Inhaling medicines: delivering drugs to the body through the lungs

John S. Patton and Peter R. Byron‡*

Abstract | Remarkably, with the exception of anaesthetic gases, the ancient human practice of inhaling substances into the lungs for systemic effect has only just begun to be adopted by modern medicine. Treatment of asthma by inhaled drugs began in earnest in the 1950s, and now such 'topical' or targeted treatment with inhaled drugs is considered for treating many other lung diseases. More recently, major advances have led to increasing interest in systemic delivery of drugs by inhalation. Small molecules can be delivered with very rapid action, low metabolism and high bioavailability; and macromolecules can be delivered without injections, as highlighted by the recent approval of the first inhaled insulin product. Here, we review these advances, and discuss aspects of lung physiology and formulation composition that influence the systemic delivery of inhaled therapeutics.

In 1986, researchers at Genentech discovered that human growth hormone (hGH), a 192-amino-acid protein (~22 kDa), was naturally absorbed into the systemic circulation of rats following instillation into the lungs[1]. Until then, and to some extent for the following 20 years until the recent approval of the first inhaled insulin, non-invasive delivery of proteins has been a 'Holy Grail' among drug delivery scientists. All other non-injection routes of delivery (including oral, buccal, transdermal and nasal) were shown to be virtually impenetrable to macromolecules unless penetration enhancers were used. Typical enhancers act like detergents that break down (solubilize) cell barriers, yielding good bioavailabilities but also raising long-term safety issues[2]. All of the enhancer-based delivery programmes initiated in the 1970s and 1980s with nasal insulin and nasal hGH were eventually terminated, some after extensive human trials[3–5]. A number of different penetration enhancers are under development that might work by different mechanisms than those described above (for example, transient cell-junction opening), but their regulatory approval could be some way in the future.

The findings with hGH were not the first to demonstrate that the lungs were naturally permeable to peptides (TABLE 1). In 1925, Gänsslen showed that inhaled insulin, a 51-amino-acid peptide (5.7 kDa), lowered blood glucose in all five diabetic subjects tested[6] and other reports over the years confirmed these initial findings[5]. The reasons why it took nearly 80 years to capitalize on the fact that nature had left a door open for macromolecule entry into the body are uncertain. However, the half-page Gänsslen paper was in German and only 'rediscovered' in the 1970s, when the doomed nasal programmes still looked promising. Additionally, pulmonary delivery seemed to be impractical, complicated, inefficient and unreliable, and its long-term safety was unknown. Things have changed dramatically — the development of inhaled insulin began in l990 at a start-up company, Inhale (now Nektar), and is now being continued by a variety of companies[7]. Today there are several inhaled insulins in development that are as reliable as, or more reliable than, injections, and the growing long-term safety database is reassuring[7–10]. The furthest in development of these formulations is inhaled human insulin powder of recombinant DNA origin (Exubera; Pfizer), investigated in a large number of adult patients with type 1 or type 2 diabetes, and recently approved in Europe and the US for the treatment of adults with diabetes. An ancient delivery route is therefore now being exploited in ways never imagined. Insulin leads the way and other peptides and proteins, including some of the most exciting new therapeutics, might now have an entry route into the body that does not require needle-based injection.

Inhalation also offers great potential for rapid (within seconds or minutes) systemic delivery of small-molecule therapeutics. Because of the huge surface area of the lungs, the highly dispersed nature of an aerosol, (hundreds of millions of particles per dose), good epithelial permeability and small aqueous volume at the absorptive surface[11], small molecules deposited in the lungs are very rapidly absorbed into the systemic circulation,

**Nektar Therapeutics, 150 Industrial Road, San Carlos, California 94070, USA.*
‡Virginia Commonwealth University, BOX 980533, Richmond, Virginia 23298, USA.
Correspondence to J.S.P.
e-mail: jpatton@nektar.com
doi:10.1038/nrd2153

Table 1 | **Examples of inhaled medicines**

Year	Formulation/device	Molecule(s)	Disease
1500 BC	Egyptians used 'vapors'	?	?
1662 AD	Bennet's inhalation treatment	?	Tuberculosis
1802	Potter's cigarettes	?	Asthma
1860	Sales-Giron's portable nebulizer	?	?
1925	Aqueous/nebulizer	Insulin	Diabetes
1945	Aqueous/nebulizer	Penicillin	Lung infections
1951	Aqueous/nebulizer	Isoprenaline	Asthma
1955	Aqueous/nebulizer	Hydrocortisone	Asthma
1956	First metered-dose inhaler (MDI) (freon)	Albuterol	Asthma
1960	First dry powder inhaler (DPI)	Norsadrenaline	Asthma
1988	First multidose DPI	Terbutaline	Asthma
1996	First protein aqueous/nebulizer	DNAse	Cystic fibrosis
1998	First antibiotic aqueous/nebulizer	Tobramycin	Cystic fibrosis
1997	First hydrofluoralkane MDI	Albuterol	Asthma
2006	First protein DPI	Insulin	Diabetes

with the fastest uptake of any route of delivery other than intravenous[12]. In addition, drug-metabolizing enzymes are in much lower concentrations in the lungs than the gastrointestinal tract and liver[13–15] and inhaled molecules that enter the circulation are less likely to be degraded than if they had been delivered orally. The numerous human ailments whose onset of symptoms can occur in seconds can potentially be counteracted by fast-acting inhaled medicines. Anxiety, hypertensive crisis, certain seizures, arrhythmias, spasms, nausea and the myriad forms of pain could be more rapidly treated with inhaled medications. The challenge with some small molecules in this regard is that they are absorbed and also cleared very rapidly, so that one needs to consider ways of slowing absorption of some of the inhaled drug so that the systemic effect can persist over enough time to be acceptable to the patient (see section below on lung retention of inhaled therapeutics). In addition, drugs with low gastrointestinal bioavailability or post-prandial effects on bioavailability could potentially be more reliably and efficiently given as aerosols.

The following review recounts some of the biology and potential mechanisms of pulmonary drug absorption; how formulation, molecular mass and molecular properties affect rate and extent of absorption; and how molecules and formulations can be designed to be retained in the lungs.

Pulmonary absorptive surfaces: the barriers

Within the lungs, the trachea, bronchi and bronchioles (collectively called the airways) are analogous to the trunk and branches of a tree, whereas the sac-like alveoli (gas-exchange surface) can be compared to the leaves. The surface area of the airways is only a few metres square in the adult human, as compared with the alveolar surface of more than 100 m^2 (REFS 11,16). In addition to the great difference in surface area between the two main functional areas of the lungs, the pseudostratified epithelium of cells that constitute the barrier to absorption into the bloodstream are markedly different in the two areas (FIG. 1). The airways are composed of a gradually thinning columnar epithelium populated by many mucus and ciliated cells that collectively form the mucociliary escalator. The airways bifurcate roughly 16–17 times before the alveoli are reached[11,16] (FIG. 2). Inhaled insoluble particles that deposit in the airways are efficiently swept up and out of the lungs in moving patches of mucus, and for those deposited in the deepest airways this can be over a time period of about 24 hours[17]. The monolayer that makes up the alveolar epithelium is completely different. Here the tall columnar mucus and cilia cells are replaced primarily (>95% of surface) by the very broad and extremely thin (<0.1 μm in places) type 1 cells[11] (FIGS 1,3). Distributed in the corners of the alveolar sacs are also the progenitor cells for the type 1 cells and the producers of lung surfactant, the type 2 cells. The air-side surface of each of the 500 million alveoli in human lungs is routinely 'patrolled' by 12–14 alveolar macrophages[18], which engulf and try to digest any insoluble particles that deposit in the alveoli. A detailed morphometric study of human lung tissue has shown that an excess of 90% of alveolar macrophages are located at or near alveolar septal junctional zones[19]. Insoluble, non-digestible particles that deposit in the alveoli can reside in the lungs for years, usually sequestered within macrophages. Molecules such as insulin are formulated either as liquids or in highly water-soluble aerosol particles that dissolve rapidly in the lungs and thereby largely avoid macrophage degradation. Protein therapeutics that are taken up by macrophages can be rapidly destroyed in the lysosomal 'guts' of the phagocytic cells[1,20].

Exactly where in the lungs it is best to deposit a drug for optimum absorption is not clear, but some general principles are emerging. Almost all of the resistance to systemic absorption of inhaled medicines into the blood stream occurs at the plasma membrane of the lung epithelium[21,22]. For the high-molecular-mass immunoglobulins of the IgG class (150 kDa), evidence suggests that the best place for absorption might be in the larger airways where receptor-mediated transcytosis of IgG occurs[23,24]. Small hydrophobic molecules are thought to be rapidly absorbed (within seconds) throughout the lungs by passive diffusion through the plasma membrane[11]. Small hydrophilic molecules can be absorbed by specific transporters or via the tight junctions[11]. It is uncertain whether peptide molecules such as insulin are absorbed primarily paracellularly through tight junctions or via transcytosis through caveoli[11] — most scientists believe the paracellular route predominates. For small peptides and insulin, it seems to be important to have the drug deposit deeply in the lungs for optimum absorption rather than in the upper airways[25,26]. Interestingly, apical-to-basal electrical resistance across the epithelium (a measure of the tightness of cell junctions) seems to go down from a maximum in the trachea to a minimum in the distal airways before returning to a high value in the alveoli — therefore the optimal site for insulin absorption might be

Bioavailability
The fraction or percentage of an administered drug or other substance that becomes available to the target tissue or blood after administration. Bioavailability is usually measured against an intravenous dose (absolute bioavailability) but can also be measured against other delivery routes such as subcutaneous injection (relative bioavailability).

Epithelium
A diverse group of tissues that covers or lines nearly all body surfaces, cavities and tubes that function as an interface between different biological compartments. Epithelial layers provide physical protection and containment, and also mediate organ-specific transport properties.

Mucociliary escalator
The self-cleansing system in the airways is composed of a moving epithelial raft of mucus secreted by goblet cells and propelled by ciliated cells. This system serves to move particles that are inhaled and deposited in the lungs up and out into the oesophagus, where material is coughed up and/or swallowed.

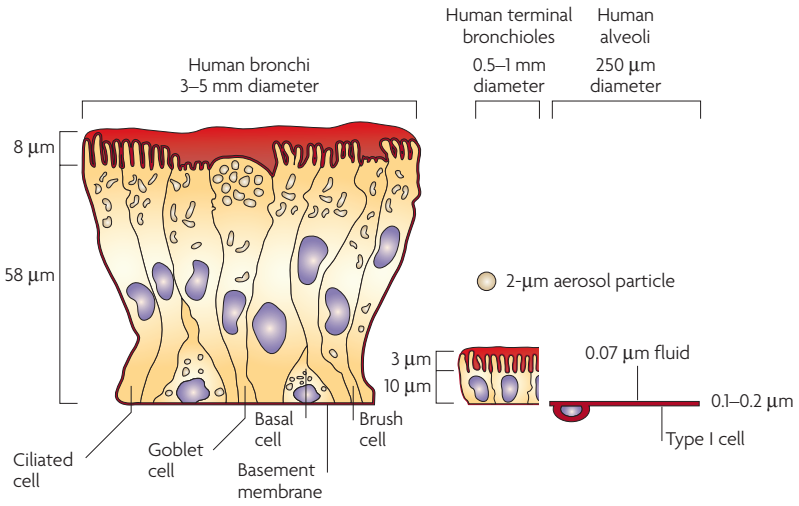

Figure 1 | **Comparison of the lung epithelium at different sites within the lungs.** Lung epithelial cells found in different regions of the lung are drawn at their relative sizes. As aerosol particles penetrate deeper and deeper into the lungs the absorptive epithelium becomes thinner until the alveolar epithelium is reached. A typical 2-µm diameter aerosol particle will contain tens to hundreds of millions of insulin molecules or hundreds of millions/billions of small molecules depending on whether the particle is liquid or solid. Solid aerosol particles are too large to be absorbed and must dissolve to release their drugs for absorption. The darker orange colour in the figure is the liquid layer, which gets thinner in thickness as the airways become smaller in diameter until finally the thickness is <0.1 µm in the alveoli. In the bronchi there are a variety of cells that make up the epithelium: the basal cells, which are the stem or progenitor cells for the epithelium and differentiate to form the other cells in the case of injury or apoptosis; the ciliated cells, which provide the mechanism for moving the mucus blanket; the goblet cells, which secrete the mucus; and the brush cells, which are involved in drug metabolism. These same types of cells persist in the smaller airways but are not as tall. The basement membrane is actually not a membrane but an extracellular matrix of different biopolymers to which the epithelial cells attach[11,16].

Macrophages
Pulmonary macrophages are scavenger cells in the lung derived from monocytes in the circulation. They help keep the lungs clean and although they have the capacity to produce many inflammatory mediators. Macrophages in the airways are relatively non-responsive to foreign materials when compared with other macrophages inside the body.

Transporters
Proteins embedded in plasma membranes of cells which facilitate the absorption of small or large molecules.

Tight junctions
The complex molecular apparatus that enables cell adhesion in epithelial and endothelial cell sheets. Tight junctions act as a mediator that retards the diffusion of solutes between cells and as a boundary between the apical and basal plasma-membrane

the distal airways right before the alveoli[27]. The density of tight junctions in the airways is roughly five times that in the alveoli[11]. There is no evidence to date that specific receptors have a role in the systemic absorption of insulin following inhalation.

Getting the drug there: the formulations

Depositing drug doses reliably into the lungs of humans is straightforward in principle, but challenging in reality. It is in this area that tremendous progress has been made in recent years, primarily through new product development activities in young and established pharmaceutical and drug delivery companies. Although we have described these developments in detail previously[28], the field is beyond the scope of this review. Even so, some general facts and issues should be mentioned. Aerosol particles with an aerodynamic diameter of about 1–2 µm, if slowly and deeply inhaled, can be deposited in the lungs with efficiencies as high as 90%, with the majority of the aerosol depositing in the peripheral regions that are rich in alveoli[29]. Drug delivery complexity derives from the need to quickly convert formulations into fixed-dose aerosol clouds with optimal properties (see below) efficiently and in phase with inspiration, and then to deliver these in a minimum number of inspirations. Adding commercial demands for a stable drug formulation in (ideally) an inexpensive, miniature device with the means of encouraging the user to inhale in a controlled way from the mouthpiece adds to the challenge.

Aerosol clouds with optimal properties should contain particles that are neither too small (these risk exhalation), nor too large (these deposit primarily in the upper airways, mouth and throat). FIGURE 4 shows deposition of monodisperse particles inhaled slowly in a single inspiration, with a breath hold after inspiration[29]. Mass fractional deposition is shown as a function of aerodynamic diameter (assuming that particles are spherical with unit density, like water droplets). If patients inhale too forcefully from a dry-powder inhaler, particle deposition in the upper airways, mouth and throat is dominant and lung deposition falls. Forceful inhalation from a pressurized metered-dose inhaler (MDI), where the aerosol is propelled from the device at high velocity, can actually increase lung penetration of an aerosol that would normally deposit primarily in the back of the throat.

Systemic delivery of small molecules

Compared with the oral delivery of small molecules, pulmonary delivery has very high bioavailabilities. From the large number of studies by Schanker and co-workers, who studied the disappearance of radiolabelled molecules from the lungs of animals, it seems that many small molecules probably have pulmonary bioavailabilities approaching 100%[11,30,31]. This can be attributed to their rapid absorption from the lungs and the low concentrations of drug-metabolizing enzymes in the lungs compared with the oral route[13–15].

Hydrophobic small molecules. Small, mildly hydrophobic molecules can show extremely rapid absorption kinetics from the lungs[12]. However, as hydrophobicity increases, molecules can become too insoluble for rapid absorption and can persist in the lungs for hours, days or weeks[12]. Absorption half-lives can be roughly estimated across species using a log-log approach detailed years ago[32,33]. Typical drug molecules with log octanol–water partition coefficients greater than 1 can be expected to be absorbed, with absorption half-lives (the time it takes half of the molecules deposited into the lungs to disappear from the tissue) of approximately 1 minute or so; decreasing the log octanol–water partition coefficient to –1 or lower can increase the half-life to around 60 seconds[34,35].

Examples of rapidly absorbed inhaled hydrophobic drugs include nicotine[36], Δ-9-tetrahydrocannabinol (THC)[37], prochlorperazine[38], rizatriptan[39], morphine and fentanyl[40–42]. There is demand for an inhaled pharmaceutical form of THC, the major psychoactive component of marijuana smoke (*Cannabis sativa*)[43]. Its therapeutic properties could be useful in cancer, HIV, migraine, multiple sclerosis and other diseases; however, the oral bioavailability of the drug is erratic and poor, due to first-pass metabolism coupled with slow absorption. A recent Phase I trial showed that THC from a new metered-dose inhaler was safe and quickly absorbed, with maximum plasma concentrations in less than 7 minutes for doses as high as 9.6 mg[37].

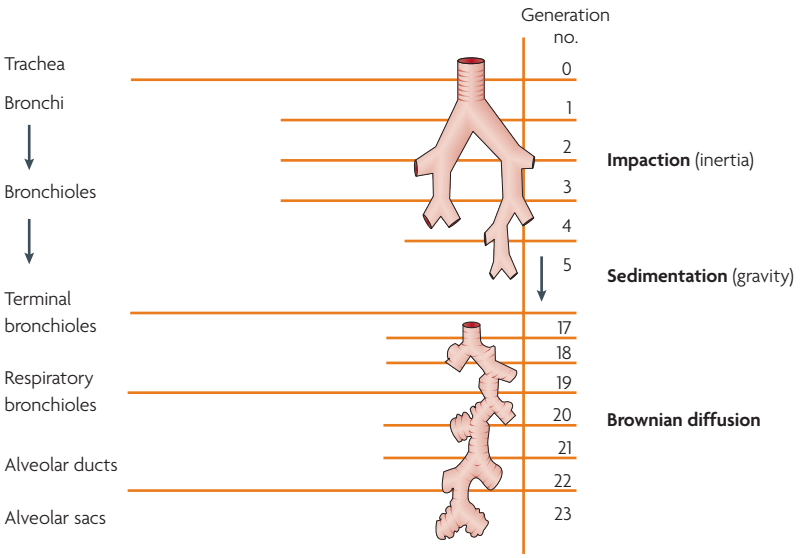

Figure 2 | **Factors that determine the deposition of inhaled particles.** The airways branch roughly 16–17 times before alveolar sacs are encountered. The surface area of the human airways averages about 2–3 square metres compared with roughly 100 square metres for the alveolar surface. The principal contribution to deposition of particles will be the force that dominates the motion of the particles. In the upper airways the inertia of the larger particles causes them to break free of the streamlines of the flow and collide with a wall to deposit. As impaction clears these larger particles in the upper airways, the slightly smaller particles are filtered out of the airstream in the middle airways by gravitational sedimentation. Finally, for very small particles, particle motion is determined by brownian diffusion which accounts for the dominant mechanism of deposition in the alveolar region[16,17,72,73].

Transcytosis
Transport through cell layers by movement directly through the cell cytoplasm (the transcellular pathway), perhaps via membrane vesicles called caveoli, in contrast to transport between cells via the tight junctions (the paracellular pathway).

Caveoli
The plasma membrane vesicles through which transcytosis can occur. These 'little caves' arise by invagination on one side of a cell and carry bound or engulfed material as a membrane vesicle or 'bubble' through the cell's cytoplasm to the other side of the cell. Here, the caveoli can fuse with the plasma membrane and release its cargo to the extracellular space.

Monodisperse particles
Aerosol particles that are all the same size. Most pharmaceutical aerosols are polydisperse. Their particle size is usually expressed as a median diameter surrounded by a spectrum of sizes.

Inhaled prochlorperazine produced serum profiles in humans similar to a 5-second intravenous push[38]. Inhaled morphine and fentanyl offer rapid pain relief, avoiding metabolism and slower absorption associated with oral administration[40–42] (FIG. 5). The lipophilic antimigraine drug rizatriptan also shows high bioavailability and maximum plasma concentrations in less than 5 minutes in dogs (FIG. 5). When these examples are coupled with the work on other hydrophobic drugs such as testosterone[44], the pulmonary route clearly offers distinct advantages for compounds that suffer from poor oral absorption and/or slow onset.

Once a drug is deposited and in solution on the airway surfaces, its rate of absorption should be given by the product of its membrane permeability, P, the available surface area over which it is spread, A, and its concentration in mucosal fluids, C — that is, Rate = P A C.

This 'irreversible' transfer relationship[45] presumes that the blood concentration remains insignificant as a result of rapid dilution and removal by the pulmonary circulation. The membrane permeability of the drug, P, is usually perceived as directly proportional to its partition coefficient and inversely proportional to membrane thickness. So, values for P would be largest for hydrophobic molecules deposited in the alveoli, where the barrier is the thinnest[11,16].

Hydrophilic small molecules. In general, neutral or negatively charged hydrophilic small molecules are absorbed rapidly and with high bioavailabilities from the lungs[12,30,31]. In a survey of the literature, this class of molecules has an average half-life of about 60 minutes[12], in contrast to some of the lipophilic molecules that are absorbed in seconds to minutes.

In a small number of cases, active (energy consuming) transporters have been identified that might be utilized to increase the speed of drug absorption. Differently charged oligo-aspartamides, cromolyn, phenol red and guanidine have all been shown to possess dose- or concentration-dependent pulmonary absorption in rodents[12,46]. However, the various 'drug exporters' involved in placental foetal protection at the placenta and the multidrug-resistance phenomena are either present at reduced levels, or their significance remains to be elucidated[15]. Presently, literature relating to active transport and lung metabolism of drugs in lungs is sparse.

Systemic delivery of macromolecules

The use of the lungs for the delivery of peptides and proteins, which otherwise must be injected, is one of the most exciting new areas in pulmonary delivery. For reasons that are not completely understood, the lungs provide higher bioavailabilities for macromolecules than any other non-invasive route of delivery[11,40,47]. However, unlike the situation with small molecules, for which lung metabolism is minimal, enzymatic hydrolysis of small natural peptides can be very high unless they are chemically engineered (blocked) to inhibit peptidases. Small natural peptides make poor drugs by any route of delivery because of peptidase sensitivity, whereas blocked peptides show high pulmonary bioavailabilities[47]. As molecular mass increases and peptides become proteins with greater tertiary and quaternary structure, peptidase hydrolysis is inhibited or even eliminated and bioavailabilities of natural proteins can be high[26,47]. Insulin can be considered to be a large peptide (or small protein), with enough size to avoid much of the metabolism seen with smaller peptides. The rate of macromolecule absorption is primarily dictated by size — the larger the size the slower the absorption. Molecules such as insulin, growth hormone and many cytokines typically peak in blood following aerosol inhalation in 30–90 minutes, whereas smaller blocked peptides can be absorbed faster. After a 15-year development effort, inhaled human insulin (IHI) applied regularly at meal time has been approved both in the US and the European Union for the treatment of adults with diabetes (Exubera). Following inhalation of a single dose, approximately 30–40% of the insulin dose reaches the deep lung[7].

The efficacy and safety profile of IHI has been evaluated in clinical studies of more than 2,700 patients with type 1 or type 2 diabetes[8–10]. Studies have shown that IHI achieves and maintains effective glycaemic control comparable to subcutaneously administered fast-acting insulin in type 1 and type 2 diabetics. In patients with type 2 diabetes not sufficiently controlled with oral agents alone, IHI alone or combination with oral agents produced greater improvements in glycaemic control compared with patients treated with oral agents alone. The incidence of hypoglycaemia was comparable

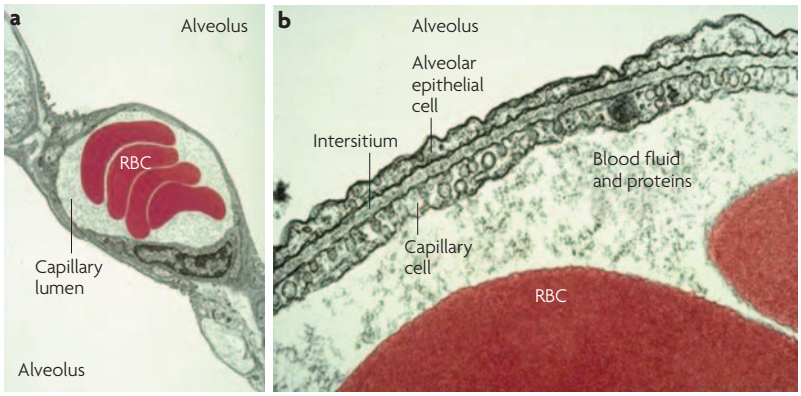

Figure 3 | **The alveolocapillary permeability barrier.** Transmission electron micrographs of cross sections of a human alveolus showing at lower magnification on the left, a section through an alveolar capillary containing four red blood cells (RBCs). At higher magnification on the right the air–blood barrier can be seen to be composed of two cells, the alveolar epithelial cell and the capillary endothelial cell. Both cell types are attached to an extracellular basement membrane (interstitium). The dominant permeability barrier is thought to be the epithelial cell and not the basement membrane or the endothelial cell. Photographs by E. R. Wiebel, reprinted with permission[16].

between IHI and subcutaneous insulin, and higher for IHI when compared with oral agents. Small treatment-group differences in the decline of forced expiratory volume in 1 second (FEV1) were observed in the IHI group relative to comparator therapy. In clinical studies for up to 2 years, there was no accelerated decline beyond 3–6 months, and discontinuation resulted in resolution of the treatment group differences within 6 weeks. Monitoring of lung function is recommended before IHI initiation and at regular intervals thereafter. Insulin antibodies developed more frequently and levels were higher compared with subcutaneous insulin. These antibodies were of the IgG type and similar to those seen in patients receiving injections[48,49]. However, no clinical significance of these antibodies has been identified. Elevated antibodies and the small lung function declines do not seem to be related[50], but further studies are planned to evaluate the longer-term pulmonary safety profile of IHI. In addition to being effective and well tolerated, IHI is also preferred by patients. In one study, when subjects initially assigned to treatment with IHI or subcutaneous insulin were allowed to select a regimen for ongoing treatment, most IHI-treated subjects (85%) elected to continue with IHI. By contrast, most subjects treated initially with subcutaneous insulin chose to switch to IHI (75%). Furthermore, patient treatment satisfaction was consistently higher in patients receiving IHI, compared with those patients on subcutaneous insulin[51].

It would be desirable to prolong the systemic duration of some proteins following inhalation. Conjugation of molecules such as interferons, follicle stimulating hormone (FSH) and erythropoietin (EPO) to the constant (Fc) region of antibodies has been shown to do just that[23,24]. Interestingly, the optimal pulmonary site of absorption of these conjugates seems to be the conducting airways, in contrast to the major site for insulin, which is in the deep lung[20]. The airways are enriched with antibody transcytosis receptor mechanisms. Fc conjugates of proteins have serum half-lives >1 day and are believed to be absorbed with high bioavailabilities (20–50%) from the lungs of primates[23,24]. Proof of principle has been shown in humans with EPO–Fc conjugates[52].

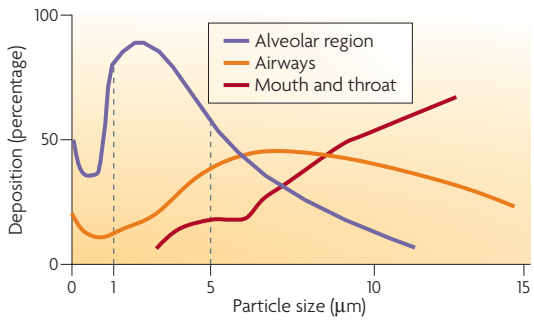

Figure 4 | **The effect of particle size on the deposition of aerosol particles in the human respiratory tract following a slow inhalation and a 5-second breath hold.** Larger particles deposit in the airways or mouth and throat, whereas smaller particles deposit in the alveolar region. Particles <1 μm can be exhaled, thereby reducing deep-lung deposition[29].

Lung retention of inhaled therapeutics

Sometimes drugs are absorbed from the lungs and cleared from the blood so quickly that their local efficacy in lung tissue or their systemic duration can be very short, which then necessitates very frequent drug administration. In most cases one would like to have a drug that is inhaled only once or twice a day. Absorption of therapeutic agents from the lungs can be prolonged by a variety of mechanisms.

Very low solubility. Presently, some of the least-soluble drugs administered by inhalation are inhaled corticosteroids (ICS) for asthma, such as beclomethasone dipropionate (BDP) and fluticasone propionate (FP). Their aqueous solubilities are about 0.1 ppm and are pH-independent[53]. Both FP and BDP, at inhaled lung doses up to 1 mg, seem to be completely absorbed from the lungs even though deposition and absorption occurs in both conducting airways and alveoli[53–57]. However, the average absorption time to get into the systemic circulation for FP, triamcinolone acetonide and budesonide are reported to be 5–7 hours, 2.9 hours and around 1 hour, respectively[58,59]. The prolonged absorption of FP relative to the other ICS is presumed to be due to its slower dissolution rate[58,59]. Whether macrophages engulf slowly dissolving aerosol particles composed of small molecules (such as FP) is uncertain. Nor is it known whether macrophage retention of slowly dissolving small-molecule particles such as inhaled FP, prevents egress of the dissolved molecules back out of the cell. Finally, two other relatively insoluble hydrophobic small molecules show prolonged lung retention. Retinoic acid has a half-life of many hours[60] and amphotericin B, an antifungal drug, has been shown to persist in animal lungs for days[61].

Octanol–water partition coefficients
The equilibrium ratio of concentrations of drug molecules dissolved in an immiscible two-phase solvent system composed of water and octanol (high values reflect lipophilicity).

First-pass metabolism
Usually refers to oral drug administration where metabolism by enzymes in the gastrointestinal wall and liver reduce passage of intact drug into the systemic circulation. Significant amounts of a drug can be lost as it 'first passes' into the body. Pulmonary metabolism of inhaled small-molecule drugs is usually very low compared with oral administration.

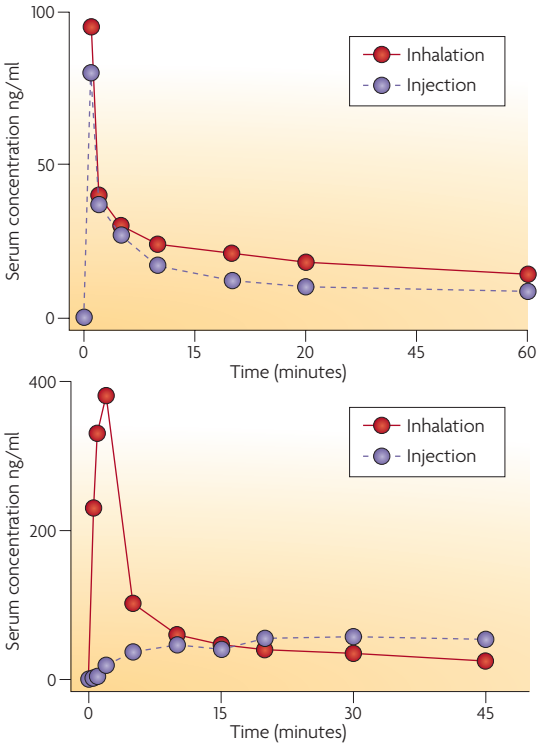

Figure 5 | **Plasma concentration versus time curves following inhalation and injection, illustrating rapid pulmonary absorption.** The upper graph shows data for inhaled morphine (dose = 8.8 mg) compared with intravenous injection (dose = 4 mg) in human volunteers. The lower graph shows rizatriptan plasma profiles in dogs following aerosol inhalation or subcutaneous injection of doses of 1.2 and 2.5 mg, respectively. Data redrawn from REFS 39,42.

Tissue retention. There are preclinical data showing that a very small percentage of some otherwise rapidly absorbed inhaled drugs are slowed in their pulmonary absorption or retained by tissue binding and cellular uptake in the airways[57,62]. Several groups have discovered that prolonged retention of trace amounts of ICS and other hydrophobic drugs occurs in airway tissues, potentially explaining the extended duration of those drug's topical pharmacological effects in the lungs[54,62]. In the case of some retained steroids, the molecules were found to have been esterified in the tissue to long-chain fatty acids, thereby rendering them very hydrophobic and insoluble. Indeed, successful efforts to increase durations in lung have so far relied only on drug structural modifications that increase hydrophobicity and lung tissue binding. This is believed to be the basis for the prolonged bronchodilation produced by formoteral and salmeterol in humans[63].

Positive charge. Moderately lipophilic compounds with positive charge under physiological conditions, such as pentamidine and verapamil, are known to bind preferentially to lung tissue[64]. It is also possible that one reason for the successful development of tobramycin as an inhaled antibiotic relates to this effect; its physiological existence as a polycation imparts a pulmonary half-life of several hours[65].

Encapsulation in controlled-release particles. Aerosol drugs can be formulated with some types of excipients that impart slow dissolution in the lungs. Examples of formulation manoeuvres to extend release are increasing in the literature. For example, drug entrapment using liposomes and microspheres has been found to extend the apparent lung duration of inhaled antibiotics, antineoplastics and anti-inflammatory steroids[66,67]. However, there are a number of unique challenges to controlling the release of drugs that are deposited on the surface of the airways. Whereas a tablet can be considered to be a single particle, an aerosol dose of 2 mg contains roughly 300 million particles with a surface area more than 1,000 times greater than that of an equivalent tablet mass. Although there can be thousands of microns of thickness to build a slowly dissolving surface on a tablet or within a tablet's matrix, there are only nanometres of thickness on an aerosol particle. 'Burst' or immediate release of a portion of a controlled-release particle's drug load is therefore a challenge for the aerosol dosage form[66,68,69]. This might not be an issue if one could ensure that the majority of the aerosol particle's mass was composed of excipient. However, unlike gastrointestinal delivery, in which grams of material can be given, only about 50–100 mgs per dose (in lung) has been shown to be well tolerated in the case of inhaled tobramycin[70,71]. Whether or not higher masses can be tolerated has not been established. Therefore if one needs a 10:1 mass of excipient relative to drug to effect controlled release, one could be limited to drugs that require ≤10 mgs per dose.

Additionally, there is the issue of deposition site. Inhaled particles usually deposit in both the airways and the alveoli of the lungs[72,73]. Insoluble particles that deposit in the airways have a maximum lifespan in the lungs of about 24 hours, as the clearing action of the mucociliary apparatus ensures that particles that land in the airways are swept up and out of the lungs[72,73]. Particles that penetrate deep into the lungs to the alveolar spaces have a chance, if they are insoluble, of staying in the lungs for many days, albeit most likely inside macrophages. This raises a final practical issue with aerosol controlled-release particles. If they are not soluble in the lung fluids, it is very likely they will be taken up by macrophages. The 1–2 μm size of inhaled particles is an ideal size for macrophages to phagocytose (cell diameters ~15–22 μm), with smaller sizes actually being taken up less efficiently[74]. Although sequestration of drug particles inside macrophages might be beneficial or at least acceptable, for controlled-release particles containing protein therapeutics, macrophage engulfment usually means eventual digestion of the protein[1,20]. It has been shown that large porous particles with geometric diameters of 10–20 μm can penetrate deep into lungs and avoid macrophage engulfment by virtue of their large size[75,76]. However, this does not preclude macrophage attachment and surface digestion of the large porous particles, a process that has been suggested by the clustering of macrophages around the large inhaled particles[75].

There is therefore some promise for controlled-release particles in the lungs[66,68,69]; however, this probably does not extend to digestion-sensitive macromolecules or drugs that require high doses formulated with large quantities of excipients to enable controlled release.

Excipients
A wide range of molecules that are used in pharmaceutical dosage forms to supply one or more of the following functions: add mass and flow properties, improve stability, mask or improve taste, improve injectability, reduce aggregation, improve dispersibility, prolong dissolution and so on.

Molecular mass increase. Another way to approach lung retention without having to resort to the design of controlled-release particles is to increase the molecular mass of the drug by conjugation with a water-soluble inert ligand (such as polyethylene glycol (PEG))[77] or another protein[23,24,52], or to decrease the solubility of the drug by conjugation with a hydrophobic molecule so that no excipients are required for its entrapment. In this respect, a variety of PEGylated proteins have been approved for human use by injection after more than 30 years of development efforts.

Unlike the gastrointestinal tract, which is virtually impermeable to most molecules >600 Da, the lung epithelium has transport mechanisms for molecules as large as 160,000 Da. In general, the larger the molecular mass of a molecule, the slower it is absorbed from the lungs. So although low molecular-mass drugs can be absorbed in seconds, soluble higher molecular-mass proteins (or slowly dissolving small-molecule particles) might be absorbed over periods of hours, days or weeks.

Peptides, which represent a growing and important therapeutic class, have been hampered for decades as therapeutics because of their very short half-lives and need to be injected. Their short half-lives are dictated by their relatively small size (1,000–3,000 Da) and their susceptibility to digestion by peptidases, which are ubiquitous in the body. Peptides can be engineered to resist digestion, then PEGylated to increase their half-life and then finally inhaled to eliminate the needle[77,78]. Therefore pulmonary controlled release has the potential to greatly increase the use of this class of therapeutics.

In summary, both particle and molecular engineering can be effective ways to control the release and absorption of inhaled drugs. Although particle engineering might be practical for small, potent molecules, molecular engineering offers a number of advantages for peptides, proteins and small molecules.

Conclusions and future directions

The enormous gas-exchange surface of the lungs represents a versatile, highly promising and, until recently, little-exploited route for drug delivery. Although not discussed in this review, challenges to reliable aerosol delivery have been largely overcome with new formulations and devices. In contrast to the gastrointestinal tract, pulmonary delivery provides much faster absorption of small molecules, with much less metabolism. Hydrophobic molecules can be absorbed within seconds, whereas polar small molecules can be absorbed over periods of an hour or so. Excess charge and insolubility can hold up pulmonary absorption of some small molecules. For proteins, the lungs represent the only significant naturally permeable, non-invasive port of entry into the systemic circulation. Peptides must be made chemically resistant to lung peptidases in order to have acceptable pulmonary bioavailabilities. Safety must always be determined on a case-by-case basis, but evidence suggests that the lungs are robust and able to safely handle chronic exposure to a large number of approved therapeutics. Because absorption can occur so quickly following inhalation of small molecules and peptides, technologies to slow absorption or retain drugs in the lungs to prolong therapeutic action will become increasingly important in the future.

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Competing interests statement

The authors declare competing financial interests: see Web version for details.

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