RDD Respiratory Drug Delivery
Essential Theory & Practice

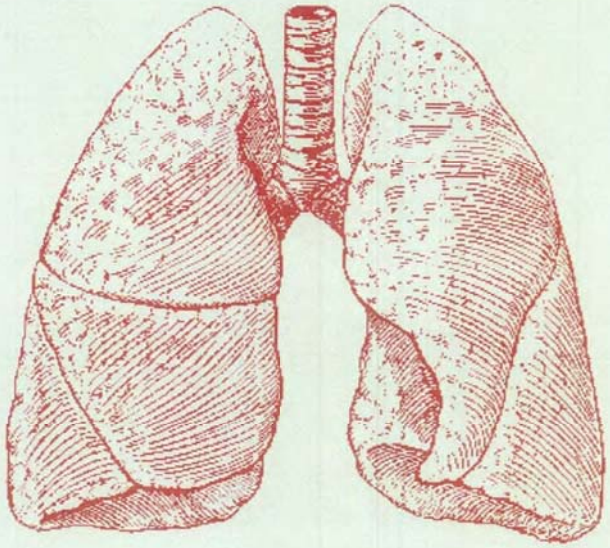

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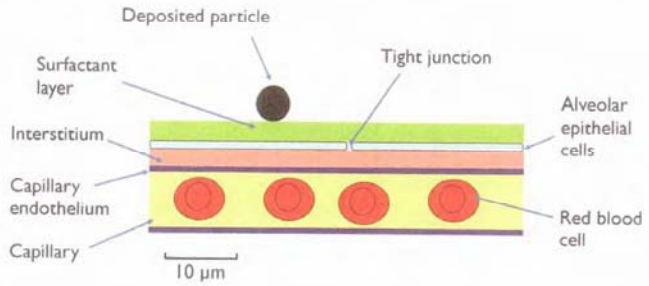
Figure 5. Schematic of the structure of the alveolar wall.



The alveoli contain macrophages that may engulf deposited material by phagocytosis, and either transport it to the foot of the mucociliary escalator, or transfer it into lymph nodes. This is another important lung defense mechanism, but it probably applies more to solid particles than to soluble drug substances. The alveoli also contain esterases that may inactivate deposited drugs in ways that depend on their chemical structure. Some molecules such as nicotine are believed to pass intact through the air / blood barrier, while large peptides can undergo significant enzymatic degradation (Adjei and Gupta, 1997).

Airflow and breathing

The lungs are highly elastic, and normal (tidal) breathing by an adult involves displacement of about 500 mL of air. Deep breathing can result in the inhalation and exhalation of much larger volumes. During inhalation, the diaphragm and the intercostal muscles contract to expand the lungs. Negative pressure is created within the lungs, resulting in the inhalation of air. The normal breathing rate in adults is around 15 breaths per minute, but higher breathing rates and smaller tidal volumes occur in infants and young children. The duty cycle is the fraction of the total respiratory cycle during which someone is inhaling (Collis et al., 1990). In healthy subjects, the duty cycle is slightly less than 0.5, but may be significantly less than 0.5 in patients with some lung diseases (Nikander, 1997). A possible consequence is that some patients receiving drug from nebulizers by tidal breathing could have less time available than healthy subjects to actually inhale drug into the lungs.

Table 3. Pulmonary drug delivery: major advantages for locally acting and systemically acting drugs.

Advantages for local treatments in the lungs
Drugs effective in low doses compared to oral route
Low incidence of systemic side effects
Rapid onset of drug action, e.g. compared to oral dose
Advantages for systemic treatments via the lungs
Avoidance of injections for drugs that are not absorbed orally
Rapid onset of drug action, e.g. compared to subcutaneous dose

Direct delivery to the airways leads to several important clinical advantages for locally acting drugs (Table 3). First, a relatively small dose is needed. As shown in Figure 8A, inhaled doses of 200 μg albuterol and 500 μg terbutaline by pMDI are therapeutically equivalent to oral doses of several milligrams (Gebbie, 1982). Second, the low dose, coupled with the use of relatively safe inhaled compounds, results in a low incidence of systemic side effects. For instance, inhaled corticosteroids are now accepted as first line therapy for asthma, and cause far fewer systemic side effects than oral corticosteroids (Barnes, 2008). Finally, as shown in Figure 8B, the onset of drug action when given by inhalation is relatively rapid (within minutes for inhaled bronchodilators), and this is a very valuable attribute when treating sudden wheezing attacks in asthma (Köhler and Fleischer, 2000).

Advantages of the pulmonary route for systemically acting drugs

Further advantages may result from giving drugs by the pulmonary route for systemic therapy (Table 3). Many drugs are either not absorbed from the gastrointestinal tract, or have such variable absorption, that they need to be given parenterally (often by subcutaneous injection) if they are to stand any chance of being delivered predictably to the required site in the body (Davis, 1999). The use of insulin in diabetic patients is an example of this, but some patients may be unwilling to inject themselves regularly. The pulmonary epithelium offers an injection-free portal of entry to the body for drugs that are poorly absorbed when given orally (Adjei and Gupta, 1997). The pulmonary route also has advantages for vaccine delivery. In the developing world, the need to immunize by injection is a serious limitation, which could be overcome by delivering vaccines by inhalation (Laube, 2005). These issues are discussed in more detail in Chapter 10.

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