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The choice of a compressor for the aerosolisation of tobramycin (TOBI®) with the PARI LC PLUS® reusable nebuliser

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Abstract

The performance of five different compressors (CR60®, Porta-Neb®, Pulmo-Aide®, TurboBoy® and Freeway® Freedom) was studied in combination with the widely recommended PARI LC PLUS® nebuliser for the aerosolisation of a marketed tobramycin solution (TOBI®). The droplet size distribution of the generated aerosol was measured with laser diffraction technique at stationary inspiratory flow rates through the nebuliser cup of 20, 30 and 40 l_N/min. The different compressors showed a distinct difference in droplet size distribution of the aerosol and nebulisation time till dry running. The finest droplets with a volume (equals mass) median diameter (mmd) of 1.84 μm (which was the same at all flow rates), as well as the narrowest size distribution were obtained with a CR60®. The Freeway® Freedom generated the largest droplets: mmd ranged between 2.63 and 3.72 μm depending on the inspiratory flow rate. The aerosol produced with this compressor also had the widest size distribution. The differences between the compressors could be explained with differences in the jet flow. A higher jet flow resulted in finer droplets, less dependence on the inspiratory flow rate and a shorter time till dry running. Thus, to obtain the required fineness of the aerosol for peripheral airway deposition of the tobramycin, independent of the inspiratory flow rate, the use of the CR60® compressor is preferred over the use of Porta-Neb®, Pulmo-Aide®, TurboBoy® and Freeway® Freedom (in order of decreasing preference). Finally, it was found that careful cleaning with warm water and liquid soap of the nebuliser cup is essential to obtain adequate performance of the LC PLUS®.

Keywords: Tobramycin; TOBI®; Nebulisation; PARI LC PLUS®; Compressor; Laser diffraction analysis

1. Introduction

Cystic fibrosis (CF) is a hereditary disease, characterised by secretions of extremely high viscosity from exocrine glands in the airways (Tiddens, 2002). The increased viscosity of the mucus leads to a reduced clearance of microorganisms from the respiratory tract (Geddes, 1997). The inflammatory response to these microorganisms, which are predominantly *Staphylococcus aureus* for children and *Pseudomonas aeruginosa* for adult CF patients, causes severe and irreversible airway damage. Once damage has occurred, it facilitates further infection and colonisation. Therefore, without proper treatment with antibiotics, gradual deterioration must be expected (Touw et al., 1995).

Antibiotics in CF are used on an intermittent basis to treat pulmonary exacerbations, as well as continuously, to lengthen the interval between the exacerbations (Davis et al., 1996). Pulmonary administration of various antibiotics has been found to improve lung function in CF and to reduce the frequency of hospital admission. When given by inhalation, the antibiotic is

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delivered directly to the target organ which increases the therapeutic index of the drug (Coates et al., 1997; Sermet-Gaudelus et al., 2002). It has been described that the airway disease in CF begins in the small peripheral airways and progresses to the development of widespread bronchiectasis, which is most marked in the upper lobes (Geddes, 1997). This may explain why the bronchial lumen (Ramsey, 1996; Van Devanter and Montgomery, 1998) and the smaller bronchioles (Touw et al., 1995; Geddes, 1997) have both been referred to as the target area for inhaled antibiotics in CF. More recently, it has been reported that the inflammatory process, and geometrical airway changes as a result of that, are significantly more severe in the peripheral than in the central airways (Tiddens, 2002). This notion indicates the need for substantial peripheral deposition and emphasises the relevance of the choice of nebuliser system for antibiotics.

For effective drug deposition in the peripheral lung, particles smaller than 2–3 μm (aerodynamic diameter) are generally recommended. In different studies, the aerosolisation of antibiotics like gentamicin (Goldman et al., 1990; Crowther Labiris et al., 1999), colistin (Dodd et al., 1997; Li et al., 2001; Le Brun et al., 2002) and tobramycin (Hurley et al., 1994; Coates et al., 1998; Ramsey et al., 1998) has been reported. Different types of inhalation devices were used in these studies. Quite recently, a new tobramycin solution (TOBI®, Chiron Corporation, Emeryville, USA) for nebulisation has been introduced to the market. Several clinical studies have been presented in which the activity, efficacy and safety of inhaled TOBI® were investigated (e.g. Otto et al., 1998; Pai and Nahata, 2001). The manufacturer of TOBI® recommends nebulisation of the solution with the reusable hand-held PARI LC PLUS® nebuliser in combination with the DeVilbiss Pulmo-Aide® compressor (Chiron product information, 2003). The preference for this combination is based on the outcome of a comparative (in vitro) evaluation study with a number of commercially available jet nebulisers. In this study, the Pulmo-Aide® compressor was selected, instead of the much more obvious PARI TurboBoy®, because of its widespread acceptance in the CF community. Several other studies are known in which comparative evaluation of different nebuliser–compressor combinations was the objective. However, in most of these investigations either the LC PLUS® (e.g. Hurley et al., 1994; Ferron et al., 1996; Coates et al., 1997; Le Brun et al., 1999a), or tobramycin solutions were excluded (e.g. Standaert et al., 2001; Ho et al., 2001). Ho et al. (2001) used an albuterol solution as test substance, because of its virtually identical nebulisation characteristics to those of tobramycin, but others showed that the tobramycin concentration (Le Brun et al., 1999b) or the addition of albuterol to a tobramycin solution (Coates et al., 1997) may change the aerosol properties and the output rate of the nebuliser substantially. The influence of the composition and physical drug properties of the drug solution on the aerosolisation process is also known from various other investigations (McCallion et al., 1995; Steckel and Eskandar, 2002). Therefore, a good recommendation for the nebuliser equipment to be used for the administration of a particular type of drug formulation can only be given on tests that are performed with this particular formulation.

The aim of this study was to test five different marketed compressors that are all approved for use with TOBI® and have quite different jet flows (through the nebuliser), so as to conclude which yields the most optimal combination with the recommended LC PLUS® for peripheral deposition of this drug. The droplet size distribution of the TOBI® aerosol was measured intermittently, starting immediately at the beginning of nebulisation and continuing into dry running of the cup. This makes investigation of changes of the size distribution in the aerosol possible, as could (for instance) be expected from an increase in the tobramycin concentration (by evaporation) during nebulisation. Monitoring of the droplet size distribution during the whole nebulisation process is an extension of various other studies, in which measurements were first started after 2–3 min to allow for steady state conditions (Coates et al., 1998; Ho et al., 2001). Such measurements do not reveal possible instabilities of the aerosol in the first phase of nebulisation, which information is relevant to a comparative evaluation study.

2. Materials and methods

2.1. Nebulisers and TOBI®

PARI LC PLUS® (Fig. 1) reusable nebulisers (PARI GmbH, München, Germany) and five different compressors were supplied by Romedic B.V.,

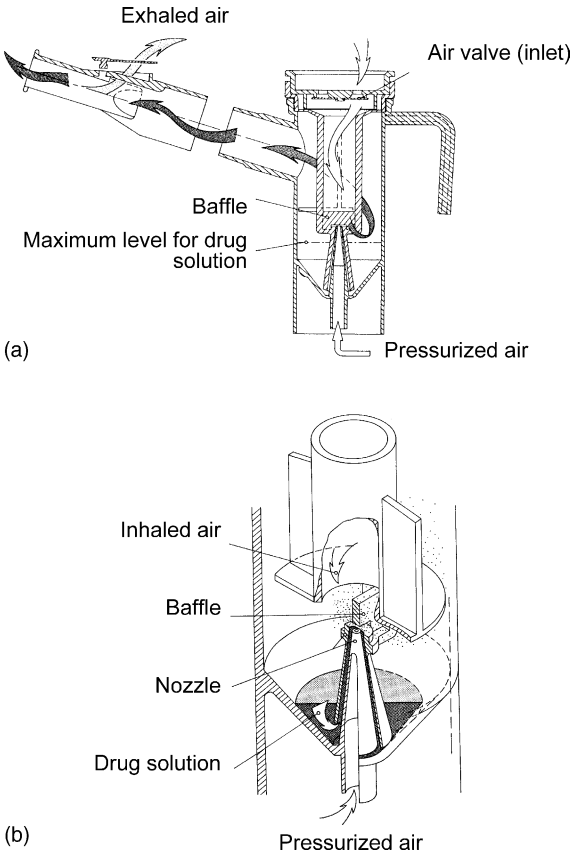

Fig. 1. Schematic presentation of the PARI LC PLUS® nebuliser cup (a) with a detail drawing of the nozzle area (b).

Meerssen, The Netherlands. The nebulisers used for the study were CR60®, Freeway® Freedom and Porta-Neb® (Medic-Aid Ltd., West Sussex, UK), PARI TurboBoy® (PARI GmbH, München, Germany) and DeVilbiss Pulmo-Aide® (DeVilbiss Company, Somerset, USA). TOBI® (Chiron Corporation, Emeryville, USA) was obtained from Chiron B.V., Amsterdam, The Netherlands. TOBI® is an aqueous 300 mg tobramycin solution in single-use ampoules of 5 ml each, containing also 11.25 mg of sodium chloride and a buffer to adjust the pH to 6.

2.2. Measurement of compressor flow rates

Stationary compressor flow rates were measured with a Brooks thermal mass flow meter type 5863S (Brooks Instruments, Veenendaal, The Netherlands), having a measuring range of 0–150 l_N/min. A pressure drop across the flow head of this meter of only 0.022 kPa at 5 l_N/min, respectively 0.068 kPa at 10 l_N/min was recorded. Consequently, compressor flows were not noticeably reduced by the experimental set up during the measurements. Measurements were replicated with a LC PLUS® connected to the compressors, yielding the actual jet flow rates during nebulisation, which are reference values for the obtained droplet size distributions.

2.3. Comparative evaluation of the compressors in combination with PARI LC PLUS®

All five compressors were tested in combination with the same LC PLUS® nebuliser cup. For each compressor–nebuliser combination, nine successive inhalations were performed at stationary inhalation flow rates of 20, 30 and 40 l_N/min, respectively, yielding three replicate measurements per flow rate. Inhalations were performed at ambient conditions with air of 20–22 °C and 45–55% relative humidity. The equipment was used and cleaned (between inhalations) according to the manufacturer's instructions and for each inhalation a new TOBI® ampoule was used. The size distributions of the generated aerosol clouds were measured intermittently with a Sympatec HELOS BF/MAGIC® laser diffraction apparatus using Windox® soft ware version 4.1.3.0 (Sympatec, Clausthal-Zellerfeld, Germany), in combination with a previously described Sympatec INHALER® adapter (de Boer et al., 2002a). Start of the first measurement was synchronised with the start of the nebulisation process, and subsequent measurements were programmed with time intervals of 50 s. Each measurement had a duration of 10 s, so as to obtain a value for the droplet size distribution each whole minute from the beginning of the nebulisation process. This procedure was continued into dry running of the nebuliser cup. The data (mean of three individual measurements per flow rate) have been presented as function of the nebulisation time (Fig. 3) and averaged for all measuring times up to dry running of the cup (Figs. 4 and 5).

During the laser diffraction measurements, the nebuliser mouthpiece with exhalation valve was removed for a better connection with the inhaler adapter, after it had been checked that this mouthpiece has no effect

on the aerosol properties. The inhaler adapter was used with an elongated front cylinder and tilted to an angle of 9° in order to maintain the nebuliser cup in perfect upright position. A minor counter flow was applied to keep the lenses free from adhering droplets. Measurements were done with a 100 mm lens and the Fraunhofer theory was preferred to Mie for the data processing because of previously explained reasons (de Boer et al., 2002b). During the droplet size distribution measurements, the optical concentration of the aerosol cloud was used to monitor the nebulisation process. The time between the start of nebulisation and dry running of the nebuliser cup was measured with a stopwatch. The exact start of dry running could be observed from a distinct change in the sound produced by the nebuliser cup. During dry running, the experiment was completed with one final laser diffraction measurement. The total amount of nebulised tobramycin solution was then calculated from the weights of the nebuliser cup before and after the experiment.

2.4. Batch variation of PARI LC PLUS® and variability in nebulisation

The batch variation of LC PLUS® was tested for 10 different nebuliser cups in combination with the Porta-Neb® compressor at a stationary flow rate of 30 l_N/min. Laser diffraction procedures were exactly the same as described for the comparative evaluation of the compressors. New nebuliser cups were used without previous cleaning. In addition, the variability of aerosolisation with LC PLUS® was measured by nebulising 10 different TOBI® ampoules with the same nebuliser cup (again in combination with Porta-Neb® at 30 l_N/min). For this test, the cup was cleaned between the nebulisations according to the prescriptions: rinsing with warm water and liquid soap and subsequent drying with a paper tissue.

3. Results and discussion

3.1. Compressor and jet flow rates

Fig. 2 shows the compressor flow rates without and with external resistance from the nebuliser cup. The flow rates through the LC PLUS® are the actual jet flow rates, reponsible for the aerosol generation during

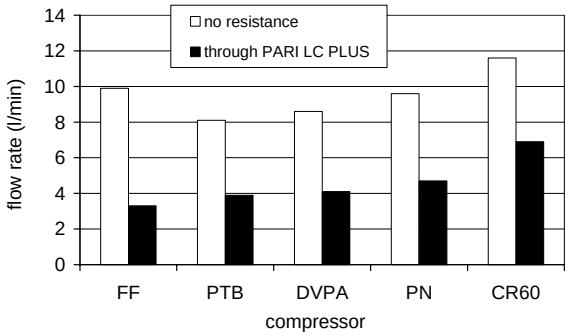

Fig. 2. Compressor flows (without external resistance) and jet flows (through LC PLUS®) for the five different compressors in the study. FF: Freeway® Freedom; PTB: PARI TurboBoy®; DVPA: De Vilbiss Pulmo-Aide®; PN: Porta-Neb®; CR60®. All data are the mean of four measurements.

nebulisation. The difference in jet flow rate between CR60® and Freeway® Freedom by a factor 2.09 is quite large, but not surprising, because a high jet flow rate has already been reported for the CR60® in previous studies (Standaert et al., 2001). The greatest reduction in flow rate from the external resistance of the nebuliser (66.7%) has been obtained for the Freeway® Freedom; the smallest (40.5%) for the CR60®. This means that the CR60® can be operated in combination with nebuliser cups with much higher air flow resistances than the Freeway® Freedom.

3.2. Droplet size distribution in the aerosol as function of the jet flow and the inspiratory flow rate

The differences in jet flow rate are reflected by the differences in droplet size distribution as shown in the Figs. 3–5. In Fig. 3, the droplet size distributions of the TOBI® aerosols are depicted as function of nebulisation time for all three flow rates. They are represented by the X_{10}, X_{50} and X_{90} values from the cumulative volume undersize curves obtained from laser diffraction analysis of the aerosol cloud. Taking into account that the droplets have (nearly) unit density and that they are perfectly spherical, the X_{50} values may be considered as mass median aerodynamic diameters (mmad's). As expected on the basis of the jet flow rates, the finest droplets are obtained with the CR60® (mean X_{50} is 1.82 μm at 20 l_N/min), whereas the coarsest are produced with the Freeway® Freedom (mean X_{50} is 3.7 μm at the same flow rate). With that,

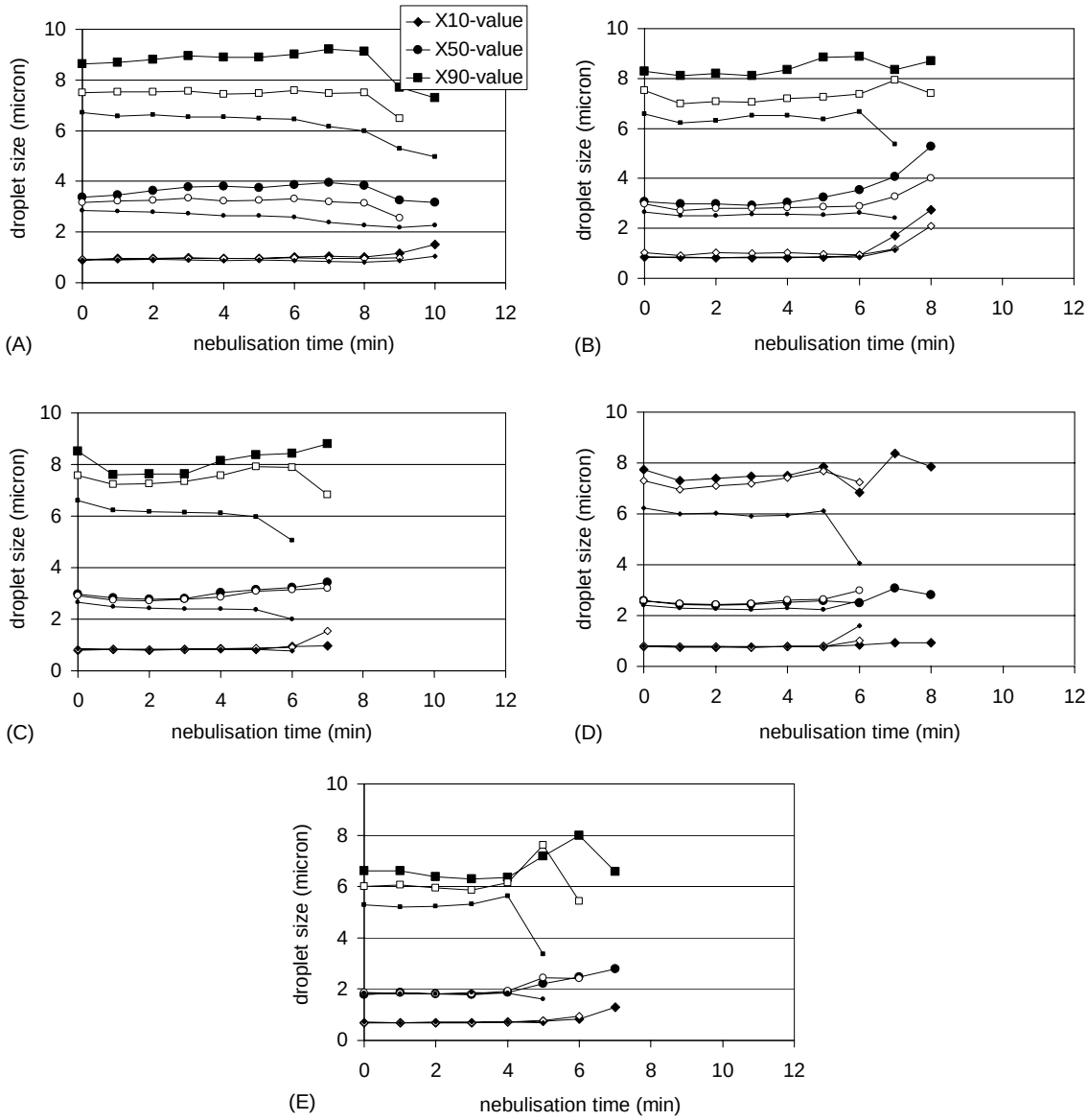

Fig. 3. X_{10}, X_{50} and X_{90} values of the TOBI® aerosol (derived from cumulative volume undersize curves) from the LC PLUS® in combination with five different compressors as function of nebulisation time. Large closed symbols refer to a stationary inspiratory flow rate of 20 l_N/min; medium sized open symbols to 30 l_N/min and small closed symbols to 40 l_N/min. A: Freeway® Freedom; B: TurboBoy®; C: Pulmo-Aide®; D: Porta-Neb®; E: CR60®. All data points are the mean of three measurements.

the ratio of median droplet sizes (2.04) for these two compressors is about the same as that for the jet flow rates (2.09) at this lowest flow rate. This jet flow rate (or pressure) dependent droplet size distribution is in good agreement with the observations in previous studies for different compressor–nebuliser combinations (Niven and Brain, 1994; McCallion et al., 1996). Also well known from literature is the effect of jet flow rate on the output rate of the drug solution (e.g. Niven and Brain, 1994). However, relatively few studies are known in which the effect of the inhalation flow rate on both the droplet size distribution and the

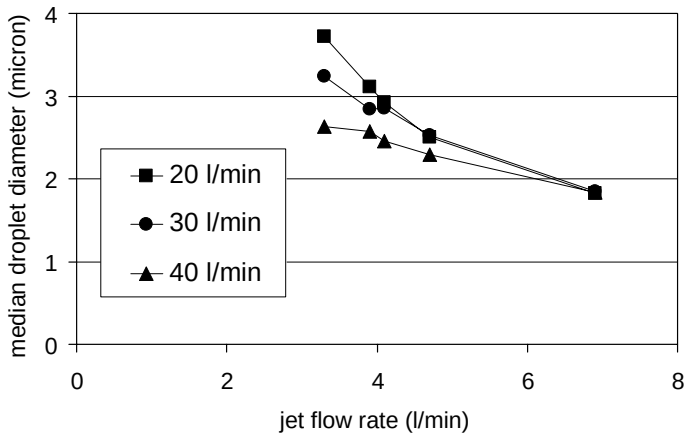

Fig. 4. Median droplet diameter of TOBI® aerosol as function of the jet flow through the LC PLUS® at three different stationary inspiratory flow rates. Mean of all measurements up to dry running of the nebuliser cup.

output rate is reported. One important reason may be that control of the inspiratory flow rate, particularly during laser diffraction analysis of the aerosol cloud, was problematic before a special inhaler adapter was developed (de Boer et al., 2002a). Instead, in some studies conditioned air (at higher than atmospheric pressure) was directed through the one-way valve system at the top of the nebuliser (Coates et al., 1998; Ho et al., 2001). With this technique, it could be shown that vented nebulisers (e.g. LC PLUS®) are more sensitive (in respect of drug output rate) to the inhalation flow rate than unvented devices, like Hudson 1730 T Up-Draft® (Coates et al., 1998). In the present study, a stationary inhalation flow rate has been adjusted to values (20, 30 and 40 l_N/min, respectively) that are within the range of peak flow rates of adult healthy volunteers (25–48 l/min) and different patient groups (17–90 l/min), as recorded during normal breathing (Denyer et al., 1997). CF patients may have quite normal lung functions in spite of the existence of areas in their lungs with end-stage lung disease (Tiddens, 2002). Bisgaard et al. (1997) however, reported a mean FEV_1 value of only 63% of predicted for 55 CF patients with a mean age of 20 years. Fig. 3 clearly shows that the effect of inspiratory flow rate on droplet size distribution for TOBI® from the PARI LC PLUS® depends on the type of compressor. The effect increases with decreasing jet flow, as shown more particularly in Fig. 4. In this figure, the median droplet diameter (X_{50} value) is presented as function of the jet flow through the LC PLUS®. Values obtained at the same flow rate are linked to emphasize the good correlations.

A direct comparison of the droplet size distributions of all five compressors is given in Fig. 5, showing more particularly the reproducibility of each combination. To produce this figure, the three replicate experiments per flow rate, were averaged first (X_{10}, X_{50} and X_{90} as function of nebulisation time). Next the mean of the averaged three experiments during total nebulisation time was computed. Data obtained during dry running of the cup were excluded from these calculations. Fig. 5 confirms that the sensitivity of LC PLUS® (in respect of median droplet size distribution) to the inhalation flow rate depends on the jet flow rate. Only for the CR60® and Porta-Neb® the median droplet diameter is (about) the same at 20 and 40 l_N/min. Fig. 5 also shows that, with decreasing median droplet diameter (X_{50}) as a result of increasing the inspiratory flow rate, the span of the range for the size distribution decreases. Consequently, higher inspiratory flow rates result in narrowing of the droplet size distribution in the aerosol cloud. Reproducibility also appears to increase with decreasing X_{50} value.

3.3. Output rate and time till dry running

Optical concentrations in the TOBI® aerosol cloud during the nebulisation process (at all three flow rates) are shown in Fig. 6. They are a measure for the output rate (droplet concentration in the cloud)

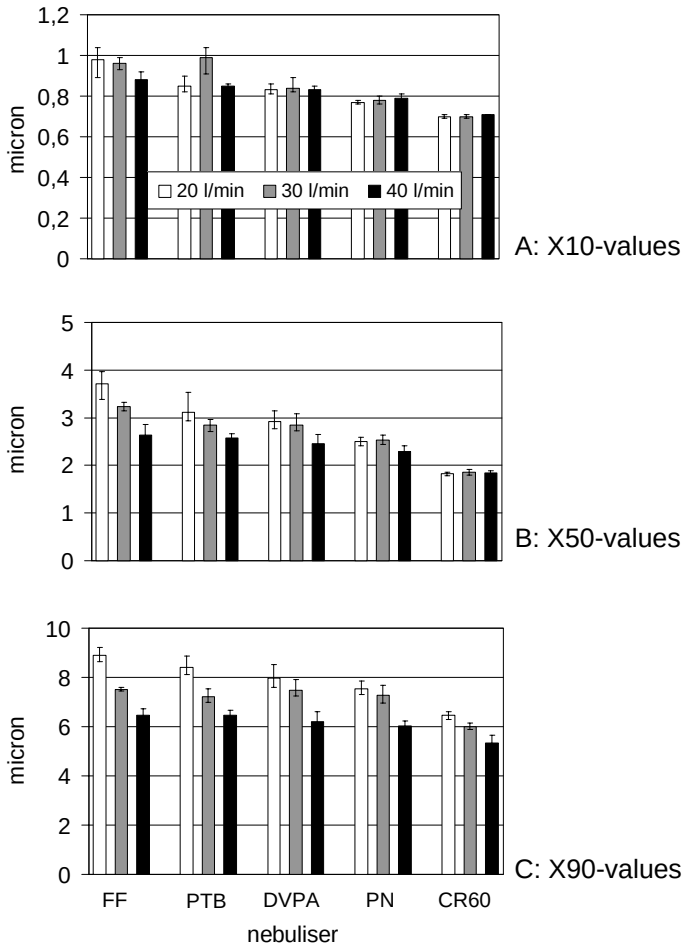

Fig. 5. Effect of stationary inspiratory flow rate on the droplet size distribution of TOBI® aerosol from LC PLUS® (represented by X_{10}, X_{50} and X_{90} values from the cumulative volume undersize curves as function of droplet diameter) in combination with different compressors. The spread bars indicate the highest and lowest averaged value obtained during nebulisation. FF: Freeway® Freedom; PTB: PARI TurboBoy®; DVPA: De Vilbiss Pulmo-Aide®; PN: Porta-Neb®; CR60®.

Table 1
Nebulisation times till dry running and nebulised amounts of TOBI® solution (in milligrams and as percent of the ampoule contents)

	Minutes till dry running			Nebulised amount of drug solution (g)			Nebulised amount (%)		
l_N/min	20	30	40	20	30	40	20	30	40
Freeway® Freedom	8.43	7.71	8.82	3.53	3.41	3.46	67	65	65
TurboBoy®	5.99	6.51	6.21	3.47	3.44	3.31	66	65	63
Pulmo-Aide®	6.04	5.52	5.35	3.19	3.08	3.33	60	58	65
Porta-Neb®	6.21	5.39	4.52	3.58	3.35	3.42	68	63	66
CR60®	5.14	4.36	3.30	3.63	3.47	3.52	68	66	67

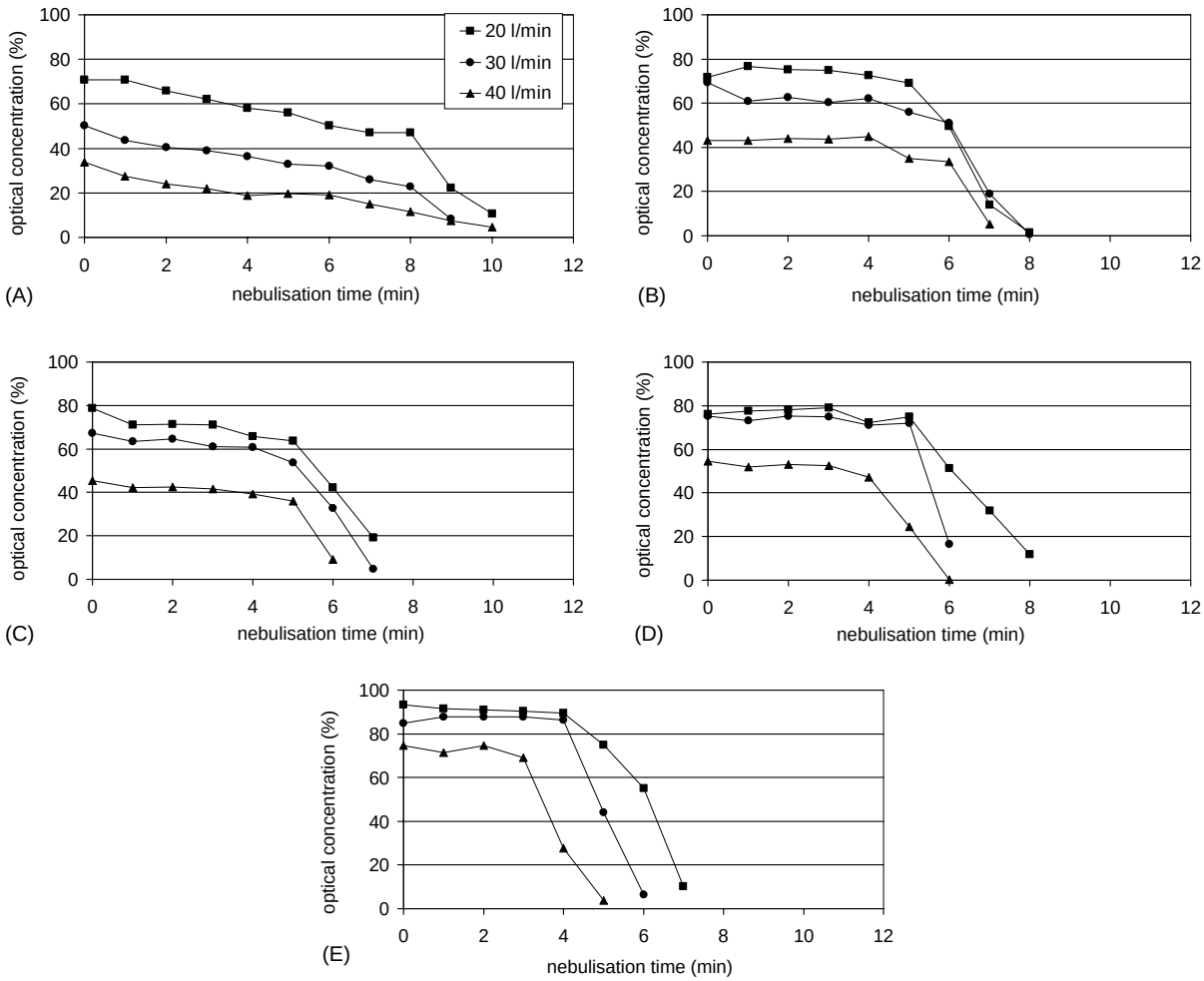

Fig. 6. Optical concentration of the TOBI® aerosol from LC PLUS®, as function of the nebulisation time, at three different stationary inspiratory flow rates for five different compressors. A: Freeway® Freedom; B: TurboBoy®; C: Pulmo-Aide®; D: Porta-Neb®; E: CR60®. All data points are the mean of three measurements.

and size distribution of the aerosol from a particular compressor–nebuliser combination. A dramatic and sudden change in optical concentration (at constant size distribution) indicates when dry running of the nebuliser cup is about to occur. Measurements have been continued into the phase of dry running of the nebuliser cup. The time between the start of the nebulisation and the moment of dry running for each compressor–LC PLUS® combination is given in Table 1 for all three stationary inspiratory flow rates. The table also shows the nebulised amounts of TOBI® solution in grams and as percent of the dose from the ampoule. Table 1 and Fig. 6 indicate that also the effect of inspiratory flow rate on the time till dry running of the LC PLUS® varies with the type of compressor used. In contrast with its effect on droplet size distribution, the effect of flow rate on the output rate seems to increase with increasing jet flow. For the Freeway® Freedom and TurboBoy®, the nebulisation time till dry running (which is proportional to the output rate at fixed volume) is about the same at all three flow rates. Only for Pulmo-Aide®, Porta-Neb® and CR60®, the output rate seems to increase with increasing inhalation flow rate. It should

be emphasized that dry running in this study (Table 1) was defined differently from certain previous investigations (Coates et al., 1998; Ho et al., 2001), where dry running was first concluded after no aerosol was visible for a 30-s period. In the present study, the exact moment of dry running was monitored on a change in sound produced by the nebuliser, indicating the start of intermittent aerosolisation. Fig. 6 shows that apparently, in some cases the optical concentration already decreases quite dramatically before the actual start of the dry running phase (as defined in Table 1) is achieved.

3.4. Batch variation of PARI LC PLUS® and variability in nebulisation

Table 2 summarises the results from the batch variation experiments with LC PLUS® and the variability in aerosol properties from repeated nebulisation with the same cup. Maximum and minimum indicate the highest and lowest individual values obtained during the runs. The results indicate that the reproducibility of LC PLUS® with the same compressor (Porta-Neb®) is quite high, whereas the the batch variation seems low. Whether 10 different cups (first use, without rinsing) are used, or 10 inhalations with the same cup are performed; on average the same droplet size distribution (the difference in mmd being only 3.9%) and variability are obtained.

The table also shows the mean optical concentration of the aerosol cloud during nebulisation, as well as the mean number of time intervals per experiment. Not given in Table 2B are the individual results, which show that there exists a clear difference in optical concentration curve and time till dry running between a non-treated new nebuliser cup and a cup that has been washed before use. It was observed that new cups are strongly hydrophobic, resulting in large droplet formation onto the inner walls of the cup. As a consequence, a high fraction of the TOBI® solution is taken from the cup by adherence to these walls. This leads to a high residual volume and reduced nebulisation time, which (in most cases) appeared to be only approximately 3 min for unrinsed cups. Nevertheless, the size distributions of all experiments, including the first, were the same.

On the basis of the differences in droplet size distribution (Figs. 3–5) and the same nebulised amount of 65% of the dose (Table 1) for all investigated compressor–nebuliser combinations, it must be concluded that the PARI LC PLUS® produces the highest fraction of the dose in the desirable size range for peripheral lung deposition when this nebuliser is used in combination with the CR60® compressor. Therefore, the CR60® seems a better compressor than the TurboBoy® (standard compressor for the LC PLUS®) or the Pulmo-Aide® (recommended by the manufacturer of TOBI®) for the LC PLUS®, particularly at a lower inspiratory flow rate of 20 l_N/min. Not only its droplet size distribution is more favourable, also its inspiratory flow dependence is much lower (Figs. 3 and 4), which is relevant considering the great variation in peak flow rates during normal breathing reported by Denyer et al. (1997). Besides, the reproducibility in

Table 2
Mean X_{10}, X_{50} and X_{90} values from the cumulative volume distribution curve of TOBI® aerosol (representing the droplet size distribution in the aerosol cloud) during nebulisation until dry running for LC PLUS® with Porta-Neb® at 30 l_N/min

	X_{10} (μm)	X_{50} (μm)	X_{90} (μm)	C_{opt} (%)	min[a]
(A) Ten inhalations with different nebuliser cups (first use without previous cleaning)					
Mean	0.79	2.41	6.49	52	4
Maximum	0.85	2.83	7.30	67	6
Minimum	0.75	2.08	5.80	47	3
(B) Ten inhalations with the same nebuliser cup (first inhalation, without previous cleaning of the cup)					
Mean	0.78	2.32	6.48	52	5
Maximum	0.84	2.53	6.98	62	6
Minimum	0.74	2.10	5.80	49	3

Mean is calculated from the individual (not averaged) measurements; maximal and minimal values indicate the most extreme individual values obtained during the nebulisation process within (in total) 10 experiments.
[a] Minutes nebulisation until dry running.

aerosol characteristics is much better for the CR60® (Fig. 5) and the nebulisation time is shorter because of a higher output rate (Table 1). There is one aspect that needs careful consideration when changing from a less efficient to a better compressor however. Long term efficacy and safety of peripheral deposition of antibiotics has not been studied yet. Several investigations up to now, could not indicate toxicity for aerosolised doses of tobramycin, but this has been related to low and unsustained serum concentrations (Prober et al., 2000). Substantial peripheral deposition might result in increased serum concentrations and therefore, clinical investigation is strongly recommended.

Finally, the nebuliser cups have to be washed (before first use) according to the recommended procedures, or the aerosolised drug fraction will be too low.

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