Discussion

Developments and strategies for inhaled antibiotic drugs in tuberculosis therapy:
A critical evaluation

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Abstract

Inhaled antibiotics have been a valuable tool in treating pulmonary infections in cystic fibrosis patients for decades, and the pulmonary route is now becoming increasingly interesting for other infectious diseases like tuberculosis too. Especially with multidrug and extensively drug-resistant tuberculosis emerging, great effort is put into the improvement of pulmonary antibiotic administration to fight this global threat. Several reviews and research reports have been written on inhalable antibiotics, giving clear overviews of the compounds of interest. Furthermore, various formulation studies and administration strategies going on with these compounds. What is often missing is a critical evaluation of these developments. Several risks may be involved varying from obtaining insufficient local drug concentrations to adverse side effects and unwanted changes in physiological processes from the excipients used. In this chapter, the pros and cons and feasibility of recent advances in pulmonary antibiotic tuberculosis therapy are presented and critically evaluated. Furthermore, the advantages of dry powder inhalation over wet nebulisation for inhaled antibiotics in developing countries where prevalence of tuberculosis is highest are discussed. It has to be concluded that a greater effort in good inhaler development and more research in the physico-chemical properties of the compounds of interest are needed.
Introduction

There is a growing interest in the pulmonary route for the administration of antibiotic drugs. Inhaled antimicrobial therapy is particularly interesting for diseases like cystic fibrosis (CF), tuberculosis (TB), non-CF bronchiectasis (non-CFB) and pneumonia [1-4]. The advantages of this route of administration are well recognised and quite pronounced [1-3, 5]. Compared to orally or parenterally given drugs, inhaled drug doses delivered directly to the target area may be considerably lower to achieve the same local effect. This results in a strong reduction in adverse systemic side effects compared to oral or parenteral administration. On the other hand, with the same dose administered directly to the respiratory tract, much higher local drug concentrations can be obtained. This may eradicate strains of micro-organisms that are considered resistant against the same drug in the same dose given via the systemic circulation as resistance is often related to the drug concentration.

CF is the disease for which most experience exists with inhaled antibiotics to date [1, 6]. Pulmonary administration of antibiotics in CF has the potential to preserve lung function and to reduce the frequency of hospital admission [7-9]. CF therapy is mostly a lifetime lasting therapy and most of the recent developments in drug delivery to CF patients aim to increase the efficiency of administration, minimise the risks of bacterial resistance building and prevent patient re-infection [10]. In contrast, the administration of inhaled antibiotics against TB and other infectious diseases is currently still in its infancy and much can be learned for TB from the experience of the CF community [11]. Also unlike CF, TB is an infectious disease and particularly because of the rapidly growing multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains considered as a world-wide threat because of high risk of transmission. It may therefore, not be surprising that there are a much greater interest and a higher effort put in finding new ways to control this disease compared to CF. This is reflected by the great number of studies on Mycobacterium tuberculosis (Mtb), including those in which specific new strategies are explored [3, 12].

Several reviews have recently been written on inhalable antibiotics giving clear overviews of the compounds of interest and the various formulation studies and administration strategies performed with these compounds [2, 12-14]. What is often missing is a critical evaluation of these developments. Some of the formulations presented require complex preparation techniques and/or involve the addition and inhalation of excipients, occasionally in large quantities, of which the long-term toxicity is still uncertain. Some strategies may seem to be based on sound reasoning and hopeful expectations, but their efficacy still
has to be proven. In many ways physiological and immunological mechanisms may be affected to yet unknown extent on the long-term. Also, local drug concentrations may be insufficient and promote bacterial resistance building rather than to guarantee effective eradication and finally, the technical feasibility of some of the strategies presented is still highly uncertain. Therefore, approaches may be highly interesting from an academic point of view, but eventually these developments have to contribute to a better therapy. The aim of this manuscript is not to review the antibiotics and their formulations presented in the literature for inhalation, but rather to evaluate the technical feasibility, therapeutic efficacy and safety of the different approaches and strategies undertaken for inhaled antibiotics in TB therapy. We did not attempt to list all the examples for the different formulation types, but we selected representative papers for a critical evaluation.

**Inhalable antibiotics**

Many existing and new drugs may in future be considered suitable for direct delivery to the lungs and they have extensively been reviewed before [13, 14]. They include first-line anti-TB drugs like rifampicin, pyrazinamide and isoniazid, and second-line anti-TB drugs from the groups of aminoglycosides (e.g. gentamicin, kanamycin, and amikacin) and fluoroquinolones (e.g. moxifloxacin and gatifloxacin). Particularly isoniazid, rifampicin and pyrazinamide seem interesting for pulmonary application against multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, as it is expected that much higher local concentrations with these drugs can be achieved via this route of administration [15]. This might make resistant *Mtb* strains in the lungs susceptible to these drugs again. Second-line antibiotics in TB treatment like the aminoglycosides gentamicin and kanamycin have already been used as adjunctive salvage inhalation therapy in patients with persistent smear-positive pulmonary TB [11]. Amikacin (with the widest antimicrobial spectrum of all aminoglycosides [16]), capreomycin (effective against species that have become resistant to other agents [17]) and moxifloxacin (a four-generation fluoroquinolone with very good activity against *Mtb* [18, 19]) are to be considered for pulmonary application in TB therapies too. Other nowadays orally and parenterally given drugs considered suitable for pulmonary administration in TB therapy are examples like clofazimine and linezolid. Finally, some new compounds like TMC207, PA-824, OPC-67683, PNU-100480, AZD-5847, SQ109 and BTZ043 are in development for application against TB and good be interesting for pulmonary delivery as well [13, 14]. A greater variety of antibiotics being available for
inhalation is urgently needed to compensate for an increasing bacterial resistance of *Mtb* against a growing number of currently used anti-TB drugs.

**Antibiotic drug formulations**

With a few exceptions, most of the early studies with inhaled antibiotics are known from the period 1965 to 1995 [20, 21] for drugs like tobramycin, colistimethate sodium, carbenicillin, gentamicin and ciprofloxacin [22, 23], but it lasted till 1998 before the first formulation (tobramycin: TOBI®, Novartis) against *Pseudomonas aeruginosa* (in CF therapy) received approval from the FDA [20]. Most of these examples are for nebulised antibiotics, and studies with dry powder formulations are relatively scarce. Because of the many disadvantages of classic nebulisation techniques [24, 25] there is a strong desire to further improve the therapies with inhaled antibiotics with new formulations and matching devices. For diseases like TB there are several arguments in favour of dry powder formulations. Such formulations can be chemically stable and administered with cheap, disposable devices which makes them suitable for developing countries in warm climates in which (MDR and XDR) TB prevalence is highest. For a few drugs (e.g. rifampicin and clofazimine) dry powder formulations seem the only alternative considering their low water solubility. Ideally, inhaled drugs as dry powders should be crystalline for maximal stability. Spray dried, spray-freeze dried and freeze dried powders from solution are mostly fully amorphous which increases their moisture sensitivity. Water uptake by amorphous powders reduces their glass transition temperature and this may result in re-crystallisation and solid bridge formation between the particles which deteriorates dispersion. Other (physico-chemical) drug properties that can play a role in the dispersion efficiency and inhaler retention are the cohesiveness, flowability and compactability, which depend on the chemical nature of the compound as well as on the size and shape distribution and surface properties of the drug particles (see chapter 3).

Most developments on anti-TB drugs for dry powder inhalation so far are primarily feasibility studies which have not yet resulted in clinical studies or commercialisation. Many of these studies have been reviewed by Traini and Young [2]. They often focus on specific delivery strategies by making use of liposomal drug formulations for sustained drug release or drug containing insoluble microspheres for targeting of the alveolar macrophages. They also often disregard the relevance of an appropriate inhaler to be used for the administration. Antibiotic dry powder inhalation has a number of specific problems and challenges, most
of them relating to adequate dispersion and inhalation of the large powder quantities. Early studies with drugs like gentamicin and colistin have shown that high powder doses can well be tolerated by the patients, although this may depend on the chemical structure of the antibiotic or the specific salt used [26, 27]. Dividing of the dose over a number of successive inhalations may nevertheless be necessary for different reasons. Smaller inhaled powder quantities could increase patient acceptance by reducing cough reactions and chest tightness. In addition, they may improve the performance of the inhaler. As an example, a single TOBI® dose from the capsule based Podhaler™ consists of four capsules filled with approximately 45 mg of powder each (of which 28 mg is the active drug). However, a large number of inhalations are likely to increase inhalation errors and worsen patient adherence to the therapy because of the increased total administration time. For these reasons, the number of inhalations per dose should be kept as low as possible. Some formulations presented in the literature contain high excipient contents which increases the total amount of powder to be inhaled even further. Such formulations with low antibiotic payloads (< 50%) for replacement of oral or parenteral administration seem to have no practical value for TB therapies. They are unlikely to make it to the market, particularly when they additionally require complex multi-step manufacturing processes which makes them expensive [28-38].

Minimising the use of excipients makes the performance of the dry powder inhaler (DPI) strongly dependent on the physico-chemical properties of the drug itself. Dispersion and retention depend on the chemical nature of a compound as well as on its particle size and shape distribution, water content, anomic composition, etcetera. But the precise effect of all solid state properties is not known and the same powder may disperse well in a venturi-like disperser, whereas dispersion in a whirl, circulation or impaction chamber may be insufficient and/or lead to extreme retention. The opposite result may be obtained for another class of antibiotics, which is the reason why more knowledge of the relevance of the solid state properties to dispersion and retention is needed. As a response to that, the inhaler design can be adjusted to the requirements for good dispersion and low retention of a particular class of antibiotics. Even for a fairly well documented drug like tobramycin, the information in the public domain is confined to polymorphism and related thermal events and does not extend to the properties that influence its dispersion behaviour in a DPI [39].

Co-processing of drugs with relatively small amounts of excipients is often considered as a good solution to improve dispersion, but the long-term effects of such excipients in the lungs have not always been investigated thoroughly. The severity and rate at which these effects manifest may also depend on the type and severity of the disease, or be masked by disease
effects and therefore, remained unnoticed. The risks increase when particles are basically water insoluble (e.g. magnesium stearate) and delivered deeper into the lung where mucociliary transport is absent and clearance depends on solubilisation, lymphatic and macrophage activity [40]. Examples of co-processed antibiotic formulations are the PulmoSphere® formulations for the antibiotics tobramycin (TOBI®) and ciprofloxacin (Ciprofloxacin DPI) as shown in Figure 7.1. PulmoSphere® tobramycin particles administered with the Podhaler™ have a rather narrow particle size distribution (PSD) and an open structure which reduces the number of contact points between the particles as well as the contact area per contact point and this has a positive effect on fluidisation and dispersion [41].

![Figure 7.1](image)

**Figure 7.1** Scanning Electron Micrograph of the TOBI® PulmoSphere® dry powder formulation (magnification 5000x).

Another major problem to deal with for a number of dry powder antibiotics is their hygroscopic nature. An example is the class of aminoglycosides, particularly tobramycin when it is used as spray dried sulphate, as was shown in chapter 3. Upon water sorption already at an intermediate relative air humidity (40–50%) a highly viscous layer of dissolved drug is formed around tobramycin particles which makes the powder sticky. When the moisture sorption is further increased (at 50–70% RH), liquefaction occurs which ends as fusion of the separate particles into big droplets. Co-processing with excipients does not change the physico-chemical properties of the drug itself, although added surfactants or coating of the particles with hydrophobic substances (e.g. magnesium stearate) may
slow down moisture uptake. The hygroscopic nature of tobramycin is the reason why the Podhaler™ for TOBI® has to be placed and stored in a tightly closed storage box (after wiping the mouthpiece with a dry cloth) immediately after use and why the Podhaler™ has to be replaced after 1 week use. Also exhalation through the inhaler is a serious risk for following administrations and the only way to minimise this risk for hygroscopic formulations is to use disposable inhaler devices.

**Strategies for pulmonary TB therapy**

Most TB infections are located in the respiratory tract as primary port of entry for Mtb and for that reason the airways are the main target area for antibiotic drugs [42, 43]. TB treatment always consists of multiple antibiotic drug administration to prevent resistance building. Standard therapy for new TB patients with drug-susceptible (non-resistant) strains consists of orally or intravenously given isoniazid, rifampicin, pyrazinamide and ethambutol in the 2 month intensive phase, followed by a 4 month continuation phase with isoniazid and rifampicin alone [15]. Replacement of oral and intravenous therapies with inhaled antibiotics has the advantages of obtaining higher local concentrations and less systemic side effects from the same dose. A great challenge for pulmonary delivery in TB is in the treatment of patients infected with MDR and XDR TB. Different approaches for the pulmonary route are possible and basically four different strategies can be distinguished: (1) pulmonary antibiotics as replacement for, or as add-onto oral and parenteral therapy [11] (2) searching for synergistic drug combinations [44], (3) specific targeting of alveolar macrophages [12], and (4) clearing the upper airways from pathogenic micro-organisms to stop transmission [45].

**Replacement of, or add-onto oral and parenteral therapy**

Replacement of high dose oral and/or parenteral administration of antibiotics by dry powder inhalation, or using inhalation as add-on therapy, is the most straightforward approach in improving TB therapy. Direct administration to the target area either by nebulisation or as dry powder aerosol reduces the systemic side effects, but there is uncertainty about how well the antibiotics are tolerated by patients in the quantities needed for inhalation. A good example for that is colistin which causes severe adverse side effects when it is inhaled as the sulphate. Le Brun et al. [46] reported a decrease in pulmonary function and the occurrence of non-productive cough after dry powder inhalation of the sulphate,
whereas Westerman et al. [47] showed that the sulphomethate from the same inhaler is much better tolerated. This may be the same for wet and dry aerosols. Different salts may not always be available however, and the most well tolerated salt by patients could have the least favourable physico-chemical properties for dispersion and inhaler retention as a dry powder. Salts also increase the dose considerably compared to the free base because of their higher molecular weights.

Whether complete replacement of oral or parenteral antibiotics in TB treatment by pulmonary administration is possible or not depends primarily on delivering a sufficiently high fraction of the inhaled dose to the whole lung. Several deposition modelling and in vitro deposition studies have shown that this depends on the aerodynamic PSD of the aerosol and the inhalation manoeuvre [48, 49]. For dry powder aerosols, it has been reported that very roughly one third of the dose is deposited in the conducting airways (generations 0–11), one third in the transitional airways (generations 12–16) and one third in the peripheral airways (generations 17–23) [48, 50, 51]. This is partly a consequence of the polydisperse nature of dry powder aerosols which may not be too different from that of wet aerosols however. Taking the exponentially increasing surface area of the lungs towards the alveoli into account, it may be clear that there will be great differences in drug concentration between the upper and lower airways. At an even distribution (1:1:1) over all three regions, the average drug concentration (µg/m³) in the conducting airways is approximately 5 times higher than in the transitional airways and 130 times higher than in the peripheral airways, based on the Weibel model [52]. In addition, drug concentration in the transitional airways is 25 times higher than that in the peripheral airways. Differences in drug concentrations become even greater when the deposition distribution 1:1:1 cannot be achieved and relatively more particles are lost in the larger airways. This may be the result of a high inspiratory flow rate, a short breath hold period or an unfavourable PSD for the aerosol. It could have the serious consequence that micro-organisms are eradicated in the upper airways very effectively, whereas in the most distal airways resistance against the antibiotic can be developed, because the concentrations remain below the MIC-value. Therefore, to give inhaled antibiotics a chance, the most distal airways should be targeted.

Whether peripheral deposition or an appropriate drug distribution over the whole lung can be achieved with equal effectiveness for dry powder and wet aerosols should be questioned. This depends not only on the aerodynamic PSD of the aerosol and the velocity with which these particles are inhaled. Additional differences between dry and nebulised aerosol delivery exist and it is likely that different lung distributions are obtained. First of all, lung
delivery with nebulisation is mostly during tidal breathing. With this mode of inhalation convective aerosol transport directly into the alveoli is not to be expected, because the residual volume in the lungs after exhalation is higher than the total alveolar volume which is in the lowest part of the lungs. Dry powder inhalation mostly is at higher flow rates than what is needed for nebulisation. More particularly, correct dry powder inhalation is from residual volume after maximum exhalation. Inhalation from residual volume can bring the finest aerosol particles directly into the alveoli by convection. In contrast, the higher flow rate spreads deposition over a larger area, including the upper airways, due to the higher speed of entry. Furthermore, aerosol administration is continued over a period of several minutes with classic nebulisation. Reaching the lowest airways is probably rather the result of repeated mixing of newly inhaled and residual (particle loaded) air in the lungs, than that of convective aerosol transport. Lung deposition is a process partly based on chances, as described in terms of deposition probability equations of for instance Landahl [53], and the chance of deposition by sedimentation for a certain particle increases when its residence time in the lungs is increased, as during nebulisation. From these differences in aerosol transport, residence time and deposition probability, it may not be expected that drug distribution over the entire lung is the same for nebulisation and dry powder inhalation. The finding that dry powder tobramycin and colistin against *Psa* can be as effective as with nebulisation may not lead to the expectation that this replacement will be equally successful for other antibiotics. This depends on many more aspects than drug distribution alone, including the preferential location of the micro-organisms and lung ventilation. Besides, the drug’s pharmacokinetics may be different between dry and wet aerosols due to the introduction of additional fluid during nebulisation.

A frequently proposed approach in replacing orally and intravenously given antibiotics by inhalation is to make use of liposomal formulations. The controlled (slow) release profiles of such formulations may expose the (myco)bacteria to antibiotic concentrations over elongated time periods. However, they bare the risk that the concentrations are sub-optimal. This can result in poor treatment and resistance building. Most antibiotics must be dosed highly to achieve peak concentrations that reach the desired MICs. This is particularly important for the treatment of infections by pathogens like *Psa* or *Mt*b, which are difficult to eradicate and easily become antibiotic resistant. An example of a high risk involved with this approach is the anti-TB drug rifampicin. The oral defined daily dose is 600 mg and rifampicin is notorious for resistance building [54]. Nevertheless, controlled release formulations with rifampicin drug loads as low as 1% are described in the literature [55].


**Synergistic drug combinations for inhalation**

One of the greatest challenges of antibiotics is to reduce systemic side effects. An additional challenge for dry powder aerosols is solving the problems of high dose delivery. A way to reduce the total amount of powder is to find synergistic effects from combining two, or even more antibiotics. A few successful examples are known, like the combination of pyrazinamide and rifampicin [56] in TB therapy. Moxifloxacin also seems to work synergistically with rifampicin [19, 57]. Different researchers furthermore described dry powder formulations containing isoniazid and various other anti-TB drugs [58-60]. Such combinations seem relatively safe when both antibiotics have a good safety profile, particularly when the total dose can be reduced due to the synergism, which also increases the possibilities for pulmonary administration. Moreover, by applying appropriate preparation techniques, the combination may result in improved dispersion behaviour too if one of the components has poor properties in this respect. Another approach is to combine an antibiotic with a special excipient which does not have selective antibiotic activity against the organism to be eradicated, but facilitates the action of the antibiotic given. Such excipients can for instance be compounds that destroy biofilms, inhibit bacterial cell wall biogenesis (e.g. fosfomycin) or interact with the bacterial outer membrane to solubilise this membrane in aqueous environment (e.g. colistin). The long-term use of inhaled colistin (as sulphomethate) in CF therapy has shown that this drug is safe and well tolerated by the patients, whereas reported cases of bacterial resistance against this drug are extremely scarce [61]. Also the working mechanism of colistin is well documented and by destroying the bacterial cell membrane, a drug like colistin can therefore potentially increase the efficacy of all anti-TB drugs.

**Targeting of alveolar phagocytes**

Even when sufficiently high drug concentrations can be achieved in the whole lung to exceed the necessary MIC values for eradication of *Mtb*, pulmonary antibiotic efficacy may need further improvement. *Mtb* is known to survive quite successfully in phagocytes like alveolar macrophages and dendritic cells. Moreover, *Mtb* can also replicate in the phagosomes of alveolar macrophages [3, 62]. Therefore, it could be interesting not (only) to aim for high antibiotic concentrations on the lung epithelium, but (also) to specifically target the alveolar phagocytes as well by administering so-called respirable insoluble particles that contain poly(lactic-co-glycolic acid) (PLGA), poly(lactic acid) (PLA) or other
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excipients. By using water insoluble particles, fast dissolution and systemic absorption will not take place and therefore, the particles can be taken up by alveolar macrophages, where they release the drug to eradicate intracellular mycobacteria. Several studies are known in which this approach is described and in which formulation technologies to prepare drug containing insoluble microparticles are presented [55, 58, 63]. Not only this is a different therapeutic strategy as such, but also it requires different formulation technologies and a different target area to aim at.

Although from academic point of view macropharyngeal targeting is a highly interesting strategy which has the advantage of a strongly reduced total dose, there are several uncertainties and risks involved in this approach. First of all there are still unknown long-term toxicological effects of the types of excipient used. Particularly the presence of PLA or PLGA in the insoluble microparticles brings uncertainty about the safety [64]. Such particles are expected to degrade in the lungs and in the alveoli, but the rate of degradation has to be faster or at least the same as the rate of administration, or accumulation will occur. The presence of high concentrations of lactic acid in the lungs after degradation may cause unknown effects too. It has recently been shown that metabolic lactic acid is an important mediator of myofibroblast differentiation via a pH-dependent activation of TGF-β [65]. The authors of this study proposed that the metabolic milieu of the lung, and potentially other tissues, is an important driving force behind myofibroblast differentiation and the initiation and progression of fibrotic disorders.

Also the efficacy of the strategy may be questionable. Macrophages and other professional phagocytes are abundant in healthy lung tissue and the clearance capacity of the total system is very large [66]. This is to cope with heavily polluted air and it has been suggested that it is unlikely that the system can be saturated with a therapeutic aerosol. Therefore, many infected macrophages may not be treated by this approach which gives Mtb a chance to survive and still be transported into the gastro-intestinal system by the macropharyngeal clearance mechanism. Besides, also non-professional phagocytes, like human fibroblasts and alveolar epithelial cells, can swallow micro-organisms, in which they can replicate as well [67]. Such non-immune cells are more limited in the type of particles they can take up than the professional phagocytes and it is unknown whether they also can ingest insoluble microparticles with antibiotic drug effectively. In addition, still a lot about the macrophage clearance mechanisms is uncertain. Clearance may depend on the nature of the particles and it is not unlikely that ingested microparticles alter macrophage mobility [66]. These examples show that inhaled PLA and PLGA microparticles could possibly interact with
physiological and immunological processes to yet unknown extent and therefore, caution is to be taken with this approach.

Furthermore, upscaling of the preparation process to production may be problematic. Some studies found in the literature report a very low loading of the PLA/PLGA microparticles with the drug [31, 63, 68, 69]. Hence, it may be very difficult, if not impossible, to reach sufficient batch-to-batch reproducibility for production. Successive steps like homogenisation, solvent extraction and evaporation, lyophilisation and drying (thermal, spray, spray-freeze, or supercritical) also make the powders more expensive, whereas they bear a higher risk of contamination and have a lower yield. Finally, targeting the phagocytes should be considered as an add-on strategy to oral, intravenous or inhaled antibiotics. Considering that there will always be abundant non-phagocytised micro-organisms in the lungs, treatment with antibiotics in the more classic way with high doses remains necessary. Treatment with insoluble drug containing microparticles alone will result in low local drug concentrations in the lung and this facilitates the formation of bacterial resistance against the drugs administered. Patient studies may show whether humans can accept PLA-formulations on the long-term.

**Stopping transmission**

Transmission of the disease TB is caused by inhaling droplets that contain \( \text{Mtb} \). These droplets can be produced by talking, coughing and sneezing [70]. Especially transmission of highly drug-resistant \( \text{Mtb} \) strains, affecting both patients and staff in congregate settings, threatens the success of HIV antiretroviral treatment programs in the developing world. In developing countries, facilities for patient isolation are very limited, and newly diagnosed TB patients often share open wards with HIV/AIDS patients [71, 72]. In these circumstances, reducing transmission by clearing the upper airways from pathogenic bacteria in addition to standard therapy may be a valuable strategy to protect patients and healthcare workers [45]. An effective method to rapidly stop transmission may be the inhalation of a combination of colistin and a suitable anti-TB antibiotic like kanamycin or capreomycin. Colistin will partly destroy the cell membrane after which the antibiotic can effectively eradicate the micro-organism. For this purpose, the anti-TB drug doses do not have to be as high as for treating the whole lung and neither do the particles have to travel to the most distal airways. This makes pulmonary administration quite feasible, but this approach cannot replace current oral and intravenous or future pulmonary treatments to cure the disease.
In fact, antibiotics also used for eradication of *Mtb* in the whole lung should not be given for clearing, as the upper airway targeting can result in low drug concentrations in the central and peripheral lung and thus promote bacterial resistance in these areas. Therefore, compounds have to be used for which the risk of resistance building is low, such as colistin, and stopping transmission must be confined primarily to patient groups that already have MDR or XDR TB.

**Suitable inhalers for anti-TB therapy**

Basically two types of pulmonary administration devices are suitable for inhaled antibiotics: nebulisers and DPIs. Metered dose inhalers (MDIs) seem less appropriate, because they cannot deliver the high doses required for effective therapies. Nowadays, a wide variety of classic jet and ultrasonic nebulisers is available and the weak and strong points of these devices have well been documented before [1, 73]. Although aerosolised antibiotic therapies by nebulisation have made substantial contributions to disease management and life expectancies in CF [1] and pneumonia [4], nebulisation has some serious disadvantages, especially for antibacterial programs in developing countries. The poor stability of drug solutions or the need to reconstitute powdered drug into an inhalation solution requires the presence of a cold chain or clean water respectively, and these may not always be present. Furthermore, patient re-infection and bacterial resistance building are specific risks in treatment of infectious diseases giving preference to the use of disposable devices [10, 74, 75]. Most currently used nebulisers are too expensive to be disposable however. These considerations, in combination with the long time needed for drug administration and cleaning of the nebuliser, the high dose frequency and the complexity of the patient’s daily regimen, which all are a burden to the patient [24], emphasise the need for new delivery devices for pulmonary antibacterial therapies.

Two mainstream inhaler developments can currently be recognised. On the one hand various smart nebulisers with (vibrating) membrane technology have recently been introduced to the (CF) market. They are expensive and not suitable for anti-TB programs in developing countries. On the other hand cheap and disposable nebulisers and DPIs have become available which seem to have more potential for the application against diseases like TB. The advantages of single-use disposable DPIs have been reviewed in detail by Friebel and Steckel [76]. They may be preferred over disposable nebulisers for large scale therapies in developing countries considering that they do not require a pressurised air supply or
electricity and contain more stable drug formulations. Unfortunately, the DPIs that reached the market, or will be launched in the near future for inhaled antibiotics, are all capsule based DPIs which were basically developed many years ago. These inhalers may not have the most effective dispersion principles and also have the disadvantage of low resistances to air flow. For instance the Podhaler\textsuperscript{TM} for TOBI\textsuperscript{®} (formerly known as the Turbospin, PH&T, Milan) has an air flow resistance of 0.026 kPa\textsuperscript{0.5}.min.L\textsuperscript{1} which enables to generate relatively high flow rates through this device (4 kPa corresponds with 77 L/min) and this may negatively influence the deposition in the desired site of action. Delivery of fine powders in the aerodynamic size range from 1.5 to 5.0 µm to the entire respiratory tract, including the peripheral airways, requires excellent dispersion at a low flow rate of preferably < 50 L/min. To achieve this, a clever design strategy for the dry powder inhalation system is needed which focuses not only on control of the interparticulate forces in the powder formulation, but on a high efficiency of the dispersion forces during inhalation as well. Figure 7.2 shows the desired balancing between three different types of forces needed to achieve improved lung deposition. They are the interparticulate forces in the powder, the dispersion forces generated during inhalation and the deposition forces in the respiratory tract, respectively. More kinetic energy for dispersion (higher dispersion forces) can be obtained by generating a higher flow rate through the inhaler. This may result in a better dispersion, depending on the type of DPI used, but it also increases the oropharyngeal losses (due to higher inertial deposition forces). This is at the cost of deposition in the central and peripheral airways. Therefore, a higher dispersion efficiency should be achieved with a more effective inhaler design and not with a high flow rate.

Figure 7.2  Schematic overview of the balance between three types of forces to achieve a good performance of a dry powder inhaler.
Recommendations for future developments

Previous considerations regarding the requirements for antibacterial programs in developing countries lead to some very clear objectives for future developments.

• There should be a search for more antibiotic compounds being suitable for administration via the pulmonary route. Preferably, such drugs should be highly potent to reduce the dose to be administered. Not only will a greater variety of inhaled antibiotic drugs potentially serve a greater number of infectious diseases, it might also extend the duration of the benefit of a treatment by alternation of drugs [77].

• Extending the benefit of the treatment may also be obtained by using disposable inhaler devices which eliminates the risk of bacterial resistance building and re-infection of the patient [10, 75]. Such inhalers may also be needed for vaccination programs in developing countries. They have to be cheap and their use should be safe and not require special facilities like electricity (or batteries), a cold chain, or pure water for drug reconstitution. DPIs have several advantages over nebulisers in this respect, but developing suitable (well dispersible but yet cheap and stable) dry powder formulations may remain the greatest challenge for an effective use of this type of inhaler.

• A strong reduction in the dose compared to oral and parenteral administration is desired to make the use of dry powder inhalation more feasible. This can be achieved with highly effective targeting of the site of infection or by making use of synergistic drug combinations.

• The introduction and exploration of new delivery strategies and excipients that could possibly play a role in physiological processes should be accompanied with risk assessments and feasibility studies. Particularly the long-term effects may be uncertain for compounds (e.g. surfactants) that influence the delicate balance between tissue tension and surface tension of the lining fluid or act as mediator of cell differentiation (e.g. lactic acid).

• Better targeting with dry powder aerosols underlines the necessity for DPIs to have effective dispersion principles in order to deliver high mass fractions of the drug in the most optimal PSD for the infected lung region at relatively low to moderate inspiratory flow rates.
Finally, the administration time has to be reduced to increase patient comfort and adherence to the therapy, which also opens the possibilities for a higher frequency of dosing. For a number of antibiotics this may lead to a more effective eradication of *Mtb*.

**Conclusions**

The advantages of the pulmonary route for delivery of antibiotics against infectious diseases like TB, challenge researchers to test the efficacy of existing and new drugs and drug combinations for inhalation and to develop new strategies for a better targeting of the infected sites in the lung. However, discussion in the literature about the safety and possible long-term side effects of these new strategies and their perspectives for large scale use is scarce, whereas several risks may be involved. Slow release (liposomal) formulations and formulations to target *Mtb* in alveolar phagocytes may result in (too) low local drug concentrations which may result in bacterial resistance building. Possible differences in drug distribution from (single) dry powder inhalation and (repeated) inhalation during nebulisation and the extreme difference in drug concentration between the upper and lower airways are ignored. The possible long-term effects of certain excipients in various dry powder formulations on physiological processes are still highly uncertain. Finally, some preparation processes for inhaled antibiotics are complex and expensive, include the incorporation of high excipient contents, exhibit a low batch reproducibility and are therefore, inappropriate for large scale production and use. This has to lead to the conclusion that before these strategies and formulations are put to use, more in depth investigation into these risks is needed.

From the viewpoint of poor stability of drugs in solution, dry powder systems are to be preferred for inhaled antibiotics. The focus in most of the developments is on the powder formulations indeed, but surprisingly very little attention is given to development of new, effective and preferably disposable inhalers. Such inhalers are particularly relevant to therapies in developing countries where prevalence of infectious diseases like TB is highest. Currently marketed re-usable capsule DPIs for antibiotic dry powders generally exhibit poor to moderate dispersion efficiency. This makes it necessary to divide the total dose into smaller portions to be administered in a series of subsequent inhalations. They are also a risk for resistance building, patient re-infection and, when used for hygroscopic drug formulations, extreme inhaler pollution. Therefore, a greater effort put in good inhaler development is needed giving inhaled antibiotic therapies a considerable boost.
Such inhalers should preferably be capable of administering different types of antibiotics without using an excess of excipients. This requires that the inhaler performance can easily be adapted to the physico-chemical properties of the drug. Such a concept may have great logistic advantages, minimise the costs of the therapy, ease the instructions and reduce incorrect use. To become successful, the concept requires classification of the antibiotics of interest on the basis of relevant physico-chemical properties to dispersion and retention.

References


Discussion Chapter 7


