The challenge of delivering drugs to the lungs

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Summary

The pulmonary route has an established role in the treatment of asthma and chronic obstructive pulmonary disease (COPD), and has a number of other topical and systemic applications. Successful pulmonary drug delivery requires a predictable, reproducible lung dose and clinical effect with each treatment, while minimising unwanted side-effects, and achieving these objectives at reasonable cost. The patient presents a major barrier to achieving these goals, first because of natural lung defence mechanisms, and second because of the need to use, and to master the use of, an inhaler device. The respiratory tract has evolved in such a way as to prevent the ingress of particles and droplets, and to remove inhaled materials once deposited. Formulators strive to ensure that an adequate fraction of the delivered dose consists of particles within the fine particle range (< 5 µm) for whole lung deposition, and < 3 µm for peripheral lung deposition. Once deposited, drugs may be removed from the lungs by mucociliary clearance or by phagocytosis, or may be degraded by the action of proteases. Each patient must use an inhaler as prescribed (i.e. be adherent to the treatment regimen), and must use it correctly (i.e. prepare the device for inhalation, and then inhale from it in an appropriate way). Poor adherence and inhaler misuse are widespread problems, which can be addressed via appropriate selection of an inhaler, via use of other technology, and via education. Selection of an inhaler also needs to take into account the mass of drug to be delivered; pressurized metered dose inhalers (pMDIs) and many dry powder inhalers (DPIs) are unsuitable for delivering drug doses > 1 mg. Efficient inhalers delivering a high percentage of the drug dose to the lungs generally provide the most reproducible lung dose. The pulmonary route is a relatively complex one, but the advantages it offers justify its use for a range of treatment indications.

Introduction

The inhaled route is best known as a means of delivering drugs for treatment of asthma and COPD, but it can also be used to deliver a wide range of other drugs intended to achieve either a topical effect in the lungs, or a systemic effect elsewhere in the body. Topical treatment indications include use in several “orphan” diseases, such as cystic fibrosis (CF) and pulmonary arterial hypertension (PAH). The inhaled route has several advantages that derive from drug being delivered direct to its site of action (for a topically acting drug) or site of absorption (for a systemically acting drug). [1] Relatively small drug doses are often sufficient, there is generally a low incidence of systemic side-effects, and at least for some drugs, the onset of action is rapid. Inhalation provides a way of avoiding injections for biopharmaceuticals with low oral bioavailability, and the huge alveolar surface area (> 100 m^2) is an attractive target for such drugs. Several distinct types of inhaler device are used to deliver drugs to the lungs, consisting of pMDIs, DPIs and nebulizers, as well as some novel technologies that do not fit into any of the three previous categories. [2] Each of these major types of inhaler has its own advantages and limitations. Drug delivery to the lungs presents many challenges, but some of the most important of these can perhaps be summarised as trying to ensure a predictable, reproducible lung dose and clinical effect with each treatment, while minimising unwanted side-effects, and achieving these objectives at reasonable cost.

Mechanical, chemical and immunological barriers

Unfortunately, delivering drugs by inhalation is significantly more complicated than simply taking a tablet or capsule by mouth. The respiratory tract has evolved to prevent the entry of particles and droplets, and to remove them from the body once deposited (Figure 1). The complex anatomy of the upper airways acts as a filter for all but the smallest particles. The nose is a particularly efficient filter, and is not an ideal entry point for drugs intended to reach the lungs. The filtering effect of the oropharyngeal airways has led to definition of the “fine particle fraction” (once called the “respirable fraction”) in terms of particles having an aerodynamic diameter < about 5 µm. Any particle with an aerodynamic diameter > 5 µm is more likely to deposit in the upper airways than in the lungs. Even smaller particles (e.g. aerodynamic diameter < 3 µm) are required to target the most peripheral airways and alveoli. The inhalation mode (e.g. inhaled flow rate and volume) also has a profound effect on the amount of drug entering the lungs and its distribution within the airways. Once deposited on the airway surface, drugs can be removed from the lungs by mucociliary clearance, be acted upon by metabolic enzymes, or be engulfed by alveolar macrophages (phagocytosis). [3] Small molecules (MW < 1000 Da, e.g. analgesics) tend to have systemic bioavailability close to unity, but larger molecules (e.g. insulin) often have systemic bioavailability much less than unity, and which shows a broadly inverse correlation with molecular weight.

It may be difficult to deliver an adequate amount of drug to the areas of the lung where it is most needed. The ability of aerosol particles to penetrate deep into the lung is reduced in the presence of airway narrowing in asthma and COPD. Some patients with cystic fibrosis and other conditions may have airways which are completely blocked with

mucus, and beyond which it is impossible for aerosol to penetrate. Although not caused by mucus blockage, inadequate delivery to lung apices has been one factor explaining the relative failure of inhaled pentamidine in the treatment of human immunodeficiency virus (HIV) infection.

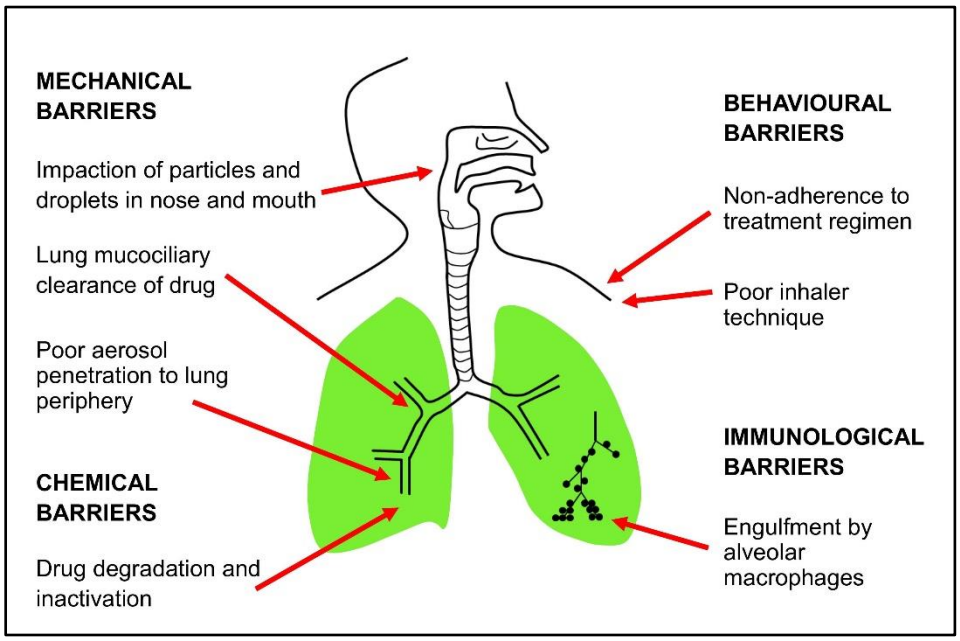

Figure 1 - Barriers to successful pulmonary drug delivery.

Inhaler misuse

The patient's behaviour presents arguably the biggest challenge to delivering inhaled drugs to the lungs. Successful pulmonary drug delivery requires a patient to use, and ideally to master the use of, an inhaler device. [4] Information about how to prepare an inhaler device for use, and then how to inhale from it, is usually presented to patients in a written package insert. Unfortunately, inhaler misuse is common, leading to a sub-optimal and potentially highly variable lung dose, or even zero lung dose. It is widely believed that pMDIs are misused to a greater degree than DPIs, but in practice this belief seems to be a myth. An increasing number of DPI devices is now available, with device-specific instructions, which could contribute to inhaler misuse by causing confusion. Inhaler misuse has clinical consequences: patients taking inhaled corticosteroids were shown to have more poorly controlled asthma if they could not use a pMDI properly, and especially if they could not coordinate actuating the pMDI with inhalation. [5] There are also financial consequences, because patients with poorly controlled asthma are likely to require more expensive treatment options. Any patient can misuse an inhaler but there are several well-recognised risk factors, including socio-economic issues, older age, severity of airway obstruction, lack of training in inhaler use, and using more than one inhaler device. Not surprisingly, young children are particularly prone to poor inhaler technique. Correct device use is now considered to be an essential factor in successful disease management. [6]

Poor adherence

An inhaler can only be effective if the patient takes the medication as prescribed. Poor adherence (compliance) to the treatment regimen is a separate, although related, problem to inhaler misuse. Poor adherence can involve not collecting (filling) a prescription, taking too few doses, or taking too many doses. One analysis showed that inhaled corticosteroids were underused on 24 to 69 % of days across a series of studies, compared with 2 to 23 % of days on which overuse occurred. [7] In practice, non-adherence can be either intentional or non-intentional; patients can choose not to take their medication, or can simply forget because they are too busy. The highest rates of non-adherence are often found in adolescents and young adults [8]. Poor adherence to an inhaler regimen has both clinical and financial consequences which are similar to those resulting from inhaler misuse. Several devices are available to monitor adherence objectively, and some are used to download adherence data to a computer or mobile phone. [9] Adherence monitoring systems are often incorporated into so-called "intelligent" inhaler systems. [10] The effects of poor inhaler technique and non-adherence are multiplicative, and their combination is sometimes caused "true adherence".

Addressing inhaler misuse and poor adherence

The challenges of inhaler misuse and poor adherence can be tackled via both technology and education. Patients unable to use a pMDI correctly may benefit from a breath-actuated pMDI, or from the addition of a spacer device. DPIs with very simple instructions (e.g. open, inhale, close) may be used more successfully than those with more

complex instructions. Patients should not be switched from one DPI brand to another without adequate instruction about how to use the new inhaler. [6] Training aids are available to help patients "press and breathe" simultaneously when using a pMDI, and to adopt an inhaled flow rate appropriate to the type of inhaler. [11] Combining a bronchodilator and corticosteroid within a single inhaler may improve adherence compared with delivering the two drug classes by separate inhalers. Data logging devices that monitor adherence objectively can provide useful feedback to patients. [9]

Education is a key issue in addressing problems of inhaler misuse and poor adherence. Management of chronic respiratory diseases has been described as "10 % medication, 90 % education". [12] Education can take the form of one-on-one sessions between patient and care-giver, written treatment action plans, group training sessions, or instruction via the internet. Undertaking one-on-one sessions may be a challenge for doctors, nurses, pharmacists and other care-givers, who may have difficulty finding time in their busy schedules to meet with individual patients regularly. Unfortunately, many healthcare professionals do not understand inhaled drug delivery any better than their patients. [13]

Influencing patterns of adherence has proved difficult. Overcoming the problems of non-adherence involves understanding and influencing patient behaviour. [8] This may need to take into account their concerns about the effectiveness and safety of inhaled medications, their trust in the medical profession, and factors such as family dysfunction. Conveying positive messages to patients about their disease and its treatment, including the need to take inhaled corticosteroids on a regular basis, is critical to the success of inhalation therapy. These messages need to be reinforced regularly.

Choosing inhalers for different drugs

Choice of inhaler is important because the patient needs to have an inhaler that he or she will use, and can use correctly, in day to day clinical practice. pMDIs and DPIs are ideal for delivering small doses of potent drugs used for asthma and COPD maintenance therapy. Ideally, the same inhaler should be used to deliver multiple drugs where this is feasible, and it should be the inhaler that a patient prefers. An inhaler must of course be affordable, but it should also be cost-effective; there is no value in a very cheap inhaler that doesn't work. Special considerations apply to the youngest and oldest patients; in both groups delivery of drugs from nebulizers, or from pMDIs plus spacer devices, is often the best option. DPI systems should be designed to achieve a lung dose that is relatively independent of inspiratory effort.

Historically, most inhalers delivered no more than 10 – 20 % of the nominal dose to the lungs; fortunately, we now have inhaler devices or device / formulation combinations capable of delivering drug to the lungs with much greater efficiency. A meta-analysis involving almost 200 data sets showed an inverse correlation between the mean value of lung deposition and its coefficient of variation. [14] Inhalers achieving a lung deposition of only c.10 % of the ex-valve dose had the highest variability, and inhalers achieving a lung deposition > 30% of the ex-valve dose had the lowest variability, the latter being virtually guaranteed to have a coefficient of variation of lung deposition < 30 %, assuming the inhaler is used correctly.

Inhalers delivering drug efficiently to the lungs, while also achieving a reproducible lung dose, are needed for drugs such as insulin, where pulmonary bioavailability may be limited by the action of proteases, and where the therapeutic window is narrow. The first marketed insulin product (Exubera®, Pfizer) utilised a large "active" dry powder device, in which a novel formulation was aerosolized into a chamber above the device prior to inhalation. The device delivered insulin efficiently and reproducibly to the lungs, but its large size may have contributed to the subsequent withdrawal of the product from the market. The second marketed insulin product (Afrezza®, MannKind) utilises a simple "passive" DPI, but containing an engineered particle formulation that ensures efficient pulmonary delivery. This product is claimed to have a higher bioavailability than other inhaled insulins, and to achieve peak plasma levels more rapidly [15]. These features may result in greater acceptance by patients and physicians.

Inhaled antibiotics require the delivery of very large doses that traditionally were the province of nebulizers. For instance, the dose of inhaled tobramycin (TOBI®, Novartis) is 300 mg, delivered by specific jet nebulizers and compressors. This was the first inhaled antibiotic approved for use in patients with CF, whose lungs are colonised with *Pseudomonas aeruginosa*. It is also possible to deliver inhaled antibiotics by single dose DPIs where the formulation is contained within capsules or blisters. Formulation of drug powder as engineered particles can ensure that a high percentage of the nominal dose is deposited in the lungs; this in turn reduces the nominal dose required, the likely variability of the lung dose, and treatment time. A reduction in treatment time is considered likely to improve adherence. Such thinking lay behind the development of a dry powder product (TOBI™ Podhaler™, Novartis) to deliver inhaled tobramycin (Figure 2), as an alternative to nebulization. [16]

The use of sophisticated nebulizer systems that control both particle size and mode of inhalation is useful for targeting some drugs reproducibly to specific sites in the lungs, e.g. the use of the AKITA® nebulizer system (Vectura) to deliver inhaled alpha-1 anti-trypsin to the alveoli of patients having a deficiency of this enzyme. [17]

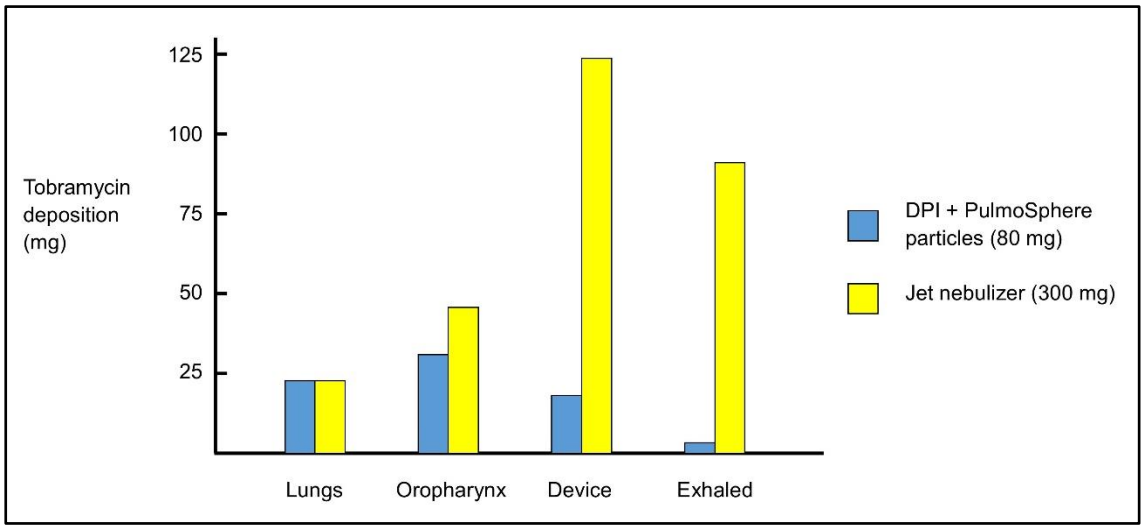

Figure 2 – Mean deposition of tobramycin by DPI and by nebulizer. Delivery as PulmoSphere particles from a Podhaler DPI can achieve the same lung dose as a jet nebulizer, despite requiring a much smaller nominal dose. [16]

Concluding remarks

Successful pulmonary drug delivery requires meeting a variety of challenges, which span scientific, medical, commercial and regulatory issues. Although the pulmonary route has been used for millennia, the scientific and medical issues have only been properly understood in the last few decades. Pulmonary drug delivery remains the cornerstone of asthma and COPD maintenance therapy and is becoming established and accepted for a range of other topical and systemic treatment indications, often fulfilling an unmet need. For these applications, the potential advantages offered by the pulmonary route is currently considered to justify the additional complexity. Judging by attendance at this and other conferences, interest in pulmonary drug delivery seems to be greater than ever.

References

1 Rau JL: *The inhalation of drugs: advantages and problems*, Respir Care 2005; 50: pp367-382.

2 Dolovich MB, Dhand R: *Aerosol drug delivery: developments in device design and clinical use*, Lancet 2010; 377: pp1032-1045.

3 Clark AR: *Limitations of pulmonary drug delivery*. In: R Dhand, (ed): ISAM Textbook of Aerosol Medicine. On-line publication, International Society for Aerosols in Medicine, Chapter 14, 2015.

4 Newman SP: *Improving inhaler technique, adherence to therapy and precision of dosing: major challenges for pulmonary drug delivery*, Expert Opin Drug Deliv 2014; 11: pp365-378.

5 Giraud V, Roche N: *Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability*, Eur Respir J 2002; 19: pp246-251.

6 Thomas M, Price D, Chrystyn H, Lloyd A, Williams AE, von Ziegenweidt J: *Inhaled corticosteroids for asthma: impact of practice level device switching on asthma control*, BMC Pulm Med 2009; 9: article 1.

7 Cochrane MG, Bala MV, Downs KE, Mauskopf J, Ben-Joseph RH: *Inhaled corticosteroids for asthma therapy: patient compliance, devices and inhalation technique*, Chest 2000; 117: pp542-550.

8 Morton RW, Everard ML: *Adherence to aerosol medication*. In: R Dhand, (ed): ISAM Textbook of Aerosol Medicine. On-line publication, International Society for Aerosols in Medicine, Chapter 12, 2015.

9 Kikidis D, Konstantinos V, Tzovaras D, Usmani OS: *The digital asthma patient: the history and future of inhaler based health monitoring devices*, J Aerosol Med Pulm Drug Deliv 2016; 29: pp219-232.

10 Denyer J, Dyche T: *The adaptive aerosol delivery (AAD) technology: past, present and future*, J Aerosol Med Pulm Drug Deliv 2010; 23 (Supplement 1): ppS1-S10.

11 Sanders M, Bruin RL: *Effect of a new training device on pMDI technique and aerosol performance,* In: Drug Delivery to the Lungs 24. Portishead: The Aerosol Society, 2013, pp86-88.

12 Fink JB: *Inhalers in asthma management: is demonstration the key to compliance?* Respir Care 2005; 50: pp598-600.

13 Pritchard JN, Nicholls C: *Emerging technologies for electronic monitoring of adherence, inhaler competence and true adherence*, J Aerosol Med Pulm Drug Deliv 2015; 28: pp69-81.

14 Borgström L Olsson B, Thorsson L: *Degree of throat deposition can explain the variability in lung deposition of inhaled drugs*, J Aerosol Med 2006; 19: pp473-483.

15 Pfützner A, Forst T: *Pulmonary insulin delivery by means of the Technosphere drug carrier mechanism,* Expert Opin Drug Deliv 2005; 2: pp1097-1106.

16 Geller DE, Weers J, Heuerding S: *Development of an inhaled dry-powder formulation of tobramycin using PulmoSphere technology*, J Aerosol Med Pulm Drug Deliv 2011; 24: pp175-182.

17 Bennett WD: *Controlled inhalation of aerosolised therapeutics*, Expert Opin Drug Deliv 2005; 2: pp763-767.