esterases</td>
<td>Yes</td>
<td></td>
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</tr>
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<td>Epoxide hydrolase</td>
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<td></td>
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</tr>
<tr>
<td>Peptidases</td>
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<td></td>
<td>Yes</td>
<td>High metabolic capacity</td>
</tr>
<tr>
<td>SULT</td>
<td>Yes</td>
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<td>Yes</td>
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</table>
Most drug-metabolizing enzymes (and several transporters, discussed below) are inducible as a response to increased exposure to their substrates. An organism adapts to the new situation with an increased metabolic capacity in order to handle the “threat” [58, 64, 110]. By contrast, suppression of enzyme levels can also occur as a response to xenobiotics or disease [96, 172]. Information around the regulation of metabolizing enzymes in pulmonary tissue is scarce. An important example of enzyme induction that changes the metabolizing capacity of the lungs is the effects of tobacco smoke. Tobacco smoke contains several 1,000 different chemicals and several of these affect metabolizing enzymes in the lung. The induction of drug-metabolizing enzymes may result in increased metabolism of drugs, which could result in impaired therapeutic effect. Clinically relevant induction of CYP1A1 activity has been observed in patients who smoke during treatment with theophylline compared with nonsmokers [80].

Several compounds have the ability to inhibit drug-metabolizing enzymes and thereby cause clinically adverse interactions [54]. Drug interactions resulting from inhibition are, however, not likely to have a major significance in the lungs because of the limited contribution of lung metabolism to systemic clearance, although the local metabolism pattern could be affected by such interactions.

### 2.6 Pulmonary Drug Absorption

The optimal absorption characteristics of a pulmonary drug depend on the site of drug action. For locally acting drugs, the drug absorption process may determine the removal and consequently the termination of action of the drug in the lungs, as well as the onset of any systemically mediated adverse effects. For systemically acting drugs, absorption from the lungs determines the therapeutic effect profile (onset, intensity, and duration of action) of the drug. Therefore, when designing drugs for pulmonary delivery, it is important to consider both lung–tissue retention and permeability, irrespective of site of action.

The air-to-blood transfer always begins with an interaction between the drug and the surfactant: following deposition onto the mucosa of the tracheobronchial airways or alveolar region, the drug solute or particle encounters at least a monolayer of surface-active agents in which the fatty acid tails of lipids project into the air. For a drug compound of macromolecular size (e.g., a peptide or a protein), this lung surfactant may induce aggregation and, thus, potentially compromise dissolution or enhance macrophage engulfment and digestion [107]. By contrast, lung surfactant can enhance solubility of small, lipophilic drug molecules, as demonstrated with glucocorticosteroids and a number of cationic compounds [85, 166], which may potentially increase the rate and extent of absorption. Immediately below the molecular layer(s) of lung surfactant lies the 0.01–10 μm thick lining fluid through which drug must diffuse to get to the epithelium. The routes of drug absorption across the epithelium include passive and active transport mechanisms involving paracellular and transcellular transport, pore formation, vesicular transport, and drainage into the lymphatics – depending on the drug and site of absorption. The drug solute will
pass through a cellular barrier that varies from a monolayer of thick (about 60 μm) columnar cells in the bronchi to a monolayer of thin (0.2 μm) broad cells in the alveoli. The epithelial cells are attached to a basement membrane, a thin matrix of fibers, and below that, there is the interstitium of the lungs containing a variety of cells, collagen, elastic fibers, interstitial fluid, and lymphatic vessels. Since plasma proteins and most solutes are thought to diffuse relatively unhindered through both the epithelial basement membrane and the interstitium [38], it is reasonable to believe that neither of these tissues is a significant restrictor of transport of drug solutes. Drug absorbed from the air spaces into the blood must traverse a final barrier after the surfactant layer, the lining fluid, the epithelium, its basement membrane, and the interstitium: the cell monolayer that makes up the walls of the microvessels, the endothelium. Also, the endothelial cells are attached to a basement membrane, but where the endothelium comes into contact with the epithelium, which is frequent throughout the alveoli, their basement membranes fuse to form one common basement membrane. The alveolar–capillary endothelium is extremely thin (0.03–0.2 μm) and has a relatively large number of endocytic vesicles. Although generally the alveolar epithelial cells and not the underlying endothelial cells are considered the major barrier to transport, the contribution of the endothelium as a barrier for drug absorption is uncertain and needs to be further investigated.

2.6.1 Passive Diffusion

The tendency of a solute to pass from a point of higher concentration to a point of lower concentration is called passive diffusion. An inhaled drug solute diffuses through the epithelial cells or via paracellular pores or junctions into the submucosa along a concentration gradient. The slope of the gradient is dependent upon the physicochemical properties of the drug, the thickness of the air–blood barrier and the rate of blood perfusion in the submucosa, i.e., the diffusion rate is both compound specific and region selective. Absorption of lipophilic compounds is generally considered to occur through transcellular diffusion [36]. Hydrophilic compounds appear to be absorbed via paracellular diffusion through intercellular junction pores [132]. Based on data from extensive in vivo preclinical research performed by Schanker and colleagues (e.g., [12, 128]), within the molecular weight (MW) range of 100–1,000 Da pulmonary drug absorption rate is size independent but dependent on aqueous solubility at physiological pH such that lipophilic drugs get absorbed rapidly (with absorption half-lives in the range of minutes) and hydrophilic drugs more slowly (with absorption half-lives in the range of hours) [109]. The exact mechanisms and pathways underlying pulmonary absorption of macromolecules remain largely unknown. It is uncertain whether peptides, such as insulin, and proteins are absorbed primarily paracellularly through tight junctions or transcellularly via receptor- or cavelae-mediated transport [15, 70, 75, 76, 108]. Likewise, the mechanisms and the relative importance on drug absorption in health and disease of the interrelations between paracellular and transcellular pathways in lung epithelia and endothelia [162] remain to be fully elucidated.
2.6.2 Drug Transporters

During the last decade, it has become evident that drug transporters play an important role in drug disposition [61, 135]. This has recently been highlighted in a review of clinically relevant drug transporters and recommendations of their assessment in drug development [71]. Transporters of the solute carrier (SLC) family facilitate transport across the cell membrane and most commonly enhance uptake of compounds into cells. Depending on subtype of SLC, the translocation of compound across the membrane is driven by different mechanisms, e.g., counter-transport of another ion or the membrane potential. Examples of drug-transporting SLCs are organic anion transporters (OAT and OATP) and organic cation transporters (OCT). By contrast, drug transporters of the ATP-binding cassette family (ABC transporters) efflux compounds out of cells via an ATP-dependent mechanism. Examples of ABC transporters are multidrug-resistance proteins (MDR), multidrug-resistance-associated proteins (MRP), and breast cancer resistance protein (BCRP). In different barriers of the body, e.g., intestine and blood–brain barrier, ABC transporters hinder foreign molecules from entering the systemic circulation or the brain, respectively. The highest impact of SLC transporters is observed for compounds with low passive permeability as the transporter-mediated uptake may be the rate limiting step in the transepithelial transport of such compounds [135]. Uptake and efflux transporters work in concert with passive diffusion to influence the absorption of drugs through an epithelial cell layer [142]. In addition, drug transporters may be important in the regulation of the intracellular concentration of a drug and consequently in influencing efficacy as well as toxicity [105] (Fig. 2.3). Although relatively little is known about the functional impact of drug transporters in the lungs, it would be expected that they would play a central role in protecting the lungs from any entering xenobiotic.

Like other barriers in the body, cells in the lung express a variety of drug transporters of the SLC/SLCO and ABC families although with a different organ-specific profile (Table 2.2, for review see [9]). Organic cation transporter expression

![Fig. 2.3 Schematic of drug transporters in lung cells. SLC transporters in lung cell membranes may mediate drug uptake into the intracellular space with the highest impact on low passive permeability drugs. ABC transporters in the lungs may mediate drug efflux out of cells. Together uptake and efflux transporters may influence the intracellular concentration of drugs](image-url)
Table 2.2  Overview of major drug transporters expressed in the lungs

<table>
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<tr>
<th>Transporter</th>
<th>Gene</th>
<th>Localization with comments</th>
<th>References</th>
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<td>OCT1</td>
<td>SLC22A1</td>
<td>Apical on ciliated epithelial cells in bronchi</td>
<td>[88]</td>
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<tr>
<td>OCT2</td>
<td>SLC22A2</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>OCT3</td>
<td>SLC22A3</td>
<td>Smooth muscle cells</td>
<td>[66]</td>
</tr>
<tr>
<td>OCTN1</td>
<td>SLC22A4</td>
<td>Apical on epithelial cells in trachea, OCTN2 also in alveolar epithelia. High expression</td>
<td>[67]</td>
</tr>
<tr>
<td>OCTN2</td>
<td>SLC22A5</td>
<td>&quot;</td>
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<tr>
<td>OATP2B1</td>
<td>SLC02B1</td>
<td>Only mRNA data published. No cellular localization reports to date.</td>
<td>[6, 23]</td>
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</tr>
<tr>
<td>OATP4A1</td>
<td>SLC04A1</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>OATP4C1</td>
<td>SLC04C1</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>PEPT2</td>
<td>SLC15A2</td>
<td>Apical, bronchial epithelium, and alveolar type II pneumocytes</td>
<td>[53, 54]</td>
</tr>
<tr>
<td>MDR1/Pgp</td>
<td>ABCB1</td>
<td>Apical, bronchial epithelium, alveolar type I, endothelium</td>
<td>[21, 85, 130, 160]</td>
</tr>
<tr>
<td>MRP1</td>
<td>ABCC1</td>
<td>Basolateral/lateral, bronchial epithelium, goblet cells, peripheral epithelium. High expression</td>
<td>[11, 130, 160]</td>
</tr>
<tr>
<td>Other MRP</td>
<td>ABCC</td>
<td>Several MRPs expressed in lung</td>
<td>[160]</td>
</tr>
<tr>
<td>BCRP</td>
<td>ABCG2</td>
<td>Basolateral, bronchial epithelium, endothelium</td>
<td>[130]</td>
</tr>
</tbody>
</table>

Includes transporters for which mRNA, protein, and immunohistochemistry have been demonstrated

has been demonstrated in human lungs. OCT1 [87], OCTN1, and OCTN2 [66] expression have been demonstrated both at the mRNA and protein level. All three transporters are localized in the apical membrane of lung epithelial cells. Solute carriers may play a key role in transporting compounds with low passive permeability through the epithelial cell barrier. A number of inhaled drugs, e.g., β₂-adrenergic agonists and anticholinergic bronchodilators, are polar and contain a positive charge at physiological pH, and OCT may therefore play a role in their absorption and distribution. Data from Ehrhardt and coworkers indicated that the polar basic β₂-adrenergic agonist salbutamol was actively transported in lung epithelial cell lines [37]. Based on transport studies in human airway primary epithelial cells, Horvath and coworkers proposed that OCTN1 or OCTN2 is involved in the translocation of inhaled organic cation bronchodilators across the pulmonary epithelial cell layer, therefore being an important part in their delivery to the site of action [66]. Similarly, Nakamura et al. [100] demonstrated that ipratropium, a muscarinic antagonist, was taken up into human bronchial epithelial cells by OCTNs.

Although a clear functional role of organic anion transporters has been demonstrated in organs such as the liver [135], there are very limited data available in the literature on expression of this subgroup of transporters in lung tissue. Bleasby et al. [6] detected mRNA of several OATPs in human lung, but no protein or cellular localization data have been published.
The peptide transporter PEPT2 is another example of an SLC expressed in lung tissue. PEPT2 is transporting di- and tripeptides, as well as some peptidomimetic drugs, and is expressed on the apical membrane of epithelial cells in bronchi and alveoli [53]. PEPT2 substrates of relevance to lung disease are antibiotics such as beta-lactams and cefadroxil, and PEPT2 has been suggested as a way of targeting drugs to their site of action in the airways.

In terms of ABC transporters, MDR1 (Pgp), BCRP, and several MRP are expressed in the lungs (Table 2.2, for review see [9, 159]). Among the ABC transporters, MRP1 is the most highly expressed in lung tissue. MRP1 is localized to the basolateral side of pulmonary epithelial cells and has been detected both in the bronchial as well as the alveolar epithelium. MRP1 transports a broad range of anionic drugs as well as metabolites following glutathione, glucuronide, and sulfate conjugation. Interestingly, it has been reported that MRP1 expression is decreased in COPD [160]. Cigarette smoke extract (CSE) has been demonstrated to increase the expression of MRP1 in pulmonary epithelial cells and at the same time inhibit MRP1 leading to an increased toxicity of CSE, indicating a protective role of MRP1 [161]. MDR1 and BCRP expression have been demonstrated on both pulmonary epithelial as well as vascular endothelial cells in the lungs (Table 2.2). Because of the heterogeneity of lung tissue, there is still a need to further investigate the drug transporter expression in different cell types in the lungs. In terms of functional activity, most studies so far are based on cell models and very limited data are available on the functional impact in vivo. Thus, the relevance of drug transporters for pulmonary pharmacokinetics is currently unclear [9].

2.6.3 Vesicle-Mediated Transport

Membrane vesicles within the alveolar epithelial type I and type II cells have been suggested to be involved in macromolecule transport across the alveolar epithelium, and caveolae have been shown to be present in the alveolar type I cells [26, 55]. The main route of alveolar epithelial protein transport is through transcytosis involving caveolae and clathrin-coated pits, although the relative contributions of these internalization steps to overall protein handling remain to be determined [56, 75]. For particles (e.g., consisting of liposomes for drug delivery) the relative contribution of caveolae- and clathrin-mediated endocytosis has been shown to be size-dependent with an upper size limit of approximately 200 nm for the clathrin-mediated pathway [120].

2.6.4 Nonspecific Particle Trapping

There is evidence that nanoparticles, defined as particles less than 100 nm in at least one dimension, are taken up by alveolar epithelial type I cells via well-known
pathways of endocytosis and also via other, less well-understood, mechanisms [74, 97]. The quantitative relationships between mechanisms remain to be established. For the translocation of particles from the lungs into the systemic circulation, lymph drainage is likely to contribute [78, 144]. Opportunities of aerosolized nanoparticles of drug for pulmonary administration are being reviewed [16], although currently available technology does not appear to allow for large-scale production of such pharmaceutical formulations.

2.6.5 Importance of Lung Physiology and Pathophysiology

It is well known that different conditions alter pulmonary drug absorption. Stretching of the lungs by, e.g., exercise-induced deep ventilation, high-altitude pulmonary edema, or mechanical ventilation at high tidal volumes causing more permeable transcellular pores and possible expansion of the surface of the alveolar epithelial type I cells and caveolae of the capillary endothelium has been reported to increase the absorption of hydrophilic solutes [92, 114, 132, 153, 165, 169]. Likewise, active or passive cigarette smoking, exposure to surface-active agents used as absorption enhancers in experimental drug aerosols, or alcohol abuse, all appear to interfere with the functional integrity of the air–blood barrier resulting in increased uptake of hydrophilic solutes [8, 18, 59, 60, 130]. By contrast, physiological changes in the lung parenchyma that occur during aging, e.g., smaller total alveolar surface area, impaired ventilation–perfusion matching, larger small airway closing volumes, and smaller effective lung volumes, would more likely result in decreased absorption of inhaled drugs.

The presence of pathological lung conditions is expected to have an effect on pulmonary drug absorption. Chronic bronchitis and cystic fibrosis are pulmonary diseases characterized by the presence of a viscoelastic mucus layer in the upper airways and bronchi. As the mucus layer may retard or even block air-to-blood transfer of drug solutes and solids, this barrier must be overcome for pulmonary drug delivery to be effective. By contrast, the presence of inflammation in the lungs would be expected to facilitate paracellular transport of hydrophilic solutes. In models of allergic airway inflammation, various inflammatory mediators have been shown to dysregulate intercellular junction pores, thereby contributing to epithelial barrier dysfunction and injury [104]. Likewise, permeability edema – a major complication of acute lung injury, severe pneumonia, and the acute respiratory distress syndrome (ARDS) – is associated with an epithelial and endothelial hyperpermeability and a disruption of the epithelial and endothelial barriers, which may increase the paracellular transport of hydrophilic drugs. Emphysema, on the other hand, is characterized by structural modifications involving loss of inter-alveolar septa and thus would be likely to decrease pulmonary uptake of drug because of the reduction in total alveolar surface area.

Caveolae-mediated transcytosis can be upregulated in response to pathological stimuli [50, 116, 150]. Indeed, as caveolae and caveolins seem to play important
roles for the airway epithelium, airway smooth muscle, airway fibroblasts, airway inflammatory cells, and the pulmonary vasculature, it has become clear that aberrant regulation of their expression and function may trigger pulmonary defects, including pulmonary fibrosis, pulmonary hypertension, and lung cancer. However, further examination of caveolae and caveolins in obstructive airways diseases, including asthma and COPD, is warranted.

Airway hyperperfusion associated with asthma is suppressed temporarily by inhaled corticosteroids via their acute vasoconstrictor action. The decrease in airway blood flow is likely to retard the uptake of inhaled bronchodilators and thereby enhance their action.

### 2.6.6 Assessing Pulmonary Drug Absorption

Further elucidation of the mechanisms involved in drug uptake after aerosol delivery is needed. In vitro models can be used to clarify the interactions between drug formulations and the epithelial barriers within the trachea, the bronchial airways, and the alveoli. A variety of airway and alveolar epithelial cell culture systems have been established as in vitro absorption models [14, 45, 139, 141]. Recently, drug transporter expression in different pulmonary epithelial cell models was reported [39]. Models of tracheobronchial epithelium include not only primary cell cultures and cell lines of healthy human and animal phenotypes but also airway cells with characteristics of lung disease such as cystic fibrosis (e.g., CFBE41o- and CuFi cell lines). Primary cell cultures more closely resemble the native epithelia, but are less reproducible, convenient, and economical compared with the cell lines, which makes them less suitable for permeability screening purposes. In contrast to gastrointestinal in vitro testing, where Caco-2 cells have emerged as the gold standard, there is no such consensus to date on the preferred cell line(s) for modeling the tracheobronchial epithelium in vitro. Since alveolar epithelium cell lines available to date do not form functional tight junctions, most in vitro studies of alveolar epithelial function have been performed using primary cultures of alveolar type II cells, which under appropriate conditions differentiate into type-I-like cells and form tight epithelial barriers that are morphologically similar to the in vivo alveolar epithelium. The isolation of alveolar epithelial type II cells, predominantly from rat and rabbit lung tissue, and their culture over time leading to a primary culture of type I-like cells is now an established technique. The use of human alveolar epithelial type II cells obtained from patients undergoing lung resection or derived from embryonic stem cells is, however, limited by lack of material, and a complex, time-consuming and cost-intensive isolation procedure. Methods for delivering aerosols directly to the surface of air-interface epithelial cell layers have been developed [17, 25, 43]. Recent research is addressing more complex cell culture systems in order to generate models that are closer to the in vivo situation. These include co-cultures of different cell types to investigate the cellular interplay after particle
deposition [48]. Although suitable cell culture models of the cellular part of the human air–blood barrier are established and well characterized, the physical barriers on top of the cellular barriers – the surfactant and lining fluid – are less well understood and their influence on the safety and efficacy of aerosol medicines may be underestimated [14].

More advanced models than cell cultures are presently required to maintain the structural and cellular integrity of the lung tissue, the interaction between different cell types, and the biochemical activity. Recently, a human breathing lung-on-a-chip microdevice has been developed to study various physiological and pathological lung functions at the alveolar-capillary interface that could provide a new capability of cell culture models [67]. The isolated perfused lung model (IPL) is the most commonly used ex vivo method [126]. Tronde and coworkers investigated a wide range of drugs administered as aerosolized aqueous solutions in the IPL rat model and found pulmonary absorption to correlate with physicochemical descriptors, in vitro assessed permeability, and pulmonary absorption determined in vivo in rats [154, 155]. The IPL rat model has also been successfully used in the study of dry powder aerosols of drug [42]. The IPL model is a valuable complement to in vivo whole animal studies, despite limitations such as short viable periods, the level of technical expertise required to set up the IPL, low-throughput and absence of tracheobronchial circulation because this model allows drug absorption to be studied in absence of the confounding factors obviously present in vivo. A variant of the IPL is the human lung reperfusion model [47].

When using in vivo animal models, the anatomical complexities and interspecies differences in the lungs have to be considered [27, 114, 126]. For instance, mice and rats lack respiratory bronchioles and appear to have a relatively fast early alveolar clearance of insoluble particles, whereas guinea pigs, dogs, monkeys, and humans have much slower alveolar clearance.

Although various approaches can be used to study factors influencing the pharmacokinetics of an orally inhaled drug aerosol in humans, no method will measure directly the transepithelial transfer of drug. Compartmental modeling of blood level data obtained for inhaled drug has been used to estimate the rate of absorption into the systemic circulation [79]. Another approach is to quantify the initial pulmonary drug distribution and subsequent disappearance from the lungs using radioisotopically labeled drug and an imaging technique [5, 21, 136]. The pulmonary drug disappearance rate assessed from a time-series of images would then make a composite measure of both transepithelial transfer and nonabsorptive clearance mechanisms.

2.7 Duration of Effect and Airway Selectivity

The aim of local respiratory treatment is to attain maximal exposure at specific lung targets (receptors, transporters, or enzymes), while concentrations elsewhere are kept at a minimum. If this is achieved, maximum therapeutic effect can be attained
by low inhaled doses, whereby risk of systemic side effects is minimized. Airway selectivity was introduced as a concept by Hochhaus in 1997 to describe these features in a pharmacokinetic context. Hochhaus showed that lung-related properties such as pulmonary deposition, pulmonary residence time, and pulmonary drug release (dissolution) are at least as important with regard to therapeutic index as intrinsic potency and traditionally recognized pharmacokinetic parameters including systemic clearance and oral bioavailability.

This chapter, so far, has discussed the various mechanisms that contribute to the elimination of inhaled drug activity in the lung: dissolution, mucociliary clearance, metabolism, passive and active transport, and trapping. In this concluding section, the perspective is changed to that of effect duration, and the crucial importance that dissolution rate, tissue affinity, and biotransformation may have on airway selectivity.

2.7.1 Dissolution Rate

Slow dissolution can be used as a strategy to increase the retention of drug in the lungs and thereby prolong the duration of effect. However, if the rate of dissolution is too slow, the drug is more susceptible to mucociliary clearance and/or phagocytic elimination, which in turn will reduce retention [95]. Hence, the solid state property of the drug is an important feature in optimizing airway selectivity. The inhaled corticosteroid (ICS) fluticasone propionate (FP), which is highly lipophilic and slowly dissolving in sputum, is retained in the lungs up to 20 h after inhalation [41]. The mean absorption time (MAT) after inhalation is prolonged compared with the more soluble ICS budesonide (MAT after inhalation is 5–7 h vs. approximately 1 h for budesonide) [148]. Increased mucociliary clearance of undissolved FP resulting from a more central deposition in asthmatic patients than in healthy volunteers has been proposed to explain reduced bioavailability in these patients [13]. Interestingly, in a recent study in COPD patients, significantly more FP was eliminated via mucociliary and cough clearance than budesonide [28]. Thus, it appears that slow dissolution of FP causes its long lung retention, which at the same time is limited in the central lung due to mucociliary and cough clearance. This may serve as one plausible explanation of why FP shows shorter effect duration than that required for once-daily dosing [118].

2.7.2 Formulation Approaches

In part, shortcomings in terms of solid-state properties can theoretically be overcome by using appropriate formulation strategies such as reducing particle size in nano-suspensions, entrapment of active drug in liposomes, or formulating large porous particles [35, 133, 168]. One such application is budesonide embedded in stealth liposomes, which significantly prolonged effect duration in experimental
asthma [77]. This and other formulation approaches to improve inhaled drug properties are discussed in Chaps. 6 and 13. Assuming that Chaps 6 and 13 still refer to overcoming lung clearance mechanisms for controlled release drug delivery, and particle engineering technologies for pulmonary drug delivery, respectively.

### 2.7.3 Tissue Affinity

Tissue affinity is a loosely defined term used to describe binding to different substructures in the tissue (such as structures in the cell membrane, target receptors, cell organelles) by multiple mechanisms, thereby slowing down lung clearance and possibly increasing local effect duration. It has been demonstrated that cationic lipophilic molecules (generally basic amines with pKa > 8) can accumulate in lung tissue. The mechanism behind this has been suggested to be a combination of lysosomal trapping and accumulation in membranes [91].

The inhaled β₂-agonists salmeterol, formoterol, and indacaterol have prolonged effect duration [82, 89, 157]. Formoterol, which has intermediary lipophilicity, is believed to be retained in the membrane and from this position be able to interact with the β₂-receptor in a rapid and prolonged manner. The more lipophilic salmeterol is retained by the same mechanism but is less available for fast onset of action [2]. The inhaled muscarinic receptor antagonist tiotropium has demonstrated prolonged effect duration; the mechanism for this has been proposed to be prolonged binding to the M3-receptor [4].

### 2.7.4 Biotransformation

The intracellular esterification of budesonide and ciclesonide active metabolite (and to some extent BDP) increases the retention time of these drugs in the airways and thereby prolongs their durations of action [10, 33, 100]. Free parent compound becomes available when these esterified forms are slowly hydrolyzed back to their active form and this mechanism contributes to the prolonged effect duration seen with these compounds.

Both inhaled steroids and bronchodilators are treatments with very favorable airway selectivity, which has improved the quality of life of millions of asthmatic and COPD patients. As exemplified above, drug developers have been successful in maintaining drug in the lung by slow dissolution, tissue retention, and/or reversible biotransformation [2, 33]. Most of the inhaled drugs on the market are high clearance compounds, characterized by a low systemic availability of the swallowed “waste” fraction and an extensive liver clearance. Many are highly bound to plasma proteins, thus reducing systemic circulation of free, active drug. Hence, it is a challenge for drug developers to improve on these already favorable therapeutic properties. Yet, some pharmacokinetic “tools” remain to be fully explored, such as
the development of prodrugs and soft drugs. Others have to be better understood, such as the impact of protein binding on airway selectivity.

### 2.7.5 Prodrugs and Soft Drugs

Attempts have been made to improve airway selectivity by esterification to either an inactive prodrug that is locally activated before or at the target in the lung, or a pharmacologically active “soft drug,” which is readily inactivated by hydrolysis in the lungs or blood. Both these structural alterations may theoretically improve airway selectivity. By inhaling an inactive prodrug, the risk of local side effects in the oropharyngeal tract can be reduced. Also, depending on the physicochemical properties of the active metabolite vs. the parent compound, the uptake and lung retention characteristics can be improved [143].

Currently approved steroid prodrugs for airway delivery include BDP and ciclesonide (CIC). Although oropharyngeal side effects have been demonstrated to diminish for CIC [40, 121], it is still unclear to what extent hydrolysis of the inactive prodrugs CIC and BDP to their respective active metabolites, CIC-AM and BMP, improves airway selectivity. Since one third of lung deposited CIC is systemically absorbed as intact prodrug, and since both absorption and airway hydrolysis are fast, the partial activation in the systemic circulation rather than in the lung will reduce rather than improve airway selectivity. Hence, the favorable airway selectivity that has been demonstrated clinically for CIC is not likely to be primarily as a result of its prodrug features [72].

Several soft-drug steroids (butixocort propionate, fluocortin butyl-ester, itrocinoside and \(\gamma\)-butyrolactone steroids) have been in clinical development as inhalation products, with the purpose of maintaining a high local intrinsic activity, but where the parent compound then is supposed to be readily inactivated in the target organ or blood to avoid systemic spillover and side effects. However, none of the soft-drug inhaled steroids has yet been found to retain sufficient clinical potency and improved airway selectivity to be taken into late stage clinical development.

### 2.7.6 Protein Binding

A basic presumption in pharmacokinetic science is that only unbound molecules are available for pharmacological effect. For inhaled drugs, high protein binding has been regarded as beneficial, since it will theoretically reduce unwanted systemic side effects and hence improve the therapeutic ratio of the drug [122]. Lung effects have, however, generally been assumed not to be affected by protein binding [29]. Evidence for the opposite was recently provided by Hochhaus [63]: in this study total and free drug levels as well as receptor occupancies were assessed after infusion of CIC-AM (the active metabolite of ciclesonide) and budesonide in rats. The two ICSs have similar potencies and basic PK properties but CIC-AM is about
tenfold more bound to plasma proteins than budesonide [33]. While the total levels of the two drugs were similar both in the lung and in all other organs assessed in the study, CIC-AM showed significantly lower free levels as well as receptor occupancies (a measure related to effect) than budesonide also in the lungs. The authors concluded that high protein binding will reduce free drug concentrations and consequently the pharmacologic effect, but that airway selectivity is not necessarily improved by high protein binding.

2.8 Concluding Remarks

Drug activity in the lung is eliminated and modified by several mechanisms, most importantly mucociliary clearance, metabolism in the lung tissue itself, and absorption into the systemic circulation. As has been discussed, these mechanisms play an important role in the overall pharmacokinetic and pharmacodynamic characteristics of any inhaled drug, influencing onset of action, duration of effect, and therapeutic index. These mechanisms act in parallel so that the rate and extent of lung clearance by any particular mechanism is dependent on the rate and extent of clearance by the other processes. It is, therefore, very difficult to study a particular mechanism in humans since what is observed is the sum total, with confounding factors influencing the results to an often unknown degree. What happens between the “particle has landed” until the drug is detected in the systemic circulation is a major “black box” in the science of inhaled medication. Various levels of abstraction have been used to shine a light into the box, e.g., animal in vivo studies, ex vivo systems, cell cultures, and pure in vitro set-ups; but rational drug and formulation design will be hampered by our lack of detailed understanding for some time yet.

Since metabolism and absorption act only on solutes, dissolution kinetics of solid particles is important for lung clearance but probably only for relatively poorly soluble formulations. Lung retention may be increased by decreasing solubility, but this strategy for increasing duration of effect may be limited by the clearance mechanisms that act on undissolved drug: mucociliary and cough clearance in the central lungs and phagocytosis by alveolar macrophages in the lung periphery.

Although metabolic activity in the lungs is generally much lower than in the gut or liver, making the contribution from lung metabolism to the overall elimination of activity small, biotransformation in the lung has been shown to be important for the duration of effect of some corticosteroids that can undergo reversible esterification. Prodrugs are dependent on enzymatic activation in the lung, and airway selectivity may be improved by optimizing the balance between the kinetics of activation and the kinetics of absorption of both the prodrug and the active form. Soft drugs may also theoretically improve airway selectivity, but to date it appears that inactivation in the lungs of these labile molecules is too extensive for efficacy to be sufficiently retained.

Desired properties of pulmonary drug absorption depend on whether the target is local or systemic. For a local target, prolonged lung retention is usually desired to increase the duration of effect. Therefore, absorption into the systemic circulation
should not be too fast. Both for polar and especially for lipophilic compounds, unhindered absorption seems generally to be faster than desired. For prolonged duration, other properties, such as low solubility, reversible biotransformation, or high tissue affinity, need to be present to achieve a suitably slow elimination from the lungs. By contrast, for systemic targets of peptides and proteins, the challenge seems to be to achieve absorption at a rate that is competitive relative to the rate of other clearance mechanisms in order to secure sufficient bioavailability. The very rapid absorption of many small, lipophilic molecules offers great potential for fast onset of action for systemic targets.

In conclusion, the mechanisms of elimination of drug activity in the lungs by the various clearance processes described here are important factors to consider both in the development of new drugs and in understanding the relative merits of existing therapies. What constitute optimal characteristics in each particular case, and how these may be predicted from abstracted properties, remains far from clear cut with our present understanding.

### 2.9 Contributions

Although a collaborative work, major contributions were as follows: dissolution, Katarina; mucociliary clearance, Lars; metabolism, Tove; absorption, Eva and Lena; effect duration and airway selectivity, Staffan and Stefan. Bo was the coordinator and local editor.

### References


