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Design and application of a new modular adapter for laser diffraction characterization of inhalation aerosols

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Abstract

An inhaler adapter has been designed for the characterization of the aerosol clouds from medical aerosol generators such as nebulizers, dry powder inhalers (dpis) and metered dose inhalers (mdis) with laser diffraction technology. The adapter has a pre-separator, for separation of large particles (i.e. carrier crystals) from the aerosol cloud before it is exposed to the laser beam. It also has a fine particle collector for measuring the emitted mass fraction of fines by chemical detection methods after laser diffraction sizing. The closed system enables flow control through the aerosol generators and all test conditions, including ambient temperature and relative humidity, are automatically recorded. Counter flows minimize particle deposition onto the two windows for the laser beam, which make successive measurements without cleaning of these windows possible. The adapter has successfully been tested for nebulizers, mdis and dpis. In a comparative study with ten nebulizers it was found that these devices differ considerably in droplet size (distribution) of the aerosol cloud for the same 10% aqueous tobramycin solution (volume median diameters ranging from 1.25 to 3.25 μm) when they are used under the conditions recommended by the manufacturers. The droplet size distribution generated by the Sidestream (with PortaNeb compressor) is very constant during nebulization until dry running of the device. Comparative testing of dpis containing spherical pellet type of formulations for the drug (e.g. the AstraZeneca Turbuhaler) with the adapter is fast and simple. But also formulations containing larger carrier material could successfully be measured. Disintegration efficiency of a test inhaler with carrier retainment (acting as a pre-separator) could be measured quite accurately both for a colistin sulfate formulation with 16.7% of a lactose fraction 106–150 μm and for a budesonide formulation with a carrier mixture of Pharmatose 325 and 150 M. Therefore, it is concluded that, with this special adapter, laser diffraction may be a valuable tool for comparative inhaler evaluation, device development, powder formulation and quality control. Compared to cascade impactor analysis, laser diffraction is much faster. In addition to that, more detailed and also different information about the aerosol cloud is obtained.

Keywords: Inhalation; Aerosol cloud; Particle size analysis; Laser diffraction; Modular inhaler adapter; INHALER 2000™

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1. Introduction

Multi stage liquid impingers and cascade impactors are widely used for particle size measurement in the aerosol cloud from medical aerosol generators. The principle of classification by inertial separation is well described (Ranz and Wong, 1952; Hinds, 1982; John, 1999) and many different types of devices are available. Recently, a new apparatus has been presented, specifically for pharmaceutical applications, which is referred to as the Next Generation Impactor (Marple et al., 2000). In order to improve the performance of this device, a special high-capacity pre-separator has been designed (Roberts et al., 2000). Robot assisted inhaler handling during cascade impactor analysis (cia) and automated data processing have been developed to increase the speed and accuracy of testing (Copley, 2000; Smith, 2000). To study the effect of simulated inhalation profiles on the performance of aerosol delivery systems, different set-ups have been introduced for maintaining a constant air flow through the cascade impactor (Burnell et al., 1998; Miller et al., 2000; Finlay and Gehmlich, 2000). In order to extend the sizing range of impactors, e.g. for the characterization of agglomerated drug particles or drug particles attached to carrier crystals in the emitted aerosol cloud from dry powder inhalers (dpis), combinations of impactors and cascade sieves have been proposed (Prime et al., 2000). For many other shortcomings and limitations of cascade impaction (summarized in Table 1A, also showing some specific advantages), adequate solutions have not (yet) been found, as has been discussed recently by de Boer et al. (2002). Yet, the technique is frequently used, because the emitted dose is fractionated into aerodynamic size classes that are relevant to the deposition in the respiratory tract. Since these fractions are analysed by chemical detection methods, the drug deposition can be established in the presence of excipient.

Laser diffraction analysis (lda) has the potential to solve some major disadvantages of cia. It also has some specific features that may be particularly interesting for inhaler characterization. In addition to the aspects listed in Table 1B, lda offers a much higher number of size classes for the relevant fine particle fraction than can be obtained from cascade impactor analysis. Therefore, calculation of comparable fractions is much easier, faster and with higher accuracy. The sizing principle has no collection plates that can dry up or get heavily loaded with particles during longer measuring periods, thereby increasing the occurrence of bounce and blow off. These practical advantages are the reason why lda is already frequently applied for nebulizer testing (Clark, 1995; McCallion et al., 1995, 1996a,b; Bridges and Taylor, 1998). However, the principle has some limitations for the sizing of particles in the aerosol clouds emitted by dpis. With laser diffraction technique, random geometric particle dimensions are obtained. Only if the particles are spherical and have unit density, these dimensions are equal with aerodynamic diameters. Dry powder aerosols generally comprise both primary drug entities and small agglomerates. As a consequence, the particles in the cloud exhibit a certain range of different particle shapes and densities. Therefore, the size distributions of particles in aerosol clouds from dpis can not be expressed in aerodynamic diameters.

Standard laser diffraction equipment does not allow control of the inspiratory flow curve through the inhaler. This seems to exclude testing of breath controlled devices with this technique, unless an air flow is directed through the device by compression instead of suction (Everard et al., 1997). Lda does not exclusively yield the size distribution of the drug in the aerosol, as obtained by chemical detection. Moreover, the mass fraction of the dose that is emitted as fine particles can not be measured. This certainly does not imply that laser diffraction technique has no meaning for dpi testing. Practical solutions for a number of operational shortcomings can be obtained with special additional equipment, as will be described in this article. The application of lda for dpi development is based on reference measurements with the (laser diffraction) size distribution of the primary drug particles as the reference to aim at during powder formulation and device development (de Boer et al., 2002). Accordingly, a different way of data interpretation has to be developed; e.g. by explaining the results in terms of powder de-agglomera-

Table 1
Review of some specific advantages and limitations of (A) cascade impaction (cia) and (B) laser diffraction (lda) discussed by de Boer et al. (2002)

(A) Cascade impaction (cia)		
Advantages	✓	Quantitative and qualitative drug analysis with chemical detection methods
	✓	Mass fractions classified upon 'aerodynamic diameters'
	✓	Widespread acceptance and use
	✓	Data currently accepted by regulatory authorities
Limitations	✓	Classification into a small number of size classes
	✓	Cascade impactors can not be operated under variable flow conditions: flow curve simulation is not possible
	✓	Cut-off diameters vary with (fixed) flow rate through the impactor
	✓	High resistance limits the adjustable range of flow rates
	✓	The effect of flow increase rate on dpi performance can not be studied
	✓	Fine particle collection by adhesion and electrostatic charge may occur
	✓	Cascade impaction lacks precision
	✓	Cascade impaction is slow and laborious
(B) Laser diffraction (lda)		
Advantages	✓	Rapid data generation and processing
	✓	Accessible to automation
	✓	High accuracy and reproducibility
	✓	Size measurement independent of the flow rate: simulation of inspiratory flow curves is possible
	✓	High number of size classes within the size range relevant to lung deposition
	✓	Time sliced measurements allow sophisticated analysis of aerosols
Limitations	✓	Laser diffraction does not exclusively indicate the size distribution of the drug (no chemical detection method)
	✓	Measurement of geometric instead of aerodynamic particle size (to certain extent a limitation for dpi characterization): accuracy decreases with increasing shape factor (volume distributions are computed on the assumption that particles are spherical)

tion efficiencies, rather than transcribing them into aerodynamic size distributions. This confines lda not only to a very fast and reliable technique for nebulizers and metered dose inhalers (mdis) but stretches its application to dpi development as well. In this paper, the design and development of a modular inhaler adapter for laser diffraction characterization of different types of inhalation devices is discussed. The aim is to show that the adapter facilitates (comparative) evaluation of nebulizers (and mdis). But also the performance of breath operated dry powder inhalers can be studied quite conveniently. This includes devices containing formulations with larger carrier particles. It will be shown that reliable size distributions of the drug in the aerosol cloud can be obtained when effective pre-separators are used for removal of large excipient (e.g. carrier) particles and reference measurements with the excipient only are made that serve as a blank for the mixture with the drug.

2. Design of the modular inhaler adapter and its measurement options

The necessary additional means to obtain a practical solution for some of the major restrictions of lda for inhaler testing are:

- A closed housing to which the inhaler is connected and through which the aerosol is conducted at a controlled inspiratory flow rate through the inhaler,
- A fine particle collector, for measuring the emitted mass fraction of fine particles,
- A pre-separator for retainment of large particles, such as carrier crystals, from dry powder inhalers,
- A vacuum system with flow control unit and flow measuring device.

In addition to these primary design parameters, some secondary specifications have been listed in Table 2. They extend the range of applications and

Table 2
Some secondary design specifications for the inhaler adapter

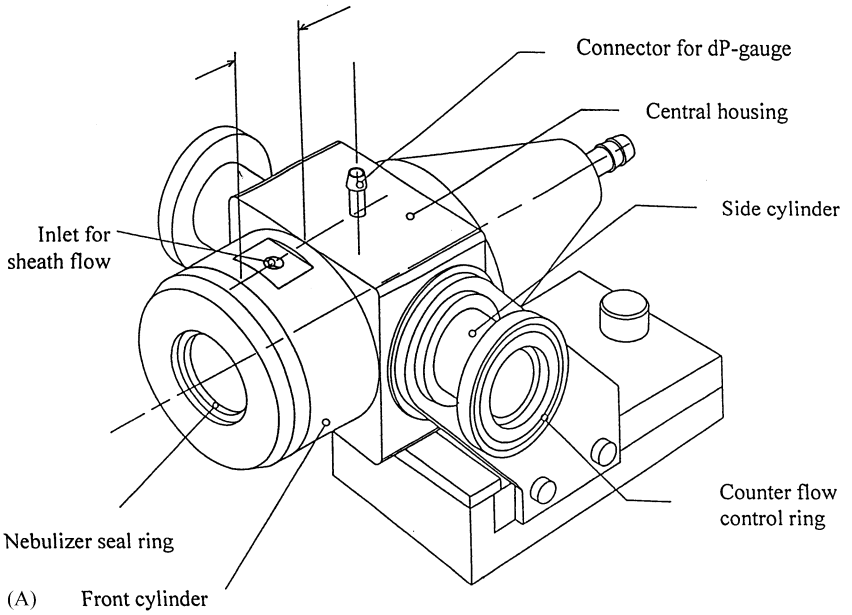
✓ Modular concept to serve different applications for dpis, mdis and nebulizers
✓ Fast exchange and cleaning of adapter parts
✓ Minimal particle (droplet) accumulation onto inner walls (particularly the windows)
✓ Tilting construction for the measurement of nebulizers with sloping mouthpieces
✓ Front cylinders with different lengths to study the effects of droplet evaporation
✓ Low air flow resistance for a wide range of PIFs and FIRs
✓ Design prepared for combination with flow curve simulators
✓ Automatic recording of data, parameter settings and room temperature and humidity

Abbreviations: PIF, peak inspiratory flow; FIR, flow increase rate.

make laser diffraction analysis of the aerosol cloud from inhalers with lda not only faster, but also more convenient and more accurate. The measuring chamber has been designed neither to interfere with the aerosol cloud nor with the laser beam. The concept is modular, so as to comply with the different demands for different types of inhalation systems, as well as to serve different types of experiments with these inhalers. In this paper, only the adapter itself is described without reference to the vacuum control system, the principles of laser diffraction and additional equipment that may be helpful in inhaler testing. Particularly for the evaluation of dpis, a highly effective dry powder dispersion system is recommended with which primary drug particle size distributions can be obtained that can be used as reference for the size distributions measured in the aerosol clouds from these devices. Also, a suitable flow meter will be necessary for establishment of the specific air flow resistance of dpis to be tested, as flow control through the inhaler connected to the adapter is upon adjustment of the corresponding pressure drop across the device.

In its basic design for nebulizer testing as shown in Fig. 1A (without venturi meter), the adapter has a closed central housing for flow control through the inhalation device, a front cylinder with an exchangeable seal ring for differently shaped mouthpieces, and a rear conical end for connection to the vacuum system, which includes a vacuum pump and flow control unit. The adapter has been developed specifically for Sympatec laser diffraction apparatus. This apparatus has two separate cabinets on a mechanical bench with a special support frame for different measuring systems in between these cabinets. The adapter is completely modular: parts can either be added to or removed from the central housing, so as to comply with the different requirements for different types of inhalation systems. The configuration shown in Fig. 1B is the most comprehensive set-up for dpi testing with pre-separator and fine particle collector (photograph of the INHALER 2000, Sympatec GmbH, Goslar, Germany). Parts can also be modified or exchanged according to user-specific demands. (Dis)assembling and cleaning are simple and fast. Different front cylinders with different lengths can be used for different types of nebulizers. All front cylinders have co-axial inner cylinders with smaller diameters to minimize the surface area to which fine particles can adhere as well as to prevent excessive widening of the discharge cloud before it passes the laser beam (Fig. 2). All inner cylinders end directly in front of the laser beam. The central housing has two side cylinders (Fig. 1B). One side cylinder has no window. After the adapter is connected to the support frame between the cabinets of the laser diffraction apparatus, the length of this side cylinder is increased so as to make close contact between the cylinder end and the housing around the lens for the laser beam. A seal ring at the cylinder end prevents uncontrolled leakage of false air into the side tube. The other side cylinder opposing the rotation unit for the Fourier lenses (MAGIC-system) has a removable window at its end, also preventing uncontrolled flows of false air. Both cylinders have adjustable vents (Fig. 1A: counter flow control ring) at their ends for the control of counter flows through these side cylinders that return fine particles to the central housing and assist in keeping the windows clean. These counter flows do not interfere with the flow control through the inhalation device.

Fig. 3 shows that the adapter can be tilted. This is to enable the connection of nebulizers with sloping mouthpieces to the adapter in a way that



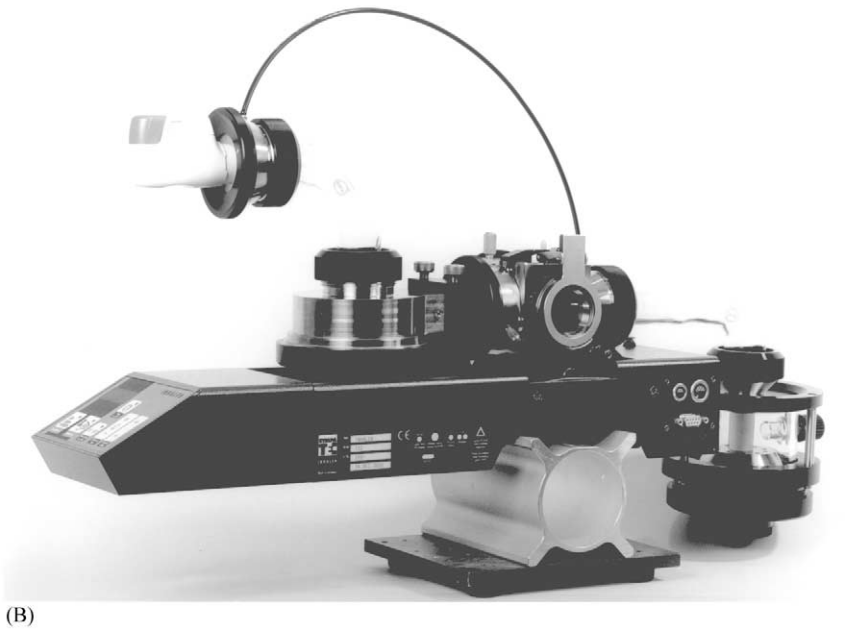


Fig. 1. (A) Bird's-eye view of the modular inhaler adapter concept: schematic presentation of the central housing part. (B) Photograph of the Sympatec INHALER 2000.

the nebulization cup stays upright. The figure also shows a calibrated venturi meter for flow measurement through the nebulizer. The venturi meter can either be connected directly to the conical end of the adapter, or to a particle collector or washing bottle downstream of the adapter. When the

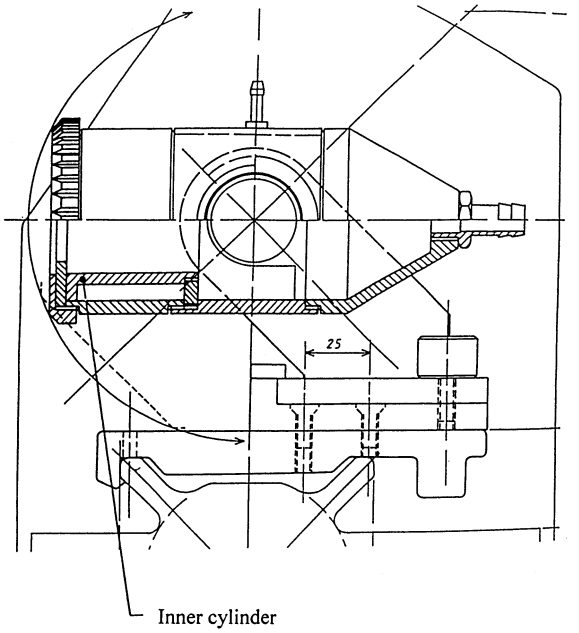


Fig. 2. Side view (top half) and cross section (bottom half) of the basic adapter concept, showing the inner cylinder.

venturi meter is used, the tube connector for a differential pressure (dP) gauge on top of the central adapter housing is closed. In the most comprehensive configuration for dpi-testing (Figs. 1B and 4) the front cylinder is replaced by a pre-separator and a fine particle collector is connected to a modified conical rear end. The present pre-separator is a single stage impactor, with a nozzle similar to the first stage of the Erweka impactor (Fig. 4). The induction port to this pre-separator is a bent glass tube which has a coupling flange with exchangeable seal rings for the inhaler. The pre-separator is only used for dpis in combination with adhesive mixtures; for pellet type of formulations, the standard front cylinder is applied. If the pre-separator is connected to the adapter, the pressure drop across the inhaler is measured at the position of the coupling flange and the tube connector on the central housing is closed. Without pre-separator, differential pressure measurement for dpis is at the top of the central housing. The pre-separator can easily be disconnected and disassembled for filter exchange (sampling) between experiments. Because powder disintegration may be propagated inside the bent glass induction port, which is an undesired aspect, a vertical pre-separator with straight inlet tube is in development. The fine particle collector is either a filter, similar to the fifth stage of the Erweka impactor, or a multi jet impinger with centrifugal action, as shown in Fig. 4. Collection of the fines allows the measurement of the released fine particle mass fraction. Similar to the pre-separator, the fine particle collector can easily be disconnected and disassembled for sampling. The vacuum system is not depicted. It consists of a rotary pump with a flow control unit, including a solenoid valve with timer and a flow controller for the adjustment of a constant flow rate over a preset inhalation time through the inhaler. A modulated sine wave generator for normal breath simulation (nebulizer testing) and a computer assisted control system for simulation

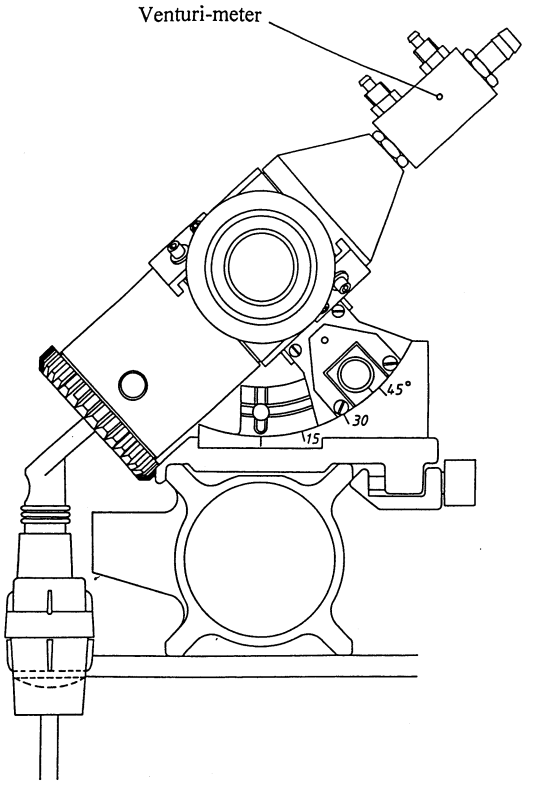


Fig. 3. Side view of the tilted adapter concept for nebulizer testing with a venturi meter connected to the conical rear end.

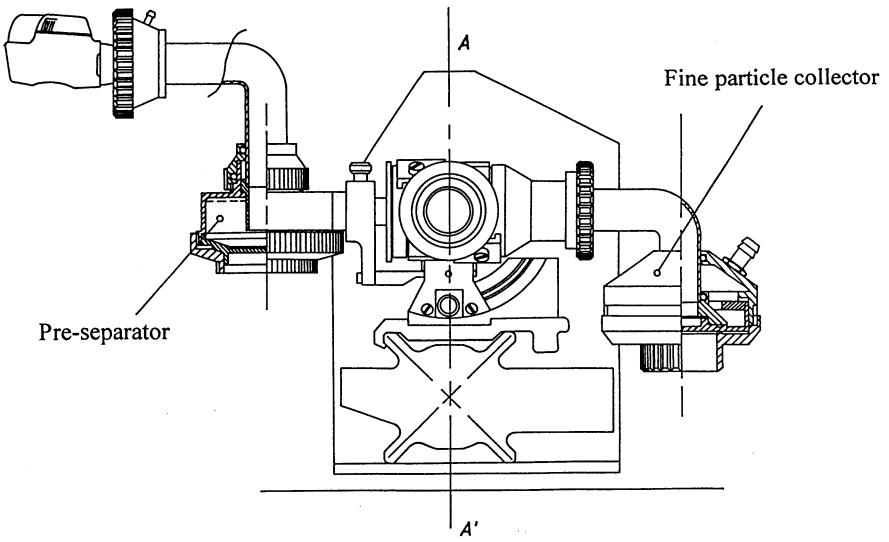


Fig. 4. Side view of the adapter configuration for dpi testing with horizontal pre-separator and multi jet impinger type of fine particle collector.

of the inspiratory flow curve (mdi and dpi testing) are currently in development.

The low air flow resistance of the adapter, in combination with its relatively small volume (compared to most cascade impactors), practically imposes no limits on PIF and FIR through the inhalers. Measurement of the particle size distribution in the aerosol cloud from an inhaler can be completed within a few minutes; computing of the results is within seconds. A very special application is the performance of time-sliced measurements, which makes it possible to follow the size distribution of the cloud as function of the inhalation time or to assess the total emission time of the inhaler. All parts of the adapter are constructed of stainless steel. They can be earthed against unwanted electrostatic effects. During measurements, the room temperature and relative humidity are automatically recorded.

3. Materials and methods

For all experiments, the first generation adapter (INHALER 2000) was used in combination with a HELOS BF/MAGIC, software version 4.1.2, and a 50 or 100 mm lens (Sympatec GmbH, Goslar Germany). All calculations were made on the basis of the Fraunhofer theory.

3.1. Nebulizers

Nebulizer experiments were conducted without pre-separator and fine particle collector, but there was a washing bottle in between the adapter and the vacuum control unit to collect the fine droplets after laser diffraction sizing. Flow rates through the devices were measured with the calibrated venturi meter; no counter flow through the side cylinders of the adapter was used. For all experiments, a 100 mm lens was used (measuring range: 0.9–175 μm). Nebulizer cups were filled with amounts of liquid according to the prescriptions given by the manufacturers. Also recommended jet flows (pressures) were applied.

A) For the comparative evaluation study with 10% aqueous Tobramycin solution, a constant flow rate of 40 l/min was adjusted through the ten different nebulizers. Droplet size distribution measurements of 10 s each, were performed 10 s; 1.5; 3; 4; 5; 6; 9 and 12 min after the start of nebulization, or stopped earlier in case of dry running of the nebulization cup.

Different front cylinders and different tilting angles were applied.

B) For the single experiment with the PortaNeb Sidestream (MedicAid, Romedic, Meersen, The Netherlands), measuring time was 5 s. Measurement was repeated every 25 s until the device, filled with demineralized water, ran dry after approximately 6 min, as could be monitored with the optical concentration of the aerosol cloud.

3.2. Marketed dry powder inhaler

For experiments with a Pulmicort 200 Turbuhaler (AstraZeneca, Sweden), a fine particle collector of the impinger type was connected to the central adapter housing, but the pre-separator was not used, because this type of dpi contains spherical pellets with micronized particles only. Comparative measurements (with a 100 mm lens) at two different flow rates were performed. Five inhalations at 30 l/min and three inhalations at 60 l/min were averaged and compared with the size distribution of the primary budesonide particles from the Turbuhaler obtained with RODOS (Sympatec, Germany) dispersion at 4 bar (mean of 3 series). Start and stop of the measurements was triggered on a detector signal of 0.2% on channel 30 (corresponding with fine particles < 0.9 μm in combination with a 100 mm lens). At 60 l/min, a minor (not recorded) counter flow through the side tubes was applied in order to keep the windows completely free of particles. To investigate the effect of this counter flow on the size distribution of the aerosol cloud, measurements were also conducted without counter flow, as well as with 45 and 90 l/min counter flow through the side cylinders (additional to the 60 l/min through the Turbuhaler). The counter flow was equally divided between both cylinders. Data given are the mean of two inhalation series per condition.

3.3. Special test inhalers with carrier retainment

Fig. 5 shows the basic concept of a test inhaler designed for formulation studies on adhesive mixtures. The concept has a disk shaped circulation chamber as disintegration principle for the

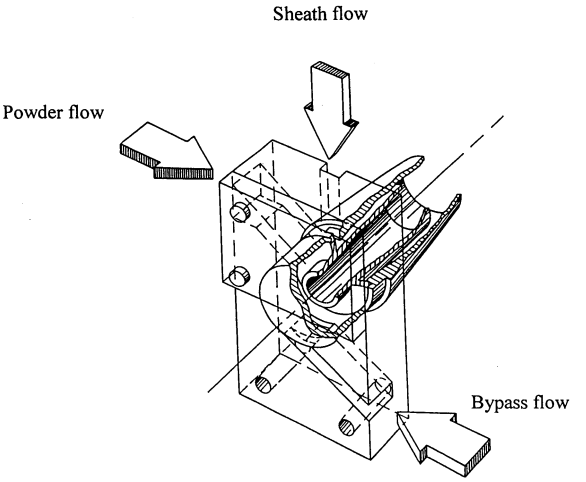


Fig. 5. Test inhaler with circulation chamber (air classifier) for powder disintegration and carrier retainment.

powder formulation, which also acts as an air classifier. A measured quantity of powder, comprising one single dose, enters the chamber through a tangential powder channel (powder flow). Bypass flow from a second channel, which also ends as a tangent to the cylindrical wall of the circulation chamber, contributes to a stable tangential flow pattern inside the chamber. During inhalation, the powder circulates by the action of the centrifugal force, unless particles have become so small (by disintegration), that they can be entrained by the inspiratory air and be discharged through the mouthpiece tube. The circulation chamber has a relatively large cylindrical inner wall. The presence of some large crystals in the formulation is required to keep chamber pollution within acceptable limits. These so-called 'sweeper crystals' remove adhering fine particles from this wall while they circulate inside the chamber. They do not noticeably contribute to the disintegration process, as can be concluded from comparative experiments with and without sweeper particles. The test inhaler acts as a pre separator for large particles when it is used in combination with the inhaler adapter. In the range of flow rates between 30 and 60 l/min, only particles smaller than 15–20 μm are discharged (density is 1.5 g/cm^3). Therefore, experiments with this test inhaler concept

have been performed without the pre-separator shown in Figs. 4 and 1B. The test inhaler itself has been used without a dose measuring principle. Small pre-weighed powder quantities were inserted into the channel for powder flow by spatula before the pre-set flow rate through the test inhaler was opened. Start (and stop) of the particle size distribution measurement was initiated upon reaching a detector signal of 0.2% (or 0.5%, dependent on the application) on channel 30. All data given are the mean of five or six inhalations.

In one application, the test inhaler has been used for development of colistin dry powder formulations. The presented mixture contained 83.3% colistin sulfate, in a size distribution between approximately 0.1 and 80 μm, and 16.7% crystalline alpha lactose monohydrate, in a size fraction of 106–150 μm obtained by air jet sieving. The size distributions of the aerosol clouds from the test inhaler at 60 l/min for six doses of 12 mg have been analysed (with a 100 mm lens) while using the adapter in combination with a washing bottle. The data have been compared with (a) the primary size distribution of the colistin sulfate obtained from RODOS dispersion at 4 bar and (b) the size distribution of the cloud from the Pharmachemie Cyclohaler (Pharbita, The Netherlands) at the same flow rate of 60 l/min. For the test with the Cyclohaler, hard gelatin capsules (no. 3) were filled with 10 mg of the pure drug and the capsules were sealed before use to prevent sliding of the cap over the body during perforation inside the inhaler. There was no lactose in the formulation for the Cyclohaler, because (a) no sweeper function is required for this inhaler device and (b) larger particles were found to block the discharge holes in the capsule.

In another application of the test inhaler, a mixture of two different marketed lactose brands was used as carrier for an adhesive mixture with 1% budesonide ($X_{50} = 1.03$ and $X_{99} = 3.95$ μm for the drug obtained with RODOS dispersion at 5 bar). The lactose mixture contained 85% (w/w) of Pharmatose 325M and 15% Pharmatose 150M (both: DMV International, The Netherlands). Both qualities of lactose are currently used as carrier for inhalation and were selected to obtain a carrier mixture with a substantial amount of fine particles in the size range of the drug (5.0% < 3.6 μm from RODOS dispersion at 5 bar). Mixing time of the carrier blend with budesonide was 10 min in a Turbula T2C tumbler mixer (W.A. Bachofen, Basel, Switzerland) at 90 rpm (batch size 25 g in a 160 ml stainless steel container). Five inhalations with 25 mg of the carrier blend from the test inhaler were performed at 30, 40 and 50 l/min respectively, as reference measurements. The mixture with 1% budesonide was then inhaled according to the same procedures. The differences between (mean) reference measurements and corresponding (mean) drug measurements (50 mm lens) were calculated and expressed as size distribution curves for the drug. For this application, a minor counter flow through the side tubes was applied.

4. Results and discussion

Fig. 6 presents the results from comparative nebulizer testing with a 10% aqueous tobramycin solution. Only minor fluctuations in time for the droplet size distribution per nebulizer were observed and differences between three duplicate series with the same device were negligible. Therefore, all data per nebulizer have been averaged, excluding the data obtained during dry running.

The volume median diameter (X_{50}-values) of the aerosol clouds from different devices vary between 1.25 and 3.25 μm at the inspiratory flow rate of 40 l/min. In general, the span of the size distribution (X_{10} to X_{90}) increases with the median droplet size from 0.63 to 2.31 μm for the MicroCirrus to 1.49–7.88 μm for the DeVilbiss PA with Sidestream. Fig. 7A shows for the PortaNeb with Sidestream that the droplet size distribution, expressed as X_{10}, X_{50} and X_{90}-values, is very constant during nebulization, until the device begins to run dry, which can be observed from a sudden decrease in the optical concentration of the aerosol cloud (Fig. 7B). Shortly before the nebulization cup is empty, large droplets may be discharged as a consequence of spatter (discontinuous flow from the two fluid nozzle and inadequate large droplet capture by the baffle).

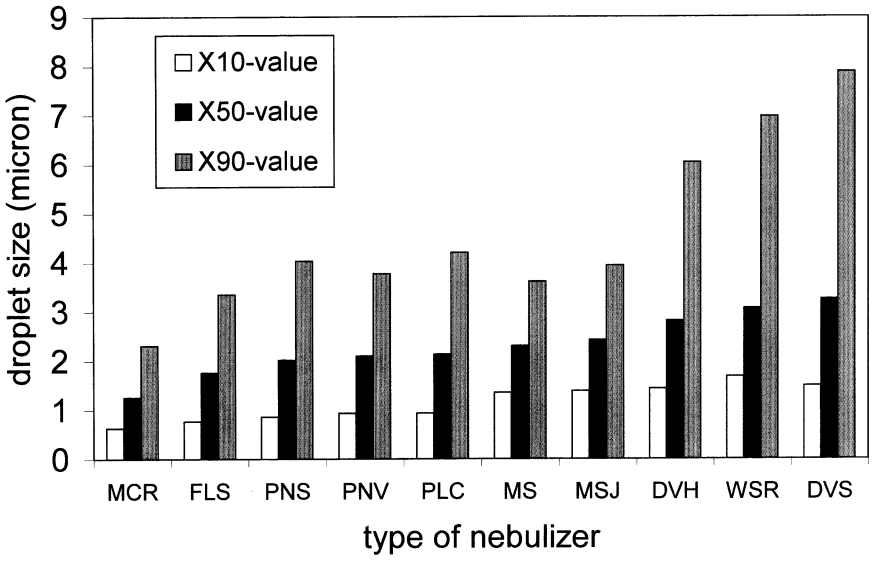


Fig. 6. Mean droplet size distribution, expressed as X_{10}, X_{50} and X_{90}-values, from marketed jet and ultrasonic nebulizers MicroCirrus (MCR), Freeway Lite with Sidestream (FLS), PortaNeb with Sidestream (PNS), PortaNeb with Ventstream (PNV), Pari LC Plus (PLC), Medix Sonic 2000 (MS), Medasonic System Jr. (MSJ), DeVilbiss Pulmo-Aide with Hudson T Updraft (DVH), Wisto Senior (WSR) and DeVilbiss Pulmo-Aide with Sidestream (DVS), for a 10% aqueous tobramycin solution. All nebulizers were used under the conditions as recommended by the manufacturers.

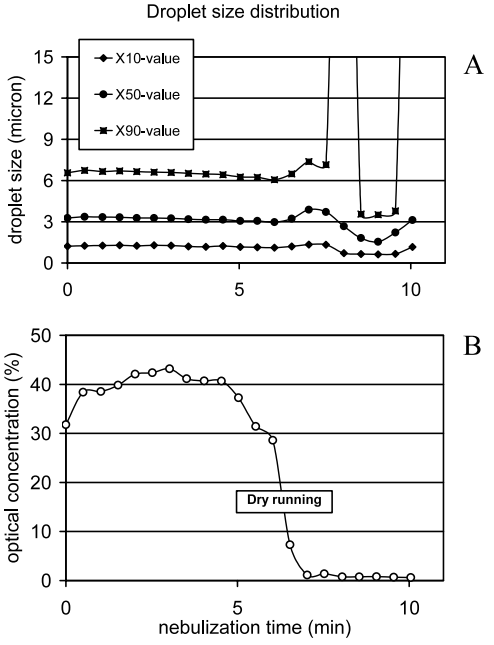


Fig. 7. (A) Droplet size distribution, expressed as X_{10}, X_{50} and X_{90}-values, as function of the nebulization time from the PortaNeb with Sidestream for demineralized water. (B) Corresponding optical concentration of the aerosol cloud as function of the nebulization time.

In Fig. 8, the size distributions of the aerosol cloud from the Pulmicort 200 Turbuhaler for two different flow rates are presented, in comparison with the size distribution of the primary drug particles from RODOS dispersion. The curves show that the disintegration efficiency of the Turbuhaler strongly improves with increasing flow rate. At 30 l/min, the volume median diameter (vmd) is still 5.52 μm (spread is 5.15–5.90 μm), versus 2.53 μm (spread: 2.16–2.76 μm) at 60 l/min. The difference with the vmd of the primary drug particles (1.61 μm with a spread from 1.58 to 1.62 μm), proves that mainly small agglomerates (instead of primary drug particles) are released from the inhaler and that the average number of entities per agglomerate decreases with increasing flow rate. The value of lda for dpi testing is therefore, to assess the disintegration efficiency of the device (from comparative measurements) as function of flow rate, inhaler design or type of powder formulation. This can serve development and optimization of devices and formulations, as well as quality control. Fig. 9 presents the size distributions of the aerosol clouds

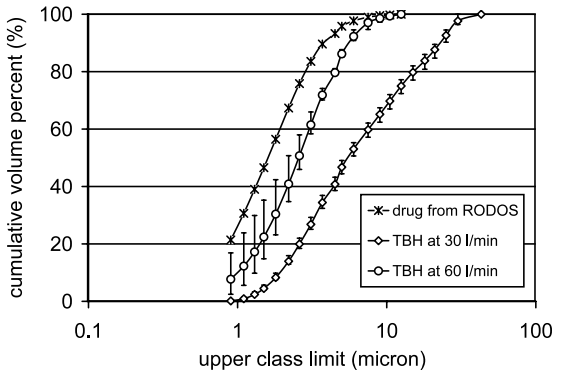


Fig. 8. Size distribution of the aerosol cloud from the Pulmicort 200 Turbuhaler as function of the flow rate (30 and 60 l/min). Bars indicate the spread (maximal and minimal values) between the individual inhalations. The curve marked with asterisks represents the primary particle size distribution of the drug obtained from RODOS dispersion at 4 bar.

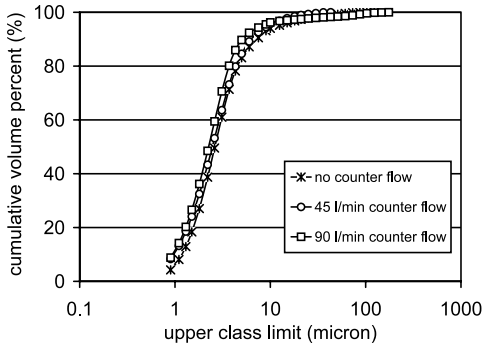


Fig. 9. The effect of the amount of counter flow on the size distribution of the aerosol cloud from the Pulmicort 200 Turbuhaler at 60 l/min.

from the Turbuhaler (at 60 l/min) obtained with different amounts of counter flow. The differences between the mean values of the different series is of the same order of magnitude as that for the individual results within each of the series. So, the effect of counter flow (up to 90 l/min) is negligible compared to the effect of inspiratory flow rate through the inhaler.

Fig. 10 shows the mean size distribution curves of the colistin aerosols from the special test inhaler (with carrier retainment) and the Cyclohaler. The spread of the individual inhalations (minimal and maximal values) is indicated with bars. The volume median diameter of the aerosol cloud

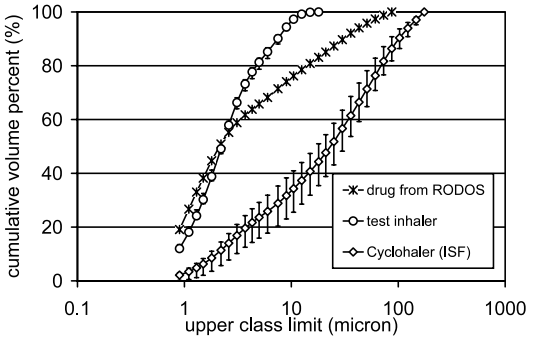


Fig. 10. Size distribution curves of colistin sulfate at 60 l/min from a special test inhaler with carrier retainment and the marketed Cyclohaler (capsule dpi) for formulations with and without 16.7% of a lactose fraction 106–150 μm, respectively. Bars indicate the spread (maximal and minimal values) between the individual inhalations. The curve marked with asterisks is for the primary drug particle size distribution from RODOS dispersion (4 bar).

from the Cyclohaler (24.33 μm) is much larger than that of the primary colistin particles (2.14 μm), which are quite cohesive and difficult to disintegrate. In contrast, the vmd of the cloud from the test inhaler is only 2.24 μm with a spread between 2.14 and 2.32 μm. The X_{100}-value for the aerosol cloud from the test inhaler is approximately 16.5 μm, which is in agreement with the cut-off diameter between 15 and 20 μm for this test inhaler at 60 l/min. This is much lower than the X_{100}-value for the used colistin fraction (80 μm), meaning that also large colistin particles have been retained by the test inhaler.

The results from the carrier mixture with 1% budesonide are depicted in Fig. 11. In spite of the emission of all lactose carrier particles that are smaller than the cut-off diameter of the test inhaler, and even a few particles larger than this cut-off value, highly indicative size distributions for the drug have been obtained. The computed mean vmd of the released drug fraction decreases from 5.75 μm at 30 l/min to 1.82 μm at 40 l/min, and further to 1.53 μm at 50 l/min (versus 1.03 μm for the drug from RODOS dispersion). The results show that powder disintegration with the test inhaler for this budesonide formulation is nearly complete at 60 l/min. But at 30 l/min, small drug agglomerates are released. This is confirmed by cascade impactor data obtained with the same

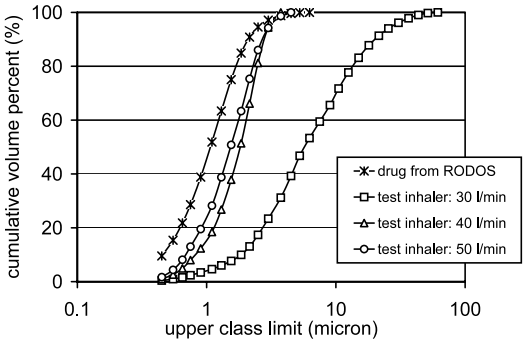


Fig. 11. Computed mean particle size distribution curves for budesonide from an adhesive mixture with 85% (w/w) Pharmatose 325M and 15% Pharmatose 150M, using the special test inhaler with carrier retainment (as pre separator) at 30, 40 and 50 l/min. The curve marked with asterisks is for the primary drug particle size distribution from RODOS dispersion (5 bar).

formulation and test inhaler. The third stage of the impactor used for the experiments, has a theoretical cut-off diameter of 6.74 μm for budesonide at 30 l/min. At this flow rate, 27.2% of the real dose is deposited on stage four. This equals 58.2 mass percent of the emitted dose (carrier with residual drug is retained by the test inhaler). In comparison, from the cumulative distribution curve of the aerosol cloud obtained with laser diffraction analysis, a volume percent of 56.3 for particles smaller than 6.47 μm can be derived. The good agreement in results proves that the subtraction method (correction of the drug measurement for the reference measurement with pure carrier) can be applied successfully for adhesive mixtures. Even if they contain amounts of active substance that are lower than the amounts of fine lactose particles in the carrier. A prerequisite is that the larger carrier particles are retained, which can not only be achieved by the special test inhaler used for the experiments, but also with the pre-separator.

Particular relevant for inhaler testing are the whole (cumulative) size distribution curves obtained with lda, comprising fourteen different size classes for the fine particle fraction (< 5.25 μm for the 50 mm lens). The significance of this high number of size classes for comparative evaluation is much greater than that of measuring geometric, rather than aerodynamic diameters, with laser diffraction. Especially, when also the fine particle mass fraction, to which this size distribution refers, from analysis of the fine particle collector is known. This enables dividing of the fine particle mass fraction into the size classes that are relevant to deposition in the human respiratory tract (assuming that particle density is independent of particle size and thus, that the volume distribution as function of the diameter equals the mass distribution). Dividing would have to be in size classes that are able to enter different regions of the respiratory tract and exhibit different deposition mechanisms in these regions. This can never be achieved with most currently used (cascade) impactors, simply because they have insufficient size classes (one to three) within the fine particle fraction (generally the fraction < 5–10 μm at 60 l/min) as has been discussed previously (de Boer et al., 2002).

5. Conclusions

The presented selection of early data obtained with the newly developed inhaler adapter (INHALER 2000) shows that laser diffraction can be a valuable technique for comparative evaluation of nebulizers and dry powder inhalers. The adapter facilitates complete control of relevant conditions, such as the inspiratory flow parameters, whereas the measuring principle operates widely independent of these conditions. This, in contrast with cascade impactor analysis. In addition, the adjustable ranges of the important inspiratory flow parameters (e.g. PIF and FIR and inhalation time) are much wider, whereas time-sliced measurements make it possible to follow the size distribution of the emitted aerosol particles as function of the inhalation time or to measure total emission time of an aerosol generator. Special (additional) parts, including the discussed pre-separator and fine particle collector, expand its application towards testing of dpis, even when these contain adhesive mixtures with relatively coarse carrier crystals. Mass fractions of the emitted fine particle dose can be measured, for which a much greater number of classes is available than can be obtained with currently used cascade impactors. For nebulizers and mdis, expression of the measured laser

diffraction diameters into aerodynamic diameters according to the definition is mostly quite well possible, if necessary. Considering the many disadvantages of cia, it may be expected that lda will become a widely accepted alternative for testing of these types of aerosol generators. For dpis, accurate data interpretation requires somewhat more insight and understanding of the working principle of both this type of inhalation system and the principle of laser diffraction. But then, lda can also be a valuable tool for development and quality control of dpis. Not only because laser diffraction is highly reproducible and sensitive, as a consequence of which the results from single inhalations can be studied. But more particularly because the technique is very fast, compared with cascade impactor analysis. The adapter presented and discussed in this paper is only a first generation device. Further developments and improvements will follow, especially regarding coarse particle pre-separation, fine particle collection and flow curve generation through the adapter. In addition, laser diffraction and adapter evaluation programs will be started and 'user-specific systems' might be developed for special applications.

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