Therapeutic Delivery

Drug delivery to the lungs: challenges and opportunities

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Pulmonary drug delivery is relatively complex because the respiratory tract has evolved defense mechanisms to keep inhaled drug particles out of the lungs and to remove or inactivate them once deposited. In addition to these mechanical, chemical and immunological barriers, pulmonary drug delivery is adversely affected by the behavioral barriers of poor adherence and poor inhaler technique. Strategies to mitigate the effects of these barriers include use of inhaler devices and formulations that deliver drug to the lungs efficiently, appropriate inhaler technique and improved education of patients. Owing to the advantages offered by the pulmonary route, the challenges that the route poses are worth addressing, and if successfully addressed, the pulmonary route offers huge opportunities, often fulfilling unmet clinical needs.

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Drugs have been given by inhalation for millennia [1], but today they have three main uses: the maintenance therapy of asthma and chronic obstructive pulmonary disease (COPD) with bronchodilators and glucocorticosteroids; topical delivery in several relatively uncommon (orphan) diseases including cystic fibrosis (CF) and pulmonary arterial hypertension (PAH); and systemic applications [2]. Of these uses, the first category is the dominant one. Few inhaled drugs for systemic delivery have yet been marketed, but their use is generally geared toward relatively common medical situations including pain control or treatment of diabetes [3]. A variety of inhaler devices are available to deliver inhaled drugs [4]. Most inhaled drugs are delivered by pressurized metered dose inhaler (pMDI) [5], dry powder inhaler (DPI) [6] or nebulizer [7]. Other technologies, involving different aerosol generation principles, are sometimes used for delivery of specific drugs.

Pulmonary drug delivery is a form of drug targeting, whether to the site of action in the lungs for topically acting drugs, or the site of absorption for systemically acting drugs. For the former, the advantages of pulmonary delivery include the possibility to use a relatively low dose, a low incidence of systemic side effects and for some drugs a rapid onset of action [8,9]. For systemically acting drugs, pulmonary delivery offers an opportunity to avoid injections for drugs that are not well absorbed via the GI tract, and the possibility for more advantageous pharmacokinetic profiles, for instance achieving plasma levels of insulin in a timescale appropriate for meal-time delivery [10]. The pulmonary epithelium, consisting of an area >100 m^2, and having an epithelial cell layer <1 µm in thickness, is an attractive target site for systemically acting drugs [11].

Delivering drugs by inhalation is relatively complex, for two main reasons. First, the respiratory tract has evolved defense

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mechanisms that are intended to keep inhaled materials out of the lungs, as well as removing or inactivating them once they have been deposited [8]. Second, it is necessary for a patient to use an inhaler device, and to use it correctly [12]. Failure to adhere to inhaled treatment regimens [13] and misuse of both pMDIs and DPIs [14] are common problems. Poor understanding of issues relating to both lung defense mechanisms and inhaler use partly explains why pulmonary drug delivery was relatively unsuccessful until the second half of the 20th century. These issues pose major challenges to the pharmaceutical industry and to healthcare professionals. In the modern era, it is generally agreed that owing to the advantages offered by the pulmonary route, the challenges that the route poses are worth addressing. The opposite side of the coin of these challenges is that, if successfully addressed, they offer huge opportunities, often fulfilling unmet clinical needs.

Mechanical barriers

The lung defense mechanisms that an inhaled drug particle may encounter can be regarded as mechanical, chemical or immunological barriers (Box 1) [15]. The human respiratory tract consists of the upper (extrathoracic) airways, the conducting (tracheobronchial) airways of the lungs and the alveolated airways connected in series (Figure 1). The upper airways (nasal and oropharyngeal) are narrow angled passages with variable dimensions, and are an excellent site for inertial impaction, which prevents entry of particles to the lungs [16]. The nasal passages act as a particularly efficient aerosol 'filter', and for delivery into the lungs, inhalation should ideally take place via the mouth. The lungs consist of a complex network of branching airways, often termed the 'bronchial tree'. If a particle is to penetrate to the alveolated region and gain access to the large epithelial target site, then it must pass numerous airway bifurcations where it could potentially be deposited.

The required aerosol size to deliver drugs to the whole lung involves an aerodynamic diameter < c. 5 μm, although there are several definitions of the 'fine particle' range [17]. For delivery to the alveolar epithelium, particles with an even smaller size, for example, aerodynamic diameter < c. 3 μm, are required [18]. However, deposition also depends critically on inhalation parameters, most notably inhaled flow rate, inhaled volume and breath-hold pause. For drugs delivered by pMDI, the inhaled flow rate should be slow [19], but for drugs delivered by DPI a 'quick', 'fast' or 'forceful' inhalation is generally recommended in patient instruction leaflets because the shear forces created by such inhalation are used to disperse the drug powder and ensure a sufficiently high respirable dose [20]. Most inhalers deposit less than 20% of the dose in lungs [21], with the majority usually being deposited in the oropharynx (for pMDIs and DPIs), or retained in the device (for nebulizers). Mechanical barriers are more marked in disease where airways may be narrowed by bronchoconstriction, mucus hypersecretion and inflammation, or may even be blocked by plugs of mucus (Figure 1).

Lung mucus comprises a gel layer above a periciliary liquid layer, within which cilia beat. Lung mucociliary clearance is a natural lung defense mechanism that serves to remove deposited materials from the conducting airways and deliver them to the oropharynx, where they are swallowed or expectorated [22]. In the healthy lung, the tracheobronchial airways are completely cleared of deposited material within 24 h. Mucociliary clearance could be detrimental to drug delivery if it moves drug away from target sites, but it could be beneficial if it moves deposited drug toward target sites from less favorable areas.

Chemical & immunological barriers

Within the lungs deposited particles are expected to dissolve in lung fluids, although this process is incompletely understood [23]. Provided drug has not been removed by mucociliary clearance, it should in theory be available either to exert a local effect in tissue or

Barriers to successful pulmonary drug delivery.

Mechanical barriers
- Impaction of inhaled drug particles and droplets in mouth and nose
- Impaction losses in large airways restrict delivery to peripheral lung regions
- Effects of disease: airway narrowing, mucus hypersecretion and mucus plugging
- Removal of drug by lung mucociliary clearance

Chemical barriers
- Drug degradation by proteolytic enzymes
- Effects of other chemicals, e.g., surfactant

Immunological barriers
- Particle engulfment by alveolar macrophages

Behavioral barriers
- Non-adherence to treatment regimen
- Poor inhaler technique

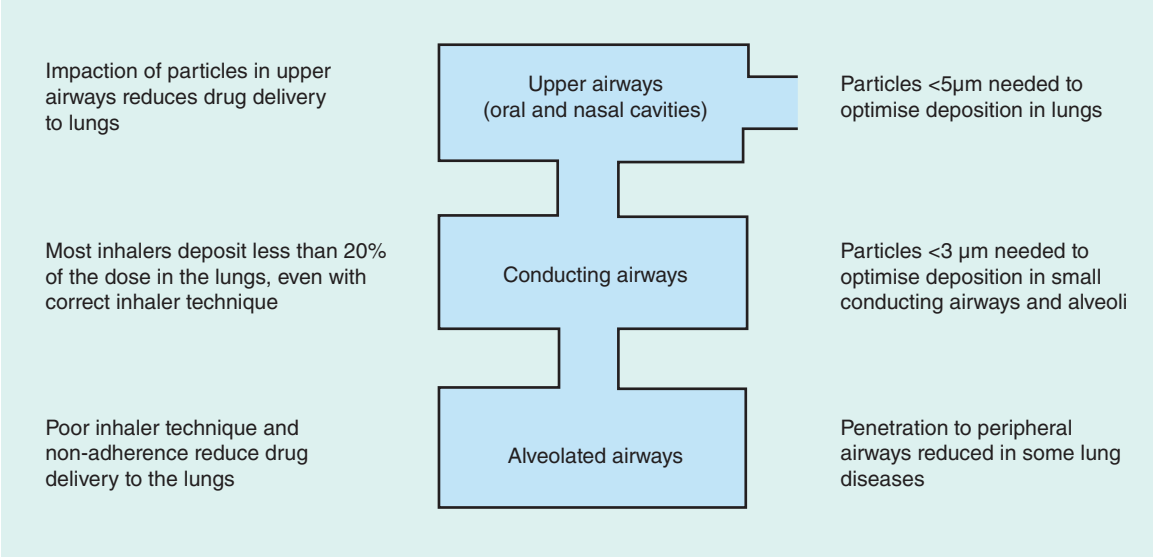

Figure 1. Schematically, the respiratory tract can be considered as the upper (extrathoracic) airways, conducting airways and alveolated airways arranged in series. Several factors influence drug deposition in the whole lung and in peripheral lung regions.

to be absorbed into the systemic circulation (Figure 2). Unfortunately, deposited drugs may be subjected to the actions of chemicals including proteolytic enzymes (proteases), and surfactant. Proteolytic enzymes, such as neutral endopeptidase and cathepsin H, may hydrolyze peptides and proteins in the lungs [8], resulting in their inactivation [23]. Undissolved drug particles may encounter alveolar macrophages, which are the predominant phagocytic cells defending against inhaled particles [8]. Alveolar macrophages constitute an immunological barrier that makes no distinction between potentially harmful substances and potentially beneficial ones [15]. The macrophages could engulf drug particles and remove them from the lungs, for instance via the lymph system, or by transferring them to the foot of the mucociliary escalator. The effects of macrophages on drug absorption has been demonstrated in animal models, but its role in man is less well understood [23]. Surfactant may prevent adhesion of inhaled particles to the lung surfaces, making them more accessible to macrophages [15].

The combined effect of mechanical, chemical and immunological barriers is that pulmonary bioavailability (for locally acting drugs) and systemic bioavailability (for systemically acting drugs) are low for drugs delivered by most inhalers, and the development of novel, more efficient inhaler systems may be desirable to mitigate the effects of these barriers [3].

Behavioral barriers

Adherence

Pulmonary drug delivery is critically influenced by what patients do, or fail to do, with their inhaler devices [12]. Adherence may be defined as the number of doses taken, expressed relative to the number of doses prescribed [24]. Nonadherence to the therapeutic regimen is common, and may be either intentional or nonintentional; a patient may feel well and decide not to take the prescribed treatment, or may simply forget to take it [25]. Cultural factors and misconceptions play a role in determining levels of adherence. For instance, a survey in India reported that 85% of patients considered use of an inhaler to carry a social stigma, and that a similar percentage believed inhalers only to be suitable for treating severe disease [26].

Inhaler technique

Poor inhaler technique has long been recognized as a limitation of inhaled drug delivery, and worryingly a recent review concluded that the ability of patients to use inhalers correctly has not really improved over the last 40 years (Figure 3) [27]. Major errors in inhaler technique for pMDIs include not actuating the inhaler while breathing in (poor coordination), and failure to inhale deeply and slowly. For DPIs, the major problems include not inhaling with sufficient force, together with device-specific handling and preparation errors that include incorrect device orientation. Most patients are capable of inhaling forcefully through a DPI, but some elderly patients may lack the inspiratory muscle strength required to use a DPI correctly [28]. Failure to exhale fully before inhaling [27] and an inadequate breath-hold pause after inhalation [29] are problems for both inhaler types. Most nebulizers can be used with relaxed tidal breathing, but patients can still misuse them, for instance, by coughing, breathing via

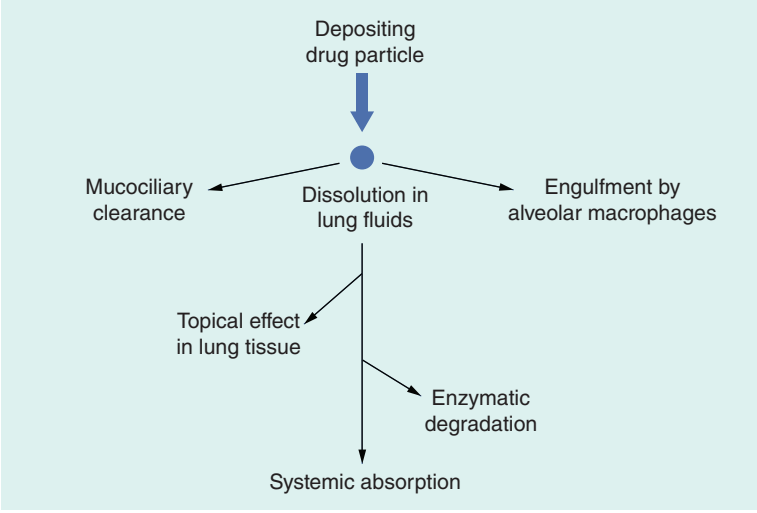

Figure 2. Schematic showing potential fate of deposited drug particles, based on several references discussed in this paper.

the nose, holding a facemask away from the face and not assembling the nebulizer equipment correctly [12]. Inadequate training in inhaler use predisposes patients toward poor inhaler technique [30].

True adherence

Nonadherence and poor inhaler technique lead to suboptimal and highly variable lung deposition [12], and can result in less well-controlled disease and more frequent emergency department visits [31], as well as an increased economic burden on the healthcare system [32]. It has been argued that inhaled drug delivery has underachieved because of failure to address these issues adequately [33]. The term 'true adherence' (or 'true compliance') has been coined as the product of adherence to the regimen and correct inhaler technique [24], and it is now considered that optimizing true adherence is essential for successful future disease management.

The manner in which mechanical, chemical, immunological and behavioral barriers influence delivery of different drug types will now be considered.

Asthma & COPD maintenance therapy

New drugs available

Drugs for the maintenance therapy of asthma and COPD have undergone significant evolution over the last few decades. Inhaled beta-agonist bronchodilators available in the 1970s and 1980s (e.g., salbutamol and terbutaline) had durations of action of 6 h at best, but changes to molecular structures have made available compounds with durations of action of 12 h (e.g., salmeterol and formoterol) and then 24 h (e.g., indacaterol and vilanterol), the latter permitting once-daily dosing [34]. Antimuscarinic bronchodilators that are widely used in COPD have undergone similar improvements, with twice-daily drugs (e.g., aclidinium) and once-daily drugs (e.g., tiotropium, glycopyrronium and umeclidinium) being introduced [35]. Long-acting beta-agonists and long-acting muscarinic antagonists are now preferred to shorter acting drugs for most applications. At the same time, novel inhaled glucocorticosteroids have been introduced with extremely low oral bioavailability and high receptor binding affinity, including fluticasone propionate and ciclesonide [36]. Increasingly, products are developed containing two of these drugs in the same inhaler device (e.g., Advair® Diskus® DPI [GlaxoSmithKline, Middlesex, UK] or Symbicort® pMDI [AstraZeneca, Cambridge, UK]) [37], and several triple therapies containing three drugs are either in development, or are already available in some countries.

Drug delivery

Although most asthma or COPD inhalers only deposit a small percentage of the nominal dose in the lungs, this is not usually considered a problem because the drugs concerned are potent, readily available and inexpensive. High oropharyngeal deposition of inhaled corticosteroids can lead to local side effects (dysphonia and candidiasis), but their effects can be limited either by washing out the mouth or using a pMDI with a spacer device [38]. Some products with a very small particle size and low plume velocity (e.g., Qvar®, 3M, MN, USA) are capable of depositing 50% of the dose in the lungs [39], and may especially be suited to target small conducting airways [40]. Although most asthma and COPD products that have been formulated as suspensions contain micronized particles, several formulations of asthma and COPD drugs within 'engineered' particles, made by processes such as spray drying, have been described in the literature [41].

Device selection

The main drug delivery challenges for asthma and COPD drugs concern the high incidences of both nonadherence and poor inhaler technique. Central to addressing these challenges is the choice of an appropriate inhaler. It has proved difficult to show differences in efficacy between different types of inhaler used to deliver the same drug in controlled clinical trials [42], and device selection requires the choice of an inhaler that the patient will use and can use correctly [43]. Ideally, this should be an inhaler that the patient prefers [43], and where possible the same inhaler should be used to deliver multiple drugs [44]. There is evidence that combination inhalers delivering two drugs in the same breath can improve adherence [45]. Instructions for using DPIs should be kept as simple as possible, and if these can be reduced to essentially 'open, inhaled,

close' it may be more likely that a patient will use the inhaler successfully.

The prohibition of chlorofluorocarbon (CFC) propellants required by the Montreal Protocol of 1987 was a major historical challenge that was successfully addressed by reformulating pMDIs with hydrofluoroalkane (HFA)-134a or HFA227ea, substances that do not deplete the ozone layer [46]. These propellants have significant global warming potential, and future regulations may require a reduction in their overall use [47]. The implications for pMDIs are unclear, but the current propellants could potentially be replaced at least in part with substances that have similar thermodynamic properties but lower global warming potential such as HFA152a.

Technologies to promote true adherence

Some patients using pMDIs may be unable to coordinate firing the inhaler with breathing in, and may find a breath-actuated pMDI [1] or pMDI plus spacer device [38] easier to use correctly. Both very young and very old patients may experience major problems using both pMDIs and DPIs successfully, and for these patients, a pMDI plus spacer or a nebulizer may be the best option. Several training aids are available to teach patients good inhaler technique, specifically to actuate the pMDI at the same time as breathing in, and to adopt an inhaled flow rate appropriate to the type of inhaler being used (Table 1) [48].

Electronic data loggers incorporated into the device are the most reliable means of quantifying adherence to the inhaled regimen [49], and can provide the patient or healthcare provider with data on actual use, often via modern digital connections such as mobile phones or computer servers [24,50,51]. In some cases, these 'connected inhalers' also issue a reminder to patients to take the next dose. Dose counters were introduced for pMDIs to inform patients about the fullness of their inhalers, and to ensure that patients do not try to use them once the stated number of doses has been exceeded. Perhaps because they make patients more aware of the status of their inhalers, the addition of a dose counter has also been reported to improve adherence [52].

Addressing challenges via education

It is essential that patients understand their illness, their treatment and their inhaler, including the importance of taking inhaled corticosteroids on a regular basis to prevent asthma attacks. The management of chronic respiratory diseases has been described as '10% medicine and 90% education' [53]. Patients need to master the use of an inhaler device, and to maintain mastery over the long term [29]. Instruction needs to be given initially, but messages need to be repeated regularly, and inhaler technique rechecked to make sure it has not deteriorated. When using a pMDI, adult patients should be instructed to inhale over 5 s, and children over 2–3 s, to ensure that inhalation is sufficiently slow [54]. One situation where re-education is doubly important concerns patients who have been switched from one inhaler to another. Since the handling requirements and inhalation maneuver may change when a new inhaler is prescribed, it is essential that adequate instruction about using the new inhaler is given [55]. This applies not only to switches between pMDI and DPI, but also to switches between different DPI brands.

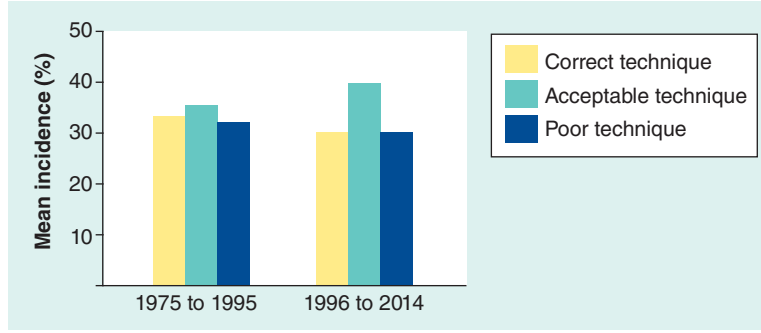

Figure 3. A meta-analysis of studies that assessed inhaler technique for both pressurized metered dose inhalers and dry powder inhalers showed that the incidences of 'correct', 'acceptable' and 'poor' inhaler techniques were similar for the periods 1975–1995 and 1996–2014, although a small increase in the incidence of acceptable technique was noted. It was concluded that inhaler technique has not really improved over the last 40 years.
Data taken from [27].

Practical demonstration in addition to written instructions are likely to be more effective than written instructions alone [56]. One-to-one discussions between patient and healthcare professional may be the ideal, but group training sessions or information disseminated over the internet are other options. It has been suggested that community pharmacists are often best placed to give instruction on inhaler use [57]. Public service initiatives aimed at increasing awareness of asthma and its treatment have been described [58].

Unfortunately, many healthcare professionals seem not to know how to use an inhaler any better than their patients, and therefore 'training the trainers' is also required [59]. Several issues faced by healthcare professionals in promoting true adherence have been pointed out, including lack of time, lack of understanding and unwillingness to confront patients about their poor adherence [60]. Ensuring adequate adherence is not only a matter of education, but also involves psychological aspects. It may be necessary to address a range of issues including patients' misconceptions, their possible mistrust of the medical profession, socio-economic

Table 1. Examples of technologies used to promote either good inhaler technique or better adherence to therapy, and hence improved true adherence.

Type of technology	Example	Company
Breath-actuated pMDI	Autohaler®	3M Drug Delivery Systems
	Easibreathe®	Teva
Training aids	2Tone Trainer™	Canday Medical
	Trainhaler™	Clement Clarke International
Monitoring inhaler use/reminders	Propeller sensor	Propeller Health
	Doser™	Meditrack
	Smartinhaler™	Adherium
Dose counters	Aerocount™	Trudell Medical International
	Landmark™	Aptar Pharma
	Integrated dose by dose counter	3M Drug Delivery Systems

pMDI: Pressurized metered dose inhaler.

concerns including possible family dysfunction and any cultural barriers that could prevent them benefitting from inhaler therapy.

Ensuring both adherence to treatment and good inhaler technique represents a major challenge, but it is now recognized that the present situation where there is a high incidence of both poor adherence and poor inhaler technique has persisted for too long [61]. There is now a real opportunity to address these limitations and to ensure that the benefits of inhaled therapy can be brought to as many patients with asthma and COPD as possible.

Optimizing delivery efficiency

While most asthma and COPD products are delivered to the lungs with relatively low efficiency, this is less desirable for drugs that are used to treat orphan diseases, or are required to be absorbed for systemic effect. It may be necessary to target the lung with greater efficiency to optimize clinical effectiveness, minimize potential side effects and for expensive or scarce drugs to render the treatment cost-effective. Drugs may have narrow therapeutic windows, so that their delivery should be as reproducible as possible. Fortunately, lung deposition and its variability appear to be inversely correlated. A meta-analysis of lung deposition data has shown that inhaler systems delivering drug relatively efficiently to the lungs (mean lung deposition >30% of the nominal dose) also have the lowest variability in lung deposition (coefficient of variation <30%) [22]. Examples of such delivery systems can be found across the range of inhaler types, including pMDIs, DPIs and nebulizers. In many cases, these high-efficiency low-variability inhaler systems are likely to be the devices of choice for delivering nonasthma, non-COPD drugs required to have topical effect in the lungs, and for systemic delivery.

Although nebulizers can be used with spontaneous tidal breathing, control of inhalation via nebulizers offers the opportunity to attain efficient and reproducible drug delivery that is difficult to match with any other type of inhaler. Owing to a combination of a vibrating mesh device with a low residual dose, an appropriate particle size distribution and a carefully controlled inhalation, the I-neb® AAD® nebulizer (Philips Respironics, PA, USA) is capable of depositing 50% of the nebulizer fill in patients' lungs, with low intersubject variability (Figure 4) [62]. Broadly similar data were obtained from another 'intelligent' inhaler, the AKITA® nebulizer system (Vectura), used with a vibrating mesh device and slow deep breathing [63].

Orphan diseases

Drug repurposing

The ability to use inhaled drugs for the treatment of respiratory conditions other than asthma and COPD has long been recognized. Currently, the main examples of this application are the delivery of mucolytics and antibiotics [64] in patients with CF and other respiratory conditions including non-CF bronchiectasis, and the delivery of inhaled prostacyclin analogs [65] in the treatment of PAH. The delivery of inhaled mucolytics, antibiotics and prostacyclin analogs are examples of the repurposing of drug delivery by the inhaled route.

Mucolytics

In CF, lung mucus is tenacious and difficult to clear, leading to the potential for infections to develop, involving pathogens such as *Pseudomonas aeruginosa*. Infection leads in turn to further lung damage and a potential downward spiral. The tenacious nature of mucus can be addressed by inhaled mucolytic

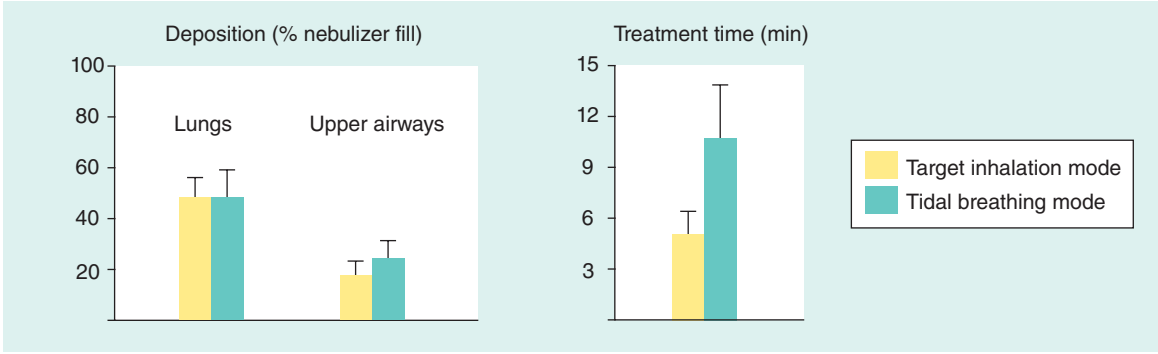

Figure 4. Lung deposition of alpha-1 proteinase inhibitor and treatment time in 15 patients with cystic fibrosis from the I-neb® AAD® nebulizer, using target inhalation mode (slow deep breathing) and tidal breathing mode.
Mean and SD data taken from [62].

substances, such as inhaled rhDNase (Pulmozyme®, Genentech, CA, USA), delivered by specific jet nebulizer systems. Neutrophil DNA present in CF sputum can be depolymerized by inhaled rhDNase, resulting in significant improvements in both lung function and symptoms [64,66]. The introduction of Pulmozyme marked the first inhaler product containing an inhaled protein manufactured by recombinant processes.

Antibiotics

Antibiotics suitable for the treatment of *Pseudomonas* infections in lungs are ineffective when given by mouth, and historically have required injections. However, the potential of achieving high sputum concentrations of antibiotics by inhalation, while minimizing systemic delivery, was recognized [67]. Inhaled antibiotics were given in the early 1980s to CF patients by placing injectable formulations in nebulizers [64,68]. The required doses of these drugs including gentamicin, carbenicillin and colistin are typically several hundred milligrams, a dose which can be administered readily by nebulizer, but which is too large to be given by pMDI or by most types of DPI [18]. Patients sometimes found these injectable formulations unpalatable when given by inhalation, and to increase patient acceptability, a formulation of tobramycin designed for inhalation was developed in the 1990s. This product (TOBI®, Novartis, Basel, Switzerland) consisted of a 300-mg nominal dose to be administered twice daily on a 4-week on, 4-week off regimen, and was found to be both effective and safe in long-term use [64]. It was recommended to be given by specific jet nebulizer systems that had either been used in pivotal Phase III trials, or which had equivalent output characteristics. Aztreonam (Cayston®, Gilead, CA, USA) is another inhaled antibiotic formulated as a solution, and approved for delivery by vibrating mesh nebulizer [69].

While TOBI was very effective, it was recognized that the approved jet nebulizer system suffered from several important limitations: its delivery to the lungs was inefficient due in part to a high residual dose remaining within the nebulizer, the treatment time was 15 min or greater and the complete delivery system comprising nebulizer plus compressor was cumbersome. Development of a powder formulation of TOBI to be delivered by a Podhaler™ DPI (Novartis) resulted in a product that was deposited with much greater efficiency, such that an equivalent lung dose to that from the nebulized product could be achieved from the contents of four powder capsules, each containing 28 mg tobramycin [70]. The powder is formulated within engineered particles (PulmoSphere® particles, Novartis), which have low density and smooth contact surfaces, such that their dispersion in an inhaled airstream is relatively independent of inspiratory effort [71]. These particles can be delivered significantly more quickly than the nebulized product, potentially enhancing patient acceptability and adherence. A form of colistin, colistimethate sodium (Colobreathe®, Forest Laboratories, NY, USA), is available as a dry powder to be delivered by Turbospin® DPI. Future developments could involve the use of a high-dose DPI capable of delivering a 100-mg dose from a single dosing unit, and reducing treatment time further [72].

Prostacyclin analogs

The use of prostacyclin and its analogs given by injection in the treatment of PAH was limited by systemic side effects [65], leading to the development of an inhaled formulation of iloprost (Ventavis®, Actelion, Basel, Switzerland), to be given by ProDose™ and then I-neb AAD nebulizers (Philips Respironics, Basel, Switzerland) [73]. Both of these nebulizers use adaptive aerosol delivery (AAD) technology in which aerosol delivery is adjusted to match the breathing patterns of individual patients [74]. The nominal dose is low (2.5 or 5 µg given 6–9 times daily), and could in theory be delivered by any type of inhaler device. An AAD nebulizer system was selected because it could be used to control inhalation and hence the lung dose, to provide

visual and tactile feedback to patients at time of dosing and to monitor adherence [75]. The use of the I-neb AAD system set the precedent for the use of 'intelligent' nebulizer systems in pulmonary drug delivery. Future developments in the delivery of inhaled prostacyclin analogs could include the introductions of other drugs with longer plasma half times that would need to be given less frequently (e.g., treprostinil) [76], or incorporation of the drug into other types of inhaler.

Systemic delivery

Small molecules

The potential of using the lungs as a portal of entry for drugs to the systemic circulation has long been recognized. Drugs given by inhalation to achieve a systemic effect are of three main types: fast-acting small molecules with a molecular weight <1000 Da; peptides and proteins; and vaccines. Although a range of small molecules for systemic action are marketed for nasal delivery, few have yet been marketed for delivery via the lungs. The pulmonary absorption of small molecules (e.g., loxapine, MW 328 Da and fentanyl, MW 336 Da) is both rapid and efficient. Lipid-soluble compounds are probably absorbed via cellular membranes, whereas lipid-insoluble compounds are more likely to pass through aqueous pores in intracellular tight junctions [77]. One of the first pMDI products launched in the late 1950s contained ergotamine for treatment of migraine, and it remained on the market for over 50 years [1]. Other pain-control products for delivery by inhalation have recently been in development [78]. A novel condensation aerosol inhaler (Staccato®, Alexza) has been marketed to deliver inhaled loxapine (Adasuve®, Alexza, CA, USA) for treatment of psychiatric disorders [79].

Peptides & proteins

Compared with smaller molecules, the absorption of peptides and proteins is both less efficient and slower [18]. Both bioavailability and time to maximum blood concentration (T_{max}) are highly compound dependent [77]. Bioavailability tends to decrease with increasing molecular weight [11]. The bulk of work in this field has involved the development of inhaled products containing insulin (MW c. 5800 Da). Insulin was first given by inhalation in 1925 [11], not long after its discovery, but marketed inhaled insulin products were not introduced until the 21st century [80]. Inhaled insulin needs to be targeted to the large surface area of the alveolar region, and to attain the required blood concentration it is required that delivery should be both efficient and reproducible. However, for most formulations, two of every three insulin molecules deposited are not absorbed intact, and this is ascribed mainly to the inactivating effect of proteolytic enzymes [18]. Hence, it was essential that novel, more efficient and reproducible delivery systems were developed.

The first inhaled insulin product (Exubera®, Pfizer, NY, USA) was approved in 2006, delivered by a large 'active' DPI (Nektar Pulmonary Inhaler, CA, USA) in which powder was dispersed by compressed air, and was inhaled slowly as a standing cloud (mass median aerodynamic diameter 3.5 µm) [81]. The novel particle formulation (Pulmosol® particles [Nektar]) was made by spray drying, in contrast to the micronized drug particles and larger carrier lactose particles in conventional DPI products. The combination of device and formulation was intended to deliver a high percentage of the dose to the lung periphery, with efficient pulmonary delivery being considered essential to counter the effects of losses resulting from natural lung defense mechanisms. In the case of Exubera, a bioavailability of approximately 10–15% was achieved relative to a subcutaneous dose, and this was considered sufficiently high to allow the product to be commercialized. This bioavailability assumes that about 40% of the dose is available to the deep lung, and that only about one in three insulin molecules is absorbed intact [11]. Exubera was withdrawn from the market after about 1 year for commercial reasons. Although probably not the main reason for the failure of the product [41], the large size and relative inconvenience of the inhaler may have been a factor.

The second inhaled insulin product launched in 2015 (Afrezza®, Mannkind, CA, USA) adopts a different approach [82]. The drug is contained with a novel powder formulation of Technosphere® particles (Mannkind), which include the excipient fumaryl diketopiperazine. The powder is delivered by a simple breath-actuated DPI (Dreamboat®, Mannkind), where the powder and not the device plays the major role in ensuring efficient and reproducible delivery. Comparative data [83,84] show that this product has a higher bioavailability than both Exubera and two nonmarketed products, possibly because the excipient fumaryl diketopiperazine acts as an absorption enhancer (Figure 5). The time to maximum plasma concentration is markedly shorter than for Exubera, which could make it more suitable for prandial use.

Most modern attempts to develop an inhaled insulin formulation have involved dry powders, to optimize physical and chemical stability [10]. Several liquid formulations of insulin have also been developed, with at least one of these being in current development [85].

The delivery of drugs by inhalation to achieve a systemic effect has yet to fulfill its promise, and it is unclear whether small molecules for rapid action or larger molecules including peptides are going to be the more

successful [3]. The desirability of delivering insulin and other peptides by inhalation is predicated in part upon the avoidance of regular injections, but recent developments in injectable technologies may make this less of an issue. Future success may depend upon showing clear clinical or economic benefits versus injectable formulations. A truly successful inhaled insulin product could open the way to developments involving many other drugs for systemic action, such as calcitonin, parathyroid hormone and growth hormone [11].

Vaccines

The use of inhalation to provide vaccines, such as measles vaccine, to children in the developing world is attractive because it avoids problems of disposal and potential injury associated with needles [1]. Superior immune response compared with injected vaccines were shown following aerosol delivery of both measles and measles–rubella vaccines [86]. Both liquid and powder formulations have been developed, but the latter have the advantage particularly in remote locations of not requiring refrigeration [87]. Dry powder devices with disposable patient interfaces have been described for delivering powder formulations of vaccines [88].

Discussion

Meeting the challenge of delivering drugs to the lungs requires selection of an appropriate inhaler and formulation. If it is to be used successfully by patients, an inhaler device should possess a range of properties. It should be convenient, unobtrusive and easy to use correctly [89]. For some treatment indications, there should be tight control over the lung dose and relative independence of the lung dose on inhaled flow rate [90]. Inhaler systems should be affordable, but perhaps even more importantly they should be cost-effective since there is no merit in an inexpensive inhaler system that does not work, and complex devices conferring only marginal clinical advantages may not be affordable. It is not easy to achieve all the desirable features of an inhaler in the same device. For asthma and COPD therapy, a convenient inhaler that patients will use and can use correctly is the dominant requirement, while for treatment of orphan diseases and for systemic delivery, efficient and reproducible pulmonary delivery is an equally important attribute. Aerosol delivery to ventilated or intubated patients presents special challenges, owing to the potential for losses of drug within tubing, but these issues are now better understood than in the past [91,92].

Choice of inhaler will be determined to some extent by the mass of drug that it is required to deliver (Figure 6). Drug doses range from a few micrograms for some bronchodilators to as much as 1 g for some antibiotics. For doses of asthma and COPD drugs up to 1 mg, pMDIs and DPIs are suitable, but only some DPIs where drug is contained within individual capsules or blisters can be used for larger doses [18]. Nebulizers will deliver essentially any drug dose, but for practical reasons, pMDIs and DPIs are generally preferred for small drug doses where possible. It is essential that the aerosolization process should not damage the drug

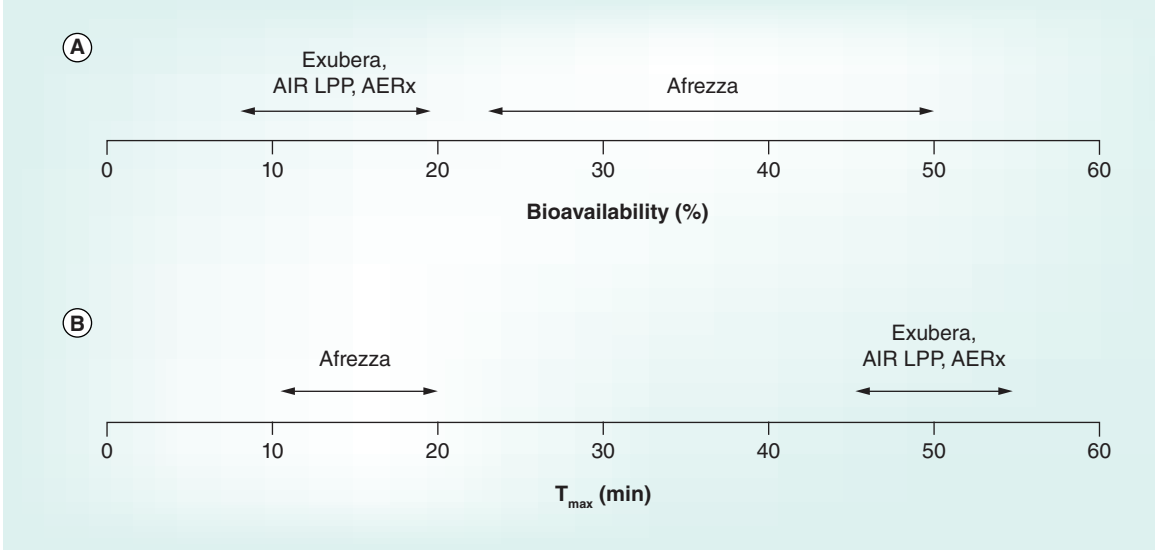

Figure 5. Bioavailability and pharmacokinetics of different inhaled insulin products. (A) Bioavailability relative to a subcutaneous dose, and **(B)** time to maximum plasma concentrations (T_{max}) for different inhaled insulin formulations. The marketed products Afrezza® and Exubera® are compared with two other products that were not marketed: AIR® LPP (Alkermes, Dublin, Ireland) and AERx® iDMS (Aradigm, CA, USA).
iDMS: Inhaled diabetes management system; LPP: Large porous particle.
Data taken from [11,83,84].

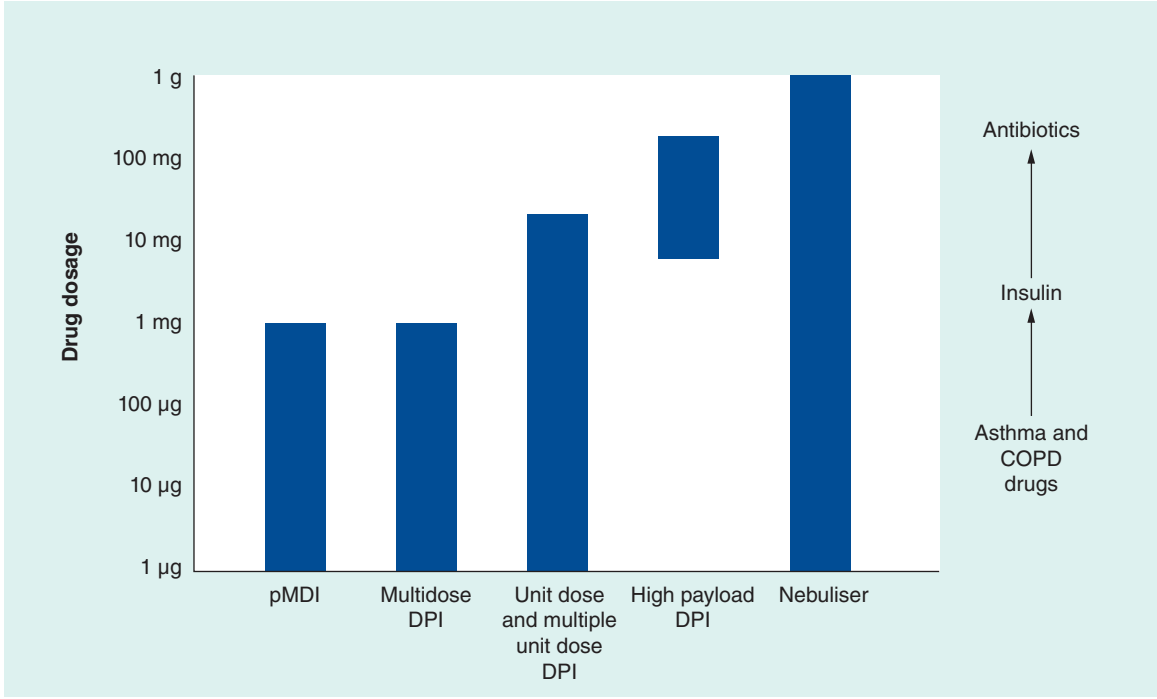

Figure 6. The mass of drug comprising a single inhaled dose varies over many orders of magnitude, from <10 µg for some asthma and chronic obstructive pulmonary disease drugs to >100 mg for some antibiotics. This drug mass is an important factor in determining which type of inhaler can be used for a specific application.
COPD: Chronic obstructive pulmonary disorder; DPI: Dry powder inhaler.

molecule [11]. Many novel inhaler devices have been described in the last 20 years, but some of these have involved novel technologies and aerosol generation principles that have proved difficult to commercialize. The challenge of converting a prototype inhaler into a marketable inhaler has sometimes proved impossible to meet [93].

Conclusion & future perspective

Successful pulmonary drug delivery presents many challenges, but interest in the pulmonary route seems to be greater than ever. Presumably, this reflects our recognition of the advantages that pulmonary delivery offers. Treatments for asthma and COPD have evolved significantly over recent years, and are likely to continue doing so, with increased emphasis on ensuring adherence and correct inhaler use. Future developments in topical delivery are likely to see the repurposing of more drugs for inhalation, attempting to fulfill unmet needs. There are several possible opportunities for repurposing drugs by inhalation for treatment of orphan diseases as well as commoner conditions. These include the use of inhaled IFN-γ in the treatment of idiopathic pulmonary fibrosis [94], inhaled cyclosporine in treatment of lung transplant rejection [95], inhaled rifampicin [96] and capreomycin [97] in the treatment of tuberculosis and inhaled voriconazole for treatment of pulmonary aspergillosis [98].

In order to optimize delivery of inhaled drugs for systemic effect, companies have sought to maximize lung deposition via design of the inhaler device or formulation, and we now have an excellent range of delivery technologies. But increasing lung deposition is not the only way to improve bioavailability. Future developments may see the utilization of other strategies, including addition of protease inhibitors into drug formulations [41], the use of PEGylation, which seems capable of shielding drug molecules from natural defense mechanisms within the lungs [99] or formulations that use immunoglobulin receptors in the airways to facilitate transcytosis of proteins [100].

There has been much interest in increasing the longevity of drugs in the lungs [101], whether for local or systemic action. The delivery of a twice-daily drug in a controlled release formulation that permits once-daily dosing could result in better adherence to the treatment regimen [41]. So far, the strategy used in marketed products to increase the duration of drug action in the lungs has been the introduction of novel long-acting beta-agonists and long-acting muscarinic antagonists in the treatment of asthma and COPD. Although a variety of controlled release formulations have been evaluated over several decades, including the use of large porous particles containing poly(lactic-co-glycolic) acid [102], only liposomal formulations have progressed so far to late-stage clinical trials [103,104].

Most inhaled drug products deliver particles in the size range <5 µm, but there are potential advantages to be gained from the use of nanoparticle formulations, that is, particles <1 µm. Nanoparticles could improve drug targeting by achieving a more uniform distribution of drug in alveolar regions [105]. Many drugs have poor aqueous solubility, and a potential way to enhance solubility is to reduce the size of particles to the nanometer scale. This results in a larger surface area per unit mass of drug, which in turn may increase the amount of drug that can dissolve in lung lining fluid [106]. The delivery of nanomedicines by inhalation is still a young science, but formulation strategies have included the use of poly(lactic-co-glycolic) acid nanoparticles loaded with drug, and incorporation of nanoparticles into liposomes [107].

Inhaled drug delivery is not inevitably the solution to treat respiratory conditions. In the 1980s, inhaled pentamidine was introduced for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV disease [36]. Subsequently, inhalation was found to be less effective than oral therapies because of poor delivery to the lung apices, leading to reoccurrences of infection there. Although several potential inhaled therapies for lung cancer have been described, none has yet become established [108]. Perhaps in these and other situations, inhalation used as an adjunct to oral or parenteral delivery could prove effective in the future.

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Executive summary

- Pulmonary drug delivery is more complex than simply taking a tablet.
- The respiratory tract has evolved to keep inhaled particles out of the lungs, and to remove or inactivate them once deposited.
- Most inhaler systems only deposit a small percentage of the dose in the lungs. For inhaled drugs used to treat asthma and chronic obstructive pulmonary disease, this is not a problem, but for other drugs such as inhaled antibiotics, analgesics and peptides for systemic action (including insulin), strategies to optimize bioavailability may be desirable. Such strategies include increasing lung deposition or reducing the effects of drug degradation within the lungs.
- A limitation of pulmonary drug delivery is that each patient needs to master the use of an inhaler device. A recent meta-analysis concluded that inhaler technique has not really improved over the last 40 years.
- Poor adherence to inhaled regimens also remains a significant problem. Poor inhaler technique and poor adherence have adverse clinical and economic consequences, but can be addressed partly by technology and partly by improved patient instruction.
- It is important to choose an inhaler that the patient will use and can use correctly. Inhaler choice is also influenced by the mass of drug that needs to be delivered, and the requirement of efficient delivery for drugs that are expensive or have narrow therapeutic windows.
- 'Connected inhalers' that can monitor adherence to inhaled treatment, and can provide feedback and reminders to patients are becoming more prevalent.
- Future developments in are likely to see the repurposing of more drugs for inhalation, attempting to fulfill unmet needs.

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