Expert Opinion

Delivery of antibiotics to the respiratory tract: an update

Daniela Traini† & Paul M Young
University of Sydney, Faculty of Pharmacy (A15), Advanced Drug Delivery Group, Sydney, NSW 2006, Australia

The use of inhaled medications for the treatment of pulmonary diseases has become an increasingly popular drug delivery route over the past few decades. This delivery route allows for a drug to be delivered directly to the site of the disease, with a lower dose than more conventional oral or intravenous delivery methods, with reduced systemic absorption and consequently reduced risk of adverse effects. For asthma this delivery route has become the 'golden standard' of therapy. It is not unexpected therefore, that there has been great interest in the prospect of using inhaled antibiotics for the treatment of both chronic and recurrent respiratory infections. Since the early 1980s, several investigations have demonstrated that antibiotics could be delivered safely by means of inhalation, using nebulisers as their delivery systems. Lately, antibiotics delivery via inhalation have seen a 'revival' in interest and most of these studies have focused on delivering antibiotics to the lungs by means of a dry powder format. This review focuses on recent advances in antibiotic inhalation therapy.

Keywords: antibiotics, dry powder, inhalation, nebuliser, pressurised metered dose

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1. Introduction

Infections always provide a challenge because it is important to eradicate the organism without causing harm to the individual receiving the treatment. Lung infections provide a further challenge because most anti-infectives on the market are delivered by traditional systemic routes (orally or parenterally), making it difficult to achieve adequate concentrations of the anti-infective in the bronchial secretions where much of the pathological damage occurs.

Respiratory-tract infections (RTIs), represent the largest segment of the antibacterial market, and have a high impact in terms of morbidity, mortality and financial cost. In 2002, RTIs led to 3.8 million deaths worldwide, accounting for 6% of the global disease burden [1]. A list of the most common microorganisms responsible for respiratory tract infections and antibacterial agents to which they are usual sensitive is presented in **Table 1**.

The treatment of chronic lung infection, especially for maintenance treatment, opens a door of opportunity for inhaled antibiotics. Delivery of antibiotics by the inhaled route is advantageous over more conventional routes, as the lungs are directly targeted. Subsequently, the therapeutic dose used is less than through oral or systemic delivery routes (leading to a decrease in drug resistance build-up) and thus results in a reduction of side effects, often associated with conventional delivery mechanisms [2]. In addition, another advantage of the pulmonary route is that issues normally associated with systemically active substances, which cannot be given by means of the oral route owing to poor bioavailability [3-5], can be overcome. Cost reduction and reasonable acceptability by the patient (particularly when compared with intravenous administration) are other advantages [6]. Although aerosol administration of antibiotics can be traced back to the 1940s,

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Table 1. Microorganisms commonly responsible for respiratory tract infections and oral or parenteral antibacterial agents to which they are usual sensitive.

Common pathogens	Antibacterial agent
Community-acquired pneumonia	
S. pneumoniae	Amoxicilli or erythromycin
H. influenzae	Amixicillin or co-amoxiclav (amoxicillin/clavulanic acid)
S. aureus	Flucloxacin
Klebsiella	Gentamicin or cefuroxime
M. pneumoniae	Erytromycin or oxytetracycline
L. pneumoniae	Erytromycin or oxytetracycline
Chlamydia B	Oxytetracycline
Hospital-acquired pneumonia	
S.pneumoniae	Co-amoxiclav (amoxicillin/clavulanic acid) or cefuroxime
S. aureus	Flucloxacin
H. influenzae	Co-amoxiclav (amoxicillin/clavulanic acid) or cefuroxime
Klebsiella	Gentamicin or parenteral cephalosporin
P. aeruginosa	Gentamicin or parenteral cephalosporin
Anaerobes	Metronidazole
COPD	
S. pneumonia	Amoxycillin or doxycycline (with clavulanic acid)
H. influenza	
Moraxella catarrhalis	
Pertussis	
Bordetella pertussis	Azithromycin or clarithromycin or erythromycin
Bronchitis	Antibacterials not indicated

this delivery route has remained relatively subdued for over half a century [2]. This is presumably because of the technical challenges associated with respiratory drug formulation. Historically, early attempts to deliver drugs topically to the respiratory tract were conducted using preparations that were formulated specifically for intravenous medication [7]. Another major constraint stemmed from the delivery devices available. Until now the preferred method has been to nebulise an antibiotic solution using commercially available ultrasonic or jet nebulisers [8]. This approach circumvented the need for device development and allowed the use of intravenous solution with little or no re-formulation. However, the time and effort required by a patient to receive a therapeutic dose, along with the fact that not all drugs were compatible with these devices, limited their wide spread use as a treatment option [3]. Recently, the delivery of antibiotic powder formulations has been investigated as an alternative delivery method [9], and new high powder dose devices, capable of delivering these powders, have been developed and reported in the literature [10,11]. These approaches may open up a new delivery avenue for respiratory antibiotic that was previously untapped. This paper reviews antibiotic treatment in the respiratory tract delivered through the inhalation route and focuses on recent trends, approaches and delivery systems reported over the past 10 years.

2. Delivery approaches

2.1 Nebulisation

Aerosolisation of aqueous solutions and suspensions is an important therapeutic option in the management of respiratory disease, and nebulisation remains a popular choice for certain groups of patients, that is, emergency room settings, where patient cooperation may be limited. In the past few years there has been a technology explosion in liquid nebuliser devices. The PARI's eFlow® is a portable, electronic aerosol device with increased efficiency and effectiveness of medication delivery, and decreased standard treatment times. The eFlow is being used for several antimicrobials in development, including aztreonam, levofloxacin, liposomal amikacin, and others. Other devices that have been tried with antibiotics include the Akita® (Activaero Technologies, Germany) and the I-neb® AAD® System (Philips Respironics, MA, USA), which improve targeting of the aerosols. With these new devices, patient compliance and average lung deposition in nebuliser antibiotic therapy is unquestionably improved.

Most nebulised drugs fall into two physicochemical categories: drug solutions containing a drug that is dissolved in saline or occasionally in other liquids (i.e., cyclosporine in alcohol [12]); and drug suspensions containing a drug that is not soluble in water or other liquids, and exist as a mixture of small drug particles, suitable for inhalation, suspended in liquid. Although nebulisers are widely used, until recently the nebulisation of aqueous solutions obtained from marketed intravenous preparations, which were not originally intended for delivery to the airways, has been the most extensively used means of delivering antibiotic drugs to the respiratory system [13-16].

The most successful application of the use of inhaled antibiotics has been for the treatment of *Pseudomonas aeruginosa* infections in patients with cystic fibrosis. Aminoglycoside antibiotics are commonly aerosolised because they are chemically stable and have a long post-antibiotic effect. They are able to exert a lethal effect after the concentration has decreased to below the minimal inhibitory concentration and have a low level of resistance.

Tobramycin is one of the aminoglycosides with low systemic toxicity (**Figure 1**) [17]. In 1998, the Food and Drug Administration (FDA) approved the licensure of tobramycin solution for inhalation (TOBI®, Novartis Pharmaceuticals). Up to now, TOBI is the only Federal Drug Administration-approved inhalation antibiotic for maintenance therapy of patients with cystic fibrosis (CF) who are known to be colonised with *P. aeruginosa* [18-24]. TOBI is also used in patients with non-CF bronchiestasis [25], chronic bronchitis, ventilator-associated pneumonia and

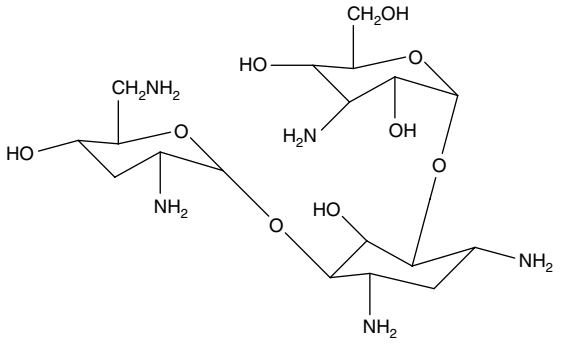

Figure 1. Tobramycin, an aminoglycoside antibiotic.

immuno-suppressed patients at risk for opportunistic infections. For a comprehensive list of published clinical trials using aerosol antibiotics to treat non-CF bronchiectasis, the authors refer to recently published papers [26-28]. In the UK, inhaled colistin (Promixin, Profile Pharma) is also approved.

Also, in some European countries, Colimycine 1 MIU for nebulisation (Sanofi-Aventis) has a marketing authorisation for the treatment of bacterial infections in patients with cystic fibrosis, in particular: treatment of *P. aeruginosa* in primo-colonisation to relay an intravenous cure and treatment of chronic pulmonary infections due to *P. aeruginosa* [29].

It is interesting to note that several more antibiotics, including other aminoglycosides, b-lactams [30,31], antibiotics in the polymyxin class, vancomycin [32], pentamidine isethionate [33], gentamicin [34] and teicoplanin (glycopeptides antibiotic) [35], have been administered as aerosols for many years; however, none is approved by the FDA for administration by inhalation [17,31,36-51]. However, meta-analysis of results indicates that, in general, the inhalation antibiotics improved lung function and reduced the frequency of hospitalisation required for treating acute infections [52,53].

Many studies are still at the bench scale. Recently, nanoparticles containing antibiotic molecules have been reported in the literature as potential nebulised formulations. Pandey and Khuller [54] investigated the chemotherapeutic potential of nebulised solid lipid particles (SLPs) incorporating rifampicin, isoniazid and pyrazinamide against tuberculosis. This study suggested that, in *Mycobacterium tuberculosis*-infected guinea pigs, there was no evidence of biochemical hepatotoxicity, a common and serious side effect of the conventional route (oral). Furthermore, improved drug bioavailability and reduced dose frequency indicated nebulised SLP-based anti-tubercular drugs to be a superior therapy for pulmonary tuberculosis. Zahoor *et al.* [55] performed similar aerosolisation studies in *M. tuberculosis*-infected guinea pigs using isoniazid, rifampicin and pyrazinamide-encapsulated alginate-based nanoparticles. Interestingly, in this study, the chemotherapeutic efficacy of three doses of drug-loaded alginate nanoparticles nebulised 15 days apart was demonstrated to be comparable to 45 daily oral doses of free drugs.

Although suspended microparticles and nanoparticles show potential, solution antibiotics are generally more widely explored. Recently, Hickey *et al.* [56] investigated the delivery of azitromycin by nebulisation. Azithromycin is a broad-spectrum antibiotic that acts by inhibiting protein synthesis. Subsequently, azithromycin is associated with systemic side effects that may be avoided if delivered as an aerosol directly to the target site (i.e., pulmonary tissue) rather than systemically. In this study, the authors also investigated three different nebulisation delivery devices (Acorn II®, Updraft® and LC Plus®) and found that the dose delivered to the lungs was maximised by adopting the LC Plus at high (100 mg/ml) azithromycin concentrations.

In recent times, older antibiotics, such as rifampicin, have been successfully complexed with cyclodextrins (HPβCD (2-hydroxypropyl-β-cyclodextrin)) or RAMEB (randomly methylated β-cyclodextrin derivative) for delivery by nebulisation. For poorly soluble molecules such as rifampicin, cyclodextrins may improve lung delivery by permitting higher dosing. These studies have shown these compounds to be suitable vectors for pulmonary nebulisation, increasing the amount of active rifampicin to optimise its pharmacokinetic profile [57].

Other antibiotics being investigated for aerosol delivery by means of nebulisation include colistin, gentamycin, ciprofloxacin and aztreonam [58,59]. Pharmaceutical industries have also been active in the area of developmental programmes focused on antibiotic inhalation by nebulisation, and have several formulations at clinical investigation stages. Gileard Science has just completed a Phase III clinical trial with Aztreonam lysinate [60,61] for inhalation in cystic fibrosis patients with *P. Aeruginosa* [62] using a new aerosol delivery device (eFlow, PARI, Midlothian, Virginia), a portable electronic nebuliser, equipped with TouchSpray® technology that uses a vibrating mesh to dictate particle size [63]. Also, Aradigm Corporation® has another multi-centre Phase II clinical trial of inhaled liposomal ciprofloxacin (ARD-3100 and 3150; 100/150 mg/day) in adult patients with CF and non-CF bronchiectasis [64].

Transave Inhalation Biotherapeutics are in the Phase II clinical trial with Arikace™ (Amikacin for inhalation) – a potential new liposomal delivery system in the treatment of Gram-negative lung infections – daily dosing of two doses (280 and 560 mg) of Arikace versus placebo in patients who have bronchiectasis, using a PARI eFlow nebuliser. This new liposomal may make it possible for the antibiotic to overcome the physical barriers presented by the CF patient's own mucus and by the infection's biofilm [65].

Amikacin inhale® [66], in a preservative-free liquid formulation, is also being developed by Nektar Therapeutics (now Novartis) in collaboration with Bayer (Phase II), to treat Gram-negative pneumonias, including hospital-acquired, healthcare-associated and ventilator-associated pneumonias. The product can be integrated with conventional mechanical ventilators or used as a hand-held 'off-vent' device for patients no longer requiring breathing assistance.

Nektar Therapeutics is also developing inhaled vancomycin, as a preservative-free, highly concentrated lyophilised version of the antibiotic vancomycin, targeted for Gram-positive pneumonia, including methicillin-resistant *Staphylococcus aureus* (MRSA), now in Phase I [66].

Mpex Pharaceuticals is assessing a new formulation of Levofloxacin solution for inhalation (MP-376, Phase II), supplied as a ready-to-use solution optimised for use with PARI eFlow technology [67]. The product is being developed as a maintenance therapy in cystic fibrosis (3 dose regimens of MP-376 administered twice or 4 times a day for 28 days) for the management of chronic respiratory infections due to *P. aeruginosa* and other serious bacterial pathogens and for prevention of exacerbations in high-risk patients with COPD (MP-376 inhalation solution given daily for 5 days in a 28-day treatment cycle). Several clinical trials have now been completed in CF and COPD patients.

2.2 Dry powder inhalation

As mentioned previously, nebulisation of aqueous solutions obtained from marketed intravenous preparations has been the most extensively used means of delivering antibiotic drugs to the respiratory system [13-16]. Although inhalation-specific formulations are now being investigated, nebulisers are generally regarded as a hospital or home setting delivery device. Furthermore, administration of aerosol antibiotics can increase concerns related to caregiver exposure. Alternative methods for the aerosolisation and delivery of medications to the respiratory tract are pressurised metered dose inhalers (pMDI) and dry powder inhalers (DPI). These systems have increasingly replaced nebulisers in delivering several therapeutic agents as they have a relatively high efficiency, provide easier and more rapid drug administration, and are more cost-effective [68]. However, these systems have been historically developed for the treatment of asthma, and thus the therapeutic doses tend to be relatively small for this particular therapeutic indication.

For example, DPI's doses range from 6 – 24 mg for Oxis Turbuhaler™ and Foradile™, to 50 – 400 µg for Ventolin Accuhaler™, Ventodisks™, Pulvinal™, Cyclohaler™ and Alvesco™, to 20 mg of the Intal Spincaps™. In comparison, the highest pMDI dose available is the Intal™ CFC-free formulation, Sodium cromoglycate, at 5 mg/dose.

As tobramycin is currently delivered by nebulisation as a 300 mg dose [69], and owing to the current limitations in pMDI construction and valve geometry, where a maximum dose of 5 mg is generally considered at the limits of current technology, the delivery vehicle of choice is more likely to be the DPI.

Although pMDIs offer great advantage in their small size and convenient portability by patients, which is a major advantage over nebulisers, and enabled patients actively to administer their own doses in any setting, the delivery of antibiotics by means of pMDIs is still an uncharted area. To the authors' knowledge, no pMDI formulation containing antibiotics has been described in the literature. Clearly, further device and valve development are warranted before pMDI delivery systems could become reality for high-dose delivery of pulmonary medications.

In comparison, DPI systems routinely contain > 20 mg powder formulation per dose, although most of this is not of a suitable size for inhalation, the formulation consisting of a sugar carrier diluent, that is, lactose monohydrate in an interactive physical mixture between the large sugar carrier diluent particles and the smaller respirable drug particles. However, it is not inconceivable that DPI devices may be modified with relative ease to reach the desired higher dose, with the only limitation then being due to patient tolerance. Interestingly, however, so far and to the authors' knowledge, no DPI antibiotic product has been marketed.

Although the pulmonary levels produced by first-generation dry powders and inhalers were more than 10-fold below what is possible with a concentrated tobramycin solution, delivered by an efficient breath-enhanced nebuliser, increasingly sophisticated DPIs have been applied to the problem of delivering aminoglycoside aerosols to the lung. In early studies, micronised gentamicin particles in the respirable size range were mixed with larger coarse lactose monohydrate particulates, and delivered by either a simple unit-dose DPI [70] (Rotahaler®, 180 mg drug and carrier, 6 capsules), or a multi-dose reservoir DPI [71] (Clickhaler®, 32 actuations each providing 10 mg of drug to produce a nominal gentamicin dose of 160 mg).

Several new methods for generating therapeutic DPI antibiotic aerosols are now under development, and are beginning to be applied to the problem of delivering antibiotics directly to the lung as an inhalation aerosol. Recent literature presents studies in this area.

In 2001, Sharma *et al.* [72] suggested the possibility of delivering a combination of antibiotic microparticles (Isoniazid and Rifampicin) by means of DPI. In this study, the powder particulates were produced by a combination of solvent extraction and evaporation, and initial results offered the promises of dose and dosing-frequency reduction, toxicity alleviation and specific lung targeting for treating tuberculosis.

In another study de Boer and co-workers studied colistin sulphate dry powder formulations *in vitro* and *in vivo* and concluded that a DPI formulation had potential as an alternative to nebulisation for patients with cystic fibrosis [73,74]. In 2003, Newhouse *et al.* evaluated the efficiency and reproducibility of a Tobramycin Pulmosphere® formulation, by dry powder inhalation, in healthy volunteers [75]. They found that a comparable dose (150 mg) could be delivered to the lung and/or the systemic circulation using the powder formulation as with the nebulised product in approximately one-tenth of the time. This was subsequently confirmed in a recent pharmacokinetic study by Geller *et al.* [76].

Further improvements in tobramicyn DPI delivery have been proposed by Pilcer *et al.* [77]. In this study, the authors developed and evaluated a lipid-coated tobramycin dry powder formulation that had particularly high lung deposition.

The study reported that lipid-coated formulations had reduced agglomeration and higher fine particle fraction values in comparison with uncoated formulations. Through phamacoscintigraphic and pharmacokinetic evaluations, Pilcer *et al.* [78] went on to show that tobramycin DPI formulations containing high drug concentrations and very low levels of excipients resulted in very high lung deposition with fine particle fraction (FPF) values of at least 68 and 53% of the nominal dose for the lipid-coated and uncoated tobramycin formulations, respectively.

More recently, Parlati *et al.* [79] presented data from spray dried powders of tobramycin containing sodium stearate (NaSt). The study shows that the presence of the NaSt fatty acid (salt form) improves aerosolisation efficiency and stability of a tobramycin DPI formulation.

Also, Novartis R&D has been conducting a clinical research study to compare the safety and effectiveness of tobramycin inhalation powder with tobramycin inhalation solution (TOBI) in patients with cystic fibrosis [66].

Further studies have compared the merit of antibiotics formulated intravenously, as a nebulised solution or a dry powder. For example, Labiris *et al.* [80] studied whether a gentamicin DPI was as safe and microbiologically active as gentamicin inhaled through a nebuliser or given intravenously. Using a randomised, single dose and triple crossover protocol, the authors studied 10 patients with cystic fibrosis or non-CF bronchiectasis and chronically infected with *P. aeruginosa* (Psa). A single dose of either 160 mg gentamicin by means of DPI or a small volume nebuliser (SVN), or 5 mg/kg gentamicin by intravenous infusion, was given to the patients. The study reported that a sevenfold lower dose of gentamicin delivered to the airways by DPI appeared to be as efficient as a SVN for treatment of Psa infections susceptible to gentamicin.

The efficacy of capreomycin, another anti-infective/anti-tuberculosis peptide antibiotic, has been investigated for the treatment of multi-drug resistant tuberculosis through the DPI inhalation route [81]. In this previous study, particles for inhalation, manufactured from a capreomycin solution (50% ethanol) containing 80% capreomycin sulphate and 20% L-leucine, were delivered as a dry powder *in vivo* to guinea-pigs using a custom-designed dry powder-dosing chamber. Local capreomycin concentrations in the lung were found to be higher in animals receiving inhaled powders compared with injection, resulting in the reduction of the bacterial burden of the lungs.

More recently, other papers have described the uses of combination antibiotic formulations as potential DPI systems. In 2008 Adi *et al.* [82] described the potential of delivering a combination antibiotic therapy, containing doxycycline and ciprofloxacin (both broad-spectrum fluoroquinolones, effective against both Gram-negative and Gram-positive bacteria), both hydrochlorides, as a DPI formulation for inhalation. This study showed that co-spray dried antibiotics particulates produced physically more stable microparticles then the analogous single spray dried antibiotic and had improved dispersion. Furthermore, the spray dried antibiotics were observed to have similar antimicrobial activity to the original antibiotics for *S. aureus*, *P. aeruginosa* and *Streptococcus pyrogenes*, suggesting the spray drying process did not affect the antibacterial activity of the drug. Tsifansky *et al.* [83] presented the delivery of two other antipseudomonal antibiotics, b-lactam ceftazidime and ciprofloxacin, containing dipalmitoylphosphatidylcholine, albumin and lactose as a model system for intrapulmonary delivery. As in the study by Adi *et al.*, Tsifansky *et al.* reported that co-encapsulation of the antibiotics in microparticles ensured co-deposition at desired ratios, improved the particles' aerosol efficiency and produced additive antipseudomonal activity.

Zhao *et al.* [84] have recently published a manuscript focused on combined liquid antisolvent precipitation and spray drying to generate spherical particles of ciprofloxacin with desired size and structure for DPI use.

A potential new therapeutic approach was presented by Arnold *et al.* [85] in 2007. In the paper the authors describe a new way to deliver Nanocipro dry powder aerosol formulations utilising monodisperse large porous poly(lactic-*co*-glycolic acid [PLGA]) microparticles as carriers. Using this method, a sustained delivery of antibiotics directly to the site of infection was achieved.

Also, azithromycin (AZI) [86], approved by the FDA for treatment of community-acquired pneumonia and exacerbations of chronic obstructive pulmonary disease, has recently been suggested [87] as the most promising antibacterial infections therapy for patients with cystic fibrosis. In a recent paper, Zhao *et al.* presented data of a DPI of AZI as an alternative to the nebuliser-based formulations [88].

In another recent investigation, Chougule *et al.* [89] demonstrated that Dapsone, an antibiotic belonging to the sulphone group (used orally for the treatment of pneumonia), could be encapsulated within nanoliposomes and then incorporated into DPIs using a spray drying technique. Using this approach, enhanced deep lung deposition was shown (FPF > 75%) with a prolonged *in vitro* drug release of up to 16 h, compared with 3 h for a DPI control.

Regarding DPI development within the pharmaceutical industry, Nektar Therapeutics (San Carlos, CA, now part of Novartis Pharmaceuticals) used a newer generation of engineered powder particles [90] for the development of inhaled antibiotics. A study of tobramycin inhalation powder (TSI) showed that the delivery efficiency to the lung was almost triple that of a jet nebuliser, and the time of administration was reduced from 16 min (TSI) to < 5 min [76]. Tobramycin and ciprofloxacin are also now in clinical trials as light, porous-particle powders for CF subjects infected by *P. aeruginosa* in their respiratory tracts.

Forest Laboratories, Inc., having developed a dry powder inhalation system for antibiotics in 2006, announced a multicentre Phase III clinical trial programme (called the 'Freedom Study') designed to confirm the efficacy of Colobreathe®.

This pharmaceutical company is using a dry powder formulation of its existing antibiotic Colomycin (colistimethate sodium) [74,91] in a new inhalation system called Colobreathe. They claim the new drug delivery system will be small, and uses an existing spring-loaded delivery device to distribute the contents of an antibiotic capsule when the patient inhales.

Also, Novartis R&D in collaboration with Bayer is developing Cipro Inhale® (Ciprofloxacine betaine), a targeted inhaled antibiotic for CF infections, developed as a dry powder, using a small, hand-held DPI inhaler [66]. However, DPI antibiotics formulations are still confined to pilot studies. Until more clinical data are available, and more sophisticated formulations that allow increased deposition efficiency are developed, the suboptimal, conventional delivery by nebulisers will remain the gold standard in inhalation therapy.

2.3 Pressurised metered dose inhalers

Most probably because of the relatively high doses of antibiotics required to achieve a therapeutic effect in the lung, to the authors' knowledge there have been no attempts to formulate this class of drugs as pressurised metered dose formulations.

3. Advances in high dose delivery devices

As mentioned in the Introduction, the problems associated with the high doses required for antibiotics in DPIs are being investigated. Interestingly, developments within the DPI arena have shown higher doses to be possible. In 2004, Young *et al.* reported an active device capable of delivering DPI doses > 150 mg [11]. Furthermore, in 2006 de Boer *et al.* [10] demonstrated a multiple air classifier technology that was able to disperse large amounts of colistin sulphomethate micronised powder (up to 25 mg), opening up the use of DPI for high antibiotics payloads. Further optimisation of the design could raise this to a dose of 50 mg. Further developments on new high payload devises are warranted.

4. Conclusion

Recent research and development and clinical trials have confirmed the effectiveness of aerosolised antibiotics and have emphasised the importance of ensuring adequate lung delivery of inhaled antibiotics. Multiple studies have recently established that it is possible to deliver substantial and measurable doses of antibiotics directly to the airway by means of aerosolisation, but controlled studies are needed to determine the efficacy and safety of this 'relatively new' inhaled therapy.

The development of new chemical entities, more efficient delivery systems and more precise techniques for the measurement of dose–response and regional pulmonary drug distribution of inhaled antibiotics suggest that this therapeutics area may be receiving an increased degree of attention.

5. Expert opinion

Great strides have been made in the past two decades in developing the treatment of respiratory infection through inhalation of antibiotics. The studies evaluating pulmonary delivery of antibiotics for the management of primarily localised lung infections have so far demonstrated considerable success. A principal contributing factor to the positive opinion that clinicians and patients have adopted is due to reduced dose and dosing frequency (because the drug is delivered topically), the subsequent reduction in both the potential side effects, and bacterial resistance [92,93] coupled with the enhanced simplification that it brings compared with the usual oral dosing regimens. Standard jet nebuliser/compressor systems, which have relatively poor efficiency for antibiotic delivery, have been used in the past. New liquid nebulisers are appearing on the market, but still as technology and knowledge advance, dry powder inhalation is increasingly recognised to be the better alternative. Recent studies with DPI systems designed for antibiotic delivery have demonstrated conclusively that this method is rapid, safe and effective for localised infections. Therefore, dry powder inhalation has excellent potential for treating lung infections as patients await a bright future in this therapeutic area.

The interest in old antibiotic therapy by means of new routes, such as inhalation, has re-emerged in medical practice in recent years and its use will probably continue to increase because new antibiotic drug entities for the treatment of local and systemic infections are not being rapidly discovered. Unfortunately, there are very substantial gaps in the knowledge of inhalation pharmacology for antibiotics. As a result, optimal inhalation dosing regimens with maximal efficacy but minimal toxicities and the potential for the development of resistance are still not entirely known, at this time. Therefore, further investigations on the pharmacokinetics, pharmacodynamics and toxicodynamics of this important class of drugs through the inhalation route and the efficacy of single antibiotic versus combination antibiotic therapy are urgently required.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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Affiliation

Daniela Traini† & Paul M Young
†Author for correspondence
University of Sydney,
Faculty of Pharmacy (A15),
Advanced Drug Delivery Group,
Sydney, NSW 2006, Australia
Tel: +61 2 93512356; Fax: +61 2 93514391;
E-mail: danielat@pharm.usyd.edu.au