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Research paper

Characterisation of solution-based pressurised metered-dose inhaler aerosols with an optical particle counter

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ABSTRACT

The White Light Aerosol Spectrometer (welas®) is an alternative method to multistage cascade impaction in the analysis of particle-size distribution (PSD) that allows measurements in high concentrations by single particle measurement. Correspondence of the PSD measured by the welas® system in combination with a new aerosol sampling system has been discussed before for aqueous aerosols from nebulisers [M. Kuhli, M. Weiss, H. Steckel, A sampling and dilution system for droplet aerosols from medical nebulisers developed for use with an optical particle counter, Journal of Aerosol Science 40 (2009) 523-533]. For aerosols from solution-based pressurised metered-dose inhalers (pMDI), both the apparent density and the dynamic shape factor of the dry solid particles come into account for correlation of aerodynamic to scattered light equivalent diameter. The aim of this study was to enable welas® measurements for pMDI aerosols. Equal particle drying properties in cascade impaction (Next Generation Impactor, NGI) and the aerosol sampling system for the welas® should be assured. Therefore, an additional, optionally preheated, extension device was included to modify the aerosol sampling system. The PSD measured with the aerosol sampling system that allowed most complete particle drying was compared to the PSD measured by NGI. The introduction of an empiric calibration allows correlation of NGI and welas® measurements for the investigated solution-based pMDIs.

1. Introduction

In the development as well as in the quality control of formulations in pressurised metered-dose inhalers (pMDIs), the particle-size distribution (PSD) as well as the amount of drug exiting the device is of significant importance. In solution-based pMDIs without non-volatile excipients, the residual particles are usually amorphous spheres [1].

The welas® system (White Light Aerosol Spectrometer, Palas® GmbH) allows the determination of PSD and particle quantity of an aerosol [2]. This measuring system features single particle measurements by detection of scattered light pulses under an angle of 90° leading to an unambiguous calibration curve. High concentrations are achieved by an optical limitation of a small measuring volume which is lit homogeneously by white light. The single particles moving through this measuring volume cause scattered light pulses of certain intensities which are detected under an angle of 90°. The interpretation of the intensity of these pulses is based on the Mie theory as the measurement relies on spherical particles and not on particle collectives. In contrast to other methods, the number of scattered light pulses measured per time unit determines the particle quantity and, therefore, the concentration. This results in a quantitative determination and sizing performed at the same time without interfering each other. Due to the T-aperture-technique, it is possible to measure particle size and quantity in high concentrations without border zone and coincidence error. Optical aerosol spectrometers are described in the VDI guideline 3867 part 1 and 4 as well as in ISO/FDIS 21501-1. Requirements for an aerosol sampling system for an optical particle counter have been discussed before [3].

Correspondence of the PSD measured by the welas® system to those measured by laser diffraction (Helos, Sympatec GmbH, Germany) and multistage cascade impaction (Next Generation Impactor, NGI, MSP Corp., MN, USA) as well as determination of a mass correlation factor between optically and chemically determined nebulised aerosol amount have been discussed before for solution [3,4] and nanosuspension [5] based aerosols from different nebulisers and a new aerosol sampling system for the welas®.

Abbreviations: DF, dilution factor; HFA, hydrofluoroalkane; IP, induction port; MFC, mass flow controller; NGI, Next Generation Pharmaceutical Impactor; Ph. Eur., European pharmacopoeia; pMDI, pressurised metered-dose inhaler; PSD, particle-size distribution; SEM, scanning electron microscopy.

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In this study, the aerosol sampling system for aqueous aerosols from nebulisers is transferred to the measurement of aerosols from solution-based pMDIs. The pharmacopoeial cascade impaction method results in the measurement of an aerodynamic diameter whereas the welas® system measures scattered light equivalent diameters. The aim of this study was to establish a calibration curve for a solution-based pMDI to allow the measurement of aerodynamic diameters with the welas® system and to test its applicability to other solution-based pMDI products containing other active ingredients. The developed calibration curve is to allow time-resolved measurements of scattered light equivalent diameters that correspond well to aerodynamic diameters. Time-resolved measurements with the welas® digital system permit insight into aerosol PSD and concentration changes over time and spray duration of single doses that cannot be obtained by cascade impaction.

2. Materials and methods

2.1. Aerosols in the study

Two solution-based pressurised metered-dose inhalers (pMDI) were included in this study: Junik® (Astellas Pharma GmbH, Munich, Germany; batch number FIJ053D) and Budes® N 0.2 mg/dose (Hexal AG, Holzkirchen, Germany; batch number YR7044).

Junik® pMDI contains 100 μg beclometasone dipropionate as active ingredient. A single dose of 50 μL solution also contains HFA134a and 4 μL ethanol. This corresponds to an ethanol content of the solution of 8% (V/V). At 20 °C, the densities of HFA134a and ethanol are 1.2 g/cm^3 and 0.791 g/cm^3, respectively. This leads to an ethanol concentration of approximately 5.5% (m/m) of the formulation and 0.2% (m/V) residual solid after droplet drying. Fig. 1 shows SEM pictures of single dried porous particles from a Junik pMDI. Image analysis of black/white-images of the SEM pictures was performed using Olympus Analysis auto software (Olympus Life and Material Science Europa GmbH, Hamburg, Germany). The shape factor resulting from image analysis is defined as ratio of the circumference of an area equivalent particle to the particle's circumference. The aspect ratio is defined as ratio of particle height to smallest width, the convexity as ratio of the particle area to area of a convex particle surrounding.

Budes® N 0.2 mg/dose pMDI contains budesonide as active ingredient. A single dose of 75.8 mg contains HFA 134a, (3-sn-phosphatidyl)-choline and 11.4 mg ethanol. This corresponds to an ethanol concentration of approximately 15% (m/m) of the formulation and 0.26% (m/m) residual solid after droplet drying.

2.2. Aerosol sampling system for the welas®

The aerosol sampling system for the welas® digital system (Fig. 2) includes the induction port (IP) for cascade impaction of the European Pharmacopoeia (Ph. Eur.). A variable air flow x was transmitted isokinetically into the dilution unit, the remaining necessary air to achieve an aerosol sampling rate of 30 Std L/min was drawn by an extra pump. The variable air flow was diluted to 4.77 Std L/min in the dilution unit and measured by a welas® 2100 sensor. A mass flow controller (MFC) with pressurised air was used to dilute the sample flow in dilution unit. The dilution factor (DF) is defined as ratio of aerosol sampling flow rate (30 Std L/min) to variable air flow x that is sampled into the dilution unit. In order to obtain dilution factors of 31, 61 and 120, mass flow controller settings of 3.86, 4.34 and 4.58 Std L/min were employed. All experiments were performed in triplicate. PSD calculation from the welas® system was based on the standard refractive index of latex (1.59 + 0i). In order to allow intensified drying conditions for the aerosol particles in the sampling system, additionally to increased dilution factors, tube extensions were included in the measuring setup. This study also includes a 34 cm extension to be built in between the Ph. Eur. IP (induction port) and the rest of the sampling system. This extension was preheated to 85 °C for 30 min prior to some experiments ("heated extension").

2.3. Reference method: multistage cascade impaction

NGI measurements were performed at 30 L/min according to the Ph. Eur. method [6]. An external filter was employed inorder to collect very fine particles. The testing was performed without preseparator at room temperature. Stage coating was applied to the impactor stages prior to measurement.

The samples were analysed by HPLC using the same method for budesonide and beclometasone dipropionate (column: RP18 LiChroCart® 125-4, LiChrospher® 100, Merck KGaA, Darmstadt, Germany; mobile phase: 75% (V/V) methanol, 25% (V/V) water, detection at 248 nm).

2.4. Calibration for welas® system

The pharmacopoeial cascade impaction method results in the measurement of an aerodynamic diameter whereas the welas® system measures scattered light equivalent diameters.

$$d_{ae} = d_E * \sqrt{\frac{\rho_P}{\chi}} \quad (1)$$

Eq. (1) shows the correlation of aerodynamic diameter d_{ae} to equivalent diameter d_E via density (ρ_P, divided by unit density) and dynamic shape factor (χ) of the particles. The correlations of the measured PSDs were based on the Mie theory for the laser diffraction experiments. The complex refractive index of water (1.33 + 0i) was used for calculations based on the Mie theory as described by Mitchell et al. [7] for these aqueous, transparent and colourless pharmaceutical aerosols. For unit density spheres like aqueous droplets from pharmaceutical nebulisers, the aerody-

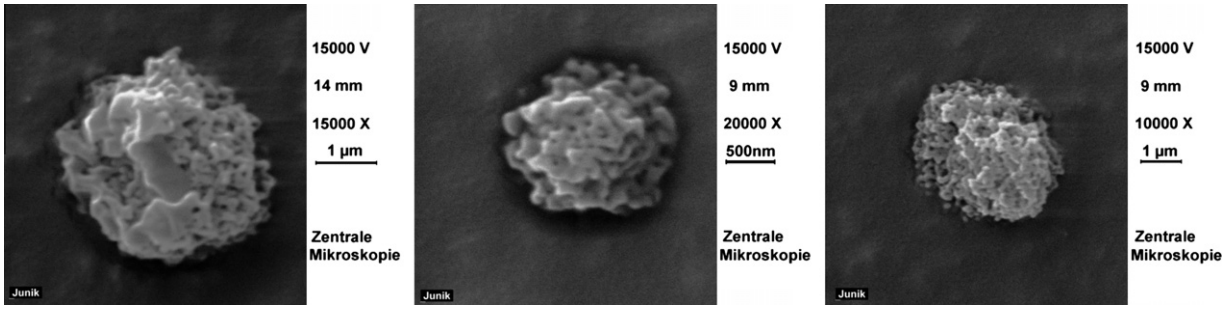

Fig. 1. SEM pictures of single particles from Junik® pMDI.

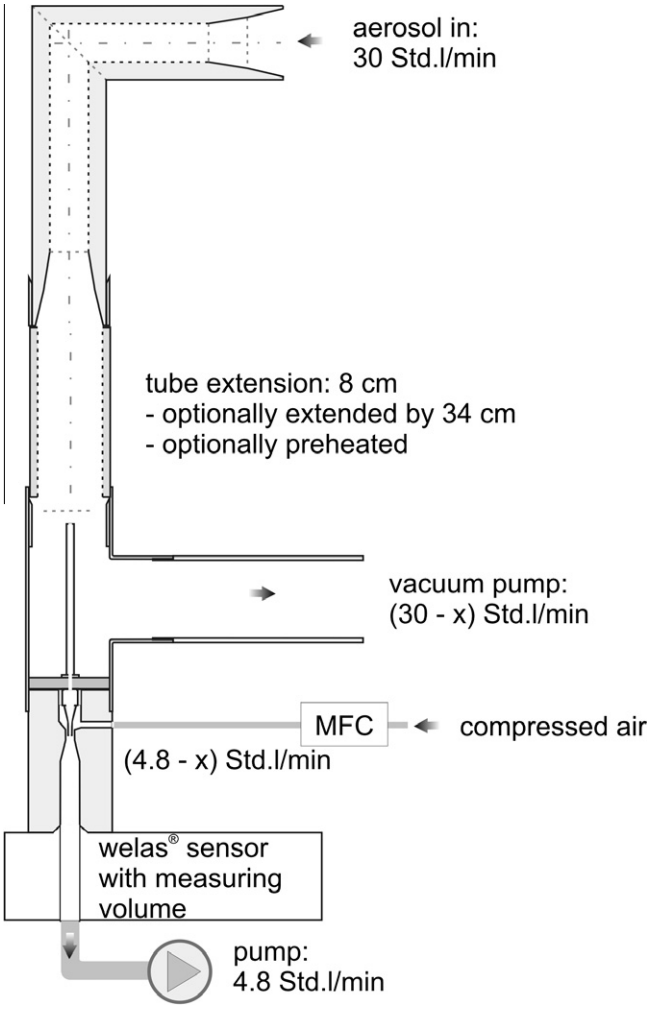

Fig. 2. Schematic measuring setup for welas® digital system.

namic diameter equals the scattered light equivalent diameter. However, aerosols from solution-based pMDIs are solid particles after evaporation of the volatile components. Therefore, evaporation of the volatile components has to be assured to the same extent as occurring during NGI measurements in order to compare the resulting PSDs from NGI and welas® measurements. Furthermore, a correction factor to account for the apparent particle density, dynamic shape factor and complex refractive index of the particles has to be determined. Neither of these parameters can be measured directly due to very small amounts of available aerosol material.

Mogalian and Myrdal [8] show incomplete evaporation of ethanol from solution-based pMDIs with different ethanol contents behind a USP induction port for cascade impaction by use of ethanol sensitive paper. The induction port described by USP is equal to the one described by Ph. Eur. For a formulation with an ethanol content of 5%, insertion of a 20 cm tube extension is sufficient to obtain dry particles. However, when analysing aerosol from a formulation with 10% ethanol, a 40 cm tube extension between induction port and ethanol sensitive paper does not insure complete particle drying [8]. When performing cascade impaction analysis, larger particles impact prior to smaller ones. The NGI possesses an internal volume of 1245 cm^3 [9]. At a flow rate of 30 L/min, the smallest particles impact 2.5 s after entering the impactor. Additionally, due to the larger surface bending of smaller particles, the vapour pressure is increased in comparison to larger particles [10]. Therefore, a systematic error occurs within cascade impaction of solution-based aerosols from pMDIs: while small particles are most likely impacting in dry state, larger particles impact with residual ethanol content – possibly increasing the measured particle size in comparison with dry large particles.

This systematic error of the established in vitro PSD measurement method of cascade impaction cannot be mimicked by a sampling system for an optical particle counter because particles of all sizes are measured within the same measuring volume. Therefore, the potential "drying time" is equal for any particle. In order to allow comparison of aerodynamic diameter measured by cascade impaction to scattered light equivalent diameter measured by the welas® system, a calibration curve for the welas® digital system based on an empiric correction factor is to be established. This approach is further described in Section 3.1.

3. Results and discussion

3.1. Junik® pMDI

The PSDs of the aerosol emitted from a Junik® pMDI were measured with the welas® digital system using different measuring setups. Neither the application of a preheated extension nor an increase of the employed dilution factor lead to a change in the measured PSD compared to the measurement at a dilution factor of 31 without preheated extension (Fig. 3a). This leads to the conclusion that no further drying of the particles takes place in the aerosol sampling system when intensified drying conditions are applied to the aerosol from Junik® pMDI. These findings are in contrast to measurements with aqueous aerosols [11]. Junik® pMDI contains HFA 134a and approx. 5.5% (m/m) of ethanol. Therefore, evaporation of the solvent takes place quickly. SEM pictures of the resulting particles are shown in Fig. 1. Image analysis of black/white images of the SEM pictures leads to a shape factor of 0.4 in combination with an aspect ratio of 1.2 and a convexity of 0.9. These data describe the particles on the two-dimensional images as round particulate material with very uneven surface. The particles are very porous spheres that are likely to have an apparent density smaller than 1 g/cm^3. However, measurements of the apparent density and dynamic shape factor of the particles that would be necessary to allow correlation of aerodynamic and scattered light equivalent diameter using Eq. (1) are not possible due to the very small accessible amount of aerosol particles. Furthermore, the complex refractive index of the particles with uneven surface is unknown. PSD based on the Mie theory is calculated using the refractive index of latex (1.59 + 0i). Also, comparison is made to cascade impaction data that includes the systematic error of less complete particle drying of larger particles in comparison with smaller ones. Therefore, an empiric correlation between aerodynamic diameter measured by NGI and scattered light equivalent diameter measured by the welas® digital system was performed for Junik® pMDI following the method described by Binnig et al. [12].

The aerodynamic PSD measured by the NGI method (Fig. 3a) is set as reference PSD for the scattered light equivalent PSD measured by the welas® system (dilution factor 31 without tube extension). A conversion curve between aerodynamic diameter and scattered light equivalent diameter (d_{opt}) is presented in Fig. 4a. The welas® digital system is calibrated using 256 channels of scattered light intensities. Each channel i is dedicated to a specific particle size $d_{opt,i}$ for a specific material. A calibration factor $\frac{d_{ae,i}}{d_{opt,i}}$ is used for each size channel i of the welas® calibration curve. The resulting empiric calibration factors for Eq. (1) are displayed in dependence of the scattered light equivalent diameter in Fig. 4b. Smaller particles seem to have a higher apparent density than

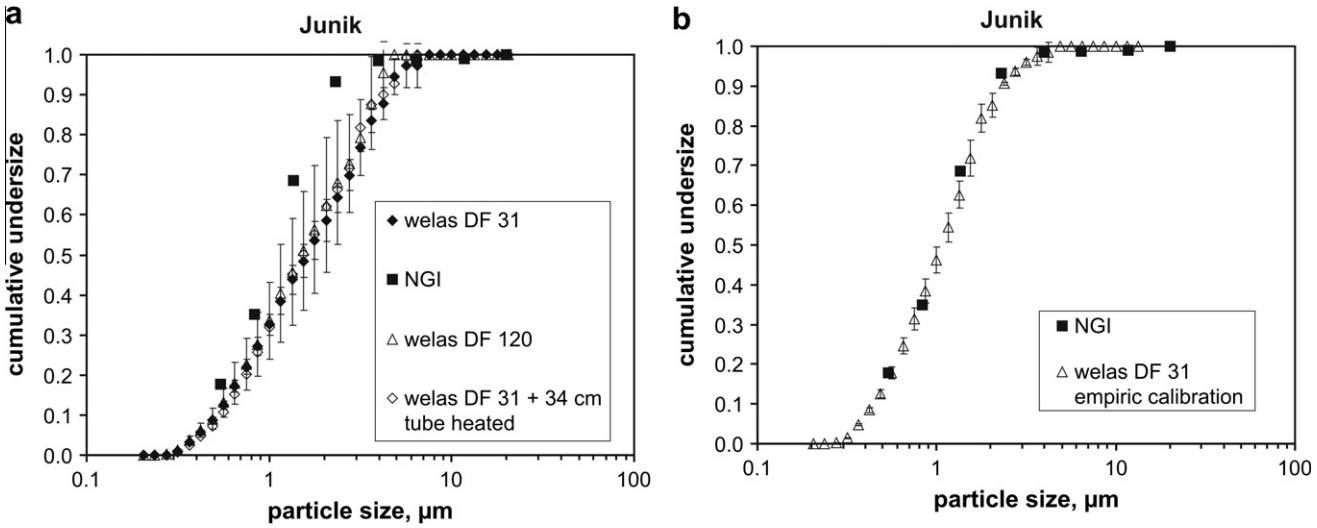

Fig. 3. Junik® pMDI: aerodynamic diameter from NGI measurements vs. scattered light equivalent diameter measured by different setups of the aerosol sampling system for the welas® (a) and employment of developed calibration curve (empiric calibration) for welas® data (b) (DF: dilution factor).

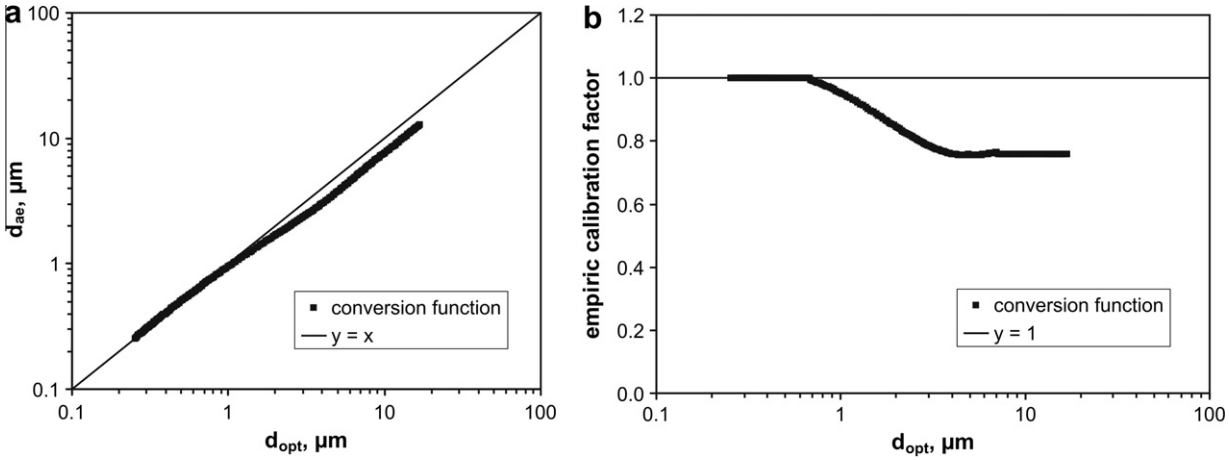

Fig. 4. Correlation of scattered light equivalent (d_{opt}) to aerodynamic diameter (d_{ae}) (a) and resulting empiric calibration factors $\sqrt{\frac{\rho_e}{\chi}}$ for correlation of aerodynamic to scattered light equivalent diameter based on welas® latex calibration for different particle sizes of the aerosol.

larger ones. This can be accounted to different evaporation rates from differently sized particles. However, Binnig et al. [12] also report a strong size dependence of the conversion factor d_{ae}/d_{opt} for inorganic mineral dust materials which cannot be explained by these authors. The resulting aerodynamic PSDs of Junik® pMDI measured by the welas® digital system employing the calibration curve based on the empiric calibration are presented in Fig. 3b. The use of this calibration curve for the welas® digital system in combination with the aerosol sampling system allows the measurement of scattered light equivalent diameters of Junik® pMDI that correspond well to the aerodynamic diameters measured by cascade impaction. This offers the opportunity for timesaving measurements of aerodynamic diameter like PSDs of aerosols from this pMDI.

The employment of the new calibration curve for the welas® digital system also allows time-resolved measurements of scattered light equivalent diameters which are corresponding to aerodynamic diameters. Time-resolved measurements allow insight into aerosol PSD and concentration changes over time as well as spray duration of single doses that cannot be obtained by cascade impaction. Fig. 5a shows an example of a time-resolved single dose measurement at a resolution of 20 ms whereas Fig. 5b shows the same measurement at a resolution of 50 ms. Data presentation at lower resolution leads to a loss of information. However, an adequate resolution has to be chosen depending on the aerosol concentration in order to allow calculation of the associated PSDs based on a sufficient particle collective. Reflection of the PSD changes over the time interval of a single dose leads to the conclusion that the measured PSD is nearly constant within the observed time frame. Due to the construction of the aerosol sampling system, measurement of the PSD is performed with dry particles. The size of these particles is amongst other factors depending on the droplet size leaving the inhaler [13]. However, the presented results of the PSD of dry aerosol particles allow no immediate conclusion on the droplet size leaving the inhaler because other factors which might influence the measured PSD cannot be excluded. Nevertheless, the presented method allows measurement of PSDs equivalent to the aerodynamic diameter measured by the established cascade impaction method [6] on a time-resolved base that cannot be accessed otherwise.

Analysis of the spray duration of 15 Junik® pMDI single doses based on a resolution of 20 ms leads to a mean value of 0.36 s and a standard deviation of 0.02 s.

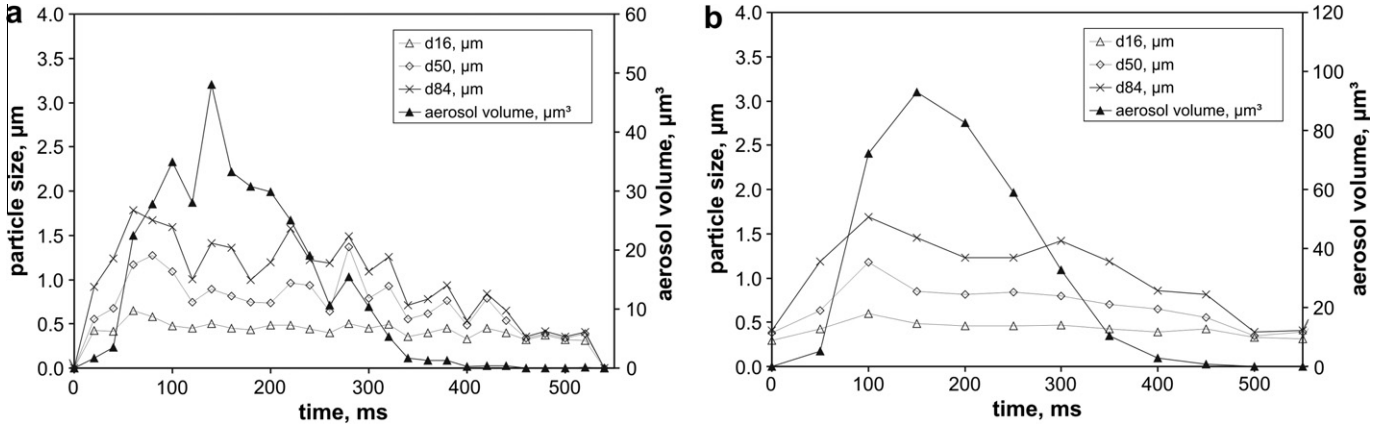

Fig. 5. Junik® pMDI: example of time resolved measurement of a single dose at resolutions of 20 ms (a) and 50 ms (b).

In order to test the transferability of the developed calibration curve to other pMDIs, measurements with a second commercially available pMDI (Budes® N) were undertaken.

3.2. Budes® N pMDI

In comparison to the aerosol emitted from Junik® pMDI, the aerosol emitted from Budes® N pMDI contains a larger concentration of ethanol (15% (m/m) vs. 5.5% (m/m)) and a different active ingredient. Fig. 6a shows the decrease in the measured particle size for the welas® digital system when an extension is included in the sampling system and the dilution factor is increased. Preheating of the extension in combination with a high dilution factor leads to no further decrease in particle size (data not shown). The necessity to intensify the sampling and dilution conditions for the aerosol from Budes® N pMDI in comparison with Junik® pMDI is due to the different ethanol concentration of the formulations. The larger ethanol concentration of Budes® N pMDI leads to less eagerly drying particles. The aerosol sampling system needs to be adapted to the pMDI to be tested in order to allow particle drying prior to PSD measurement in the welas® sensor because the calibration developed for pMDIs is based on the measurement of dry particles.

When the empiric calibration to allow correlation of aerodynamic and scattered light equivalent diameter for Junik® pMDI is applied to the PSD measured with the aerosol sampling system with extension and high dilution factor, a good correlation is found for Budes® N pMDI (Fig. 6b). The high standard deviation in the Budes® N measurements can be partially explained by the high throat deposition of this pMDI and the resulting variability of the aerosol fraction passing the induction port [14]. The use of the calibration curve developed for Junik® pMDI for the welas® digital system in combination with the aerosol sampling system allows the measurement of scattered light equivalent diameters of Budes® N pMDI that correspond well to the aerodynamic diameters measured by cascade impaction. The calibration curve is transferable to measurements with a different pMDI that contains a different ethanol concentration as well as a different active ingredient.

However, in the measurement of PSDs of aerosols from pMDIs care needs to be taken to assure particle drying in the aerosol sampling system for the welas® in order to compare the measured PSD to the one obtained from cascade impaction. Hence, an extension in combination with a high dilution factor needs to be applied when measuring the PSD emitting a pMDI with a high ethanol concentration like Budes® N. In comparison with this, measurement of the PSD of an aerosol exiting a pMDI with a low ethanol concentration like Junik® can be performed without application of an additional tube extension.

4. Conclusion

PSD measurement of aerosols from solution-based pMDIs with the welas® digital system is possible. In order to compare the mea-

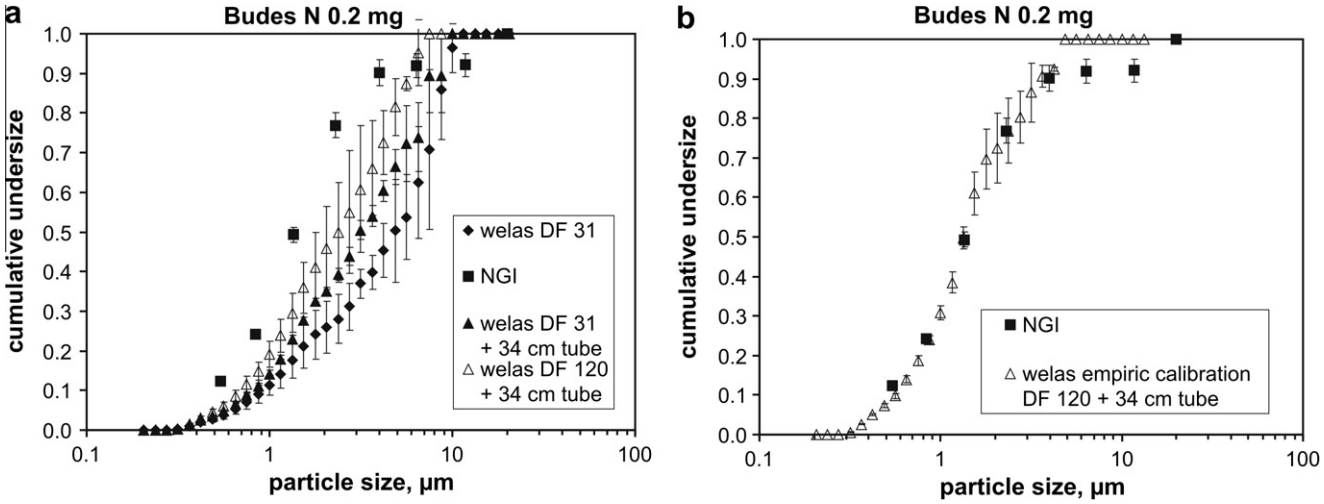

Fig. 6. Budes® N pMDI: aerodynamic diameter from NGI measurements vs. scattered light equivalent diameter measured by different setups of the aerosol sampling system for the welas® (a) and employment of developed calibration curve (empiric calibration) for welas® data (b) (DF: dilution factor).

sured scattered light equivalent diameter to the aerodynamic diameter measured by cascade impaction, an empiric correction is necessary. Cascade impaction as established PSD measurement method includes a systematic error when measuring aerosols from solution-based pMDIs which can lead to bias in the measured PSD. However, cascade impaction is an established in vitro method for the characterisation of pharmaceutical aerosols. Therefore, other PSD measurement methods aim to measure equal PSDs. A welas® calibration curve based on an empiric correction was established for Junik® pMDI and Budes® N pMDI. The employment of the new calibration curve for the welas® digital system allows time-resolved measurements of scattered light equivalent diameters which are corresponding to aerodynamic diameters. Careful selection of the measuring setup for PSDs of aerosols from solution-based pMDIs in order to assure appropriate drying of the particles is necessary. When the correlation of scattered light equivalent diameter measured by the welas® digital system is validated against the aerodynamic diameter measured by the pharmacopoeial cascade impaction method, the welas® system allows fast and accurate measurements in the development and quality control of solution-based pMDIs.

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