

White Light Spectroscopy – a new approach in Aerosol Particle Sizing

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Summary

The welas[®] system (White Light Aerosol Spectrometer, Palas[®] GmbH) is an alternative method to multistage cascade impaction and laser diffraction in the analysis of particle size distributions of pharmaceutical aerosols. It allows to measure particle size and quantity in high concentrations by single particle measurement. The aim of this study was to improve the correlation between particle size distributions (PSD) measured by Next Generation Impactor (MSP Corp., MN, USA), Laser Diffraction (Helos, Sympatec GmbH, Germany) and welas[®].

Comparison of the PSD data derived from welas[®] to those from laser diffraction (LD) using the Mie theory and those from cascade impaction using a cooled impactor with or without humidification of the air led to an improved correlation of PSDs. Whereas humidity conditioning of supply air or cooling of the impactor are necessary in NGI measurements in order to avoid bias due to shrinkage of the particles caused by evaporation, welas[®] measurements can be performed at ambient conditions. This study confirms that the PSD measured by the welas[®] system in combination with the new aerosol sampling system is well comparable to the PSD measured by the two other methods. The new sampling system for the welas[®] allows the use of white light spectroscopy in the particle sizing of aerosols from pharmaceutical nebulisers.

Introduction

In the development of formulations for pulmonary delivery and in the characterisation of different nebulisers, the particle size distribution (PSD) as well as the amount of aerosol exiting a nebuliser are of significant importance. The European Standard for respiratory therapy equipment suggests two separate methods for aerosol characterisation: multistage cascade impaction and laser diffraction measurements. Additionally, a method for the quantification of the aerosol output rate is suggested [1].

The welas[®] system (White Light Aerosol Spectrometer, Palas[®] GmbH) allows the determination of PSD and quantity of an aerosol [2]. This new 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 “true” 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 borderzone and coincidence error.

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 different nebulisers and a new aerosol sampling system for the welas[®] [3, 4, 5]. The correlations of the measured PSDs were based on the Fraunhofer theory for the laser diffraction experiments.

The aim of this study was to improve the correlation between PSD measurements from the welas[®] system, laser diffraction and multistage cascade impaction, respectively, for the Aeroneb Pro nebuliser (Aerogen Ltd., Ireland, an isotonic solution of 0.12% salbutamol sulphate (SBS) was nebulised.). The experimental setup included the option to analyse data from laser diffraction according to the Mie theory. The Mie theory is superior to the Fraunhofer theory in the determination of PSD of transparent aerosols in the small micrometer range [6]. A new humidity conditioning system allowed measurements for welas[®] and NGI at a relative humidity of 99.9% and room temperature. NGI measurements were also performed at decreased temperature as proposed by the EPAG [7].

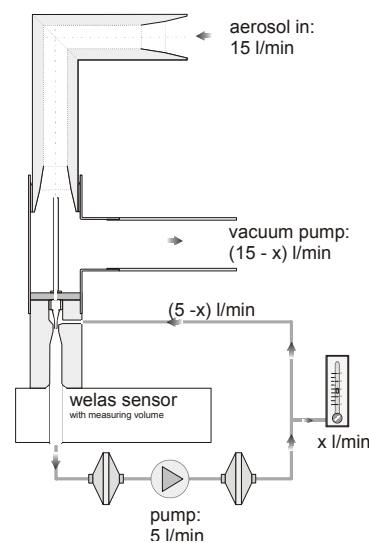


Figure 1: experimental setup for welas[®] system with Ph. Eur. Induction Port

Materials and Methods

1. Aerosol sampling system for the welas[®]

The aerosol sampling system for the welas[®] system includes a variable aerosol inlet. Figure 1 shows the aerosol sampling system with the induction port (IP) for cascade impaction of the European Pharmacopoeia. The aerosol was sampled at a total air flow rate of 15 L/min by the aerosol sampling system. A variable air flow of 0.2 to 1.0 L/min was transmitted isokinetically into the dilution unit, the other 14.0 to 14.8 L/min were drawn by an extra pump. The variable air flow was diluted to 5.0 L/min in the dilution unit and measured by the welas[®] 2070 sensor.

This study included different aerosol inlets: the Ph. Eur. induction port and a bend tube of equivalent volume. Measurements were performed at ambient conditions and at increased relative humidity (99.9%, room temperature) in order to eliminate evaporation effects in particle size measurements.

2. Reference method I: Multistage cascade impaction

NGI measurements were performed at 15 L/min with an external filter and without preseparator. Previous studies led to the conclusion, that evaporation effects have an influence on PSD measurements with the NGI due to the internal volume of the NGI of 1245 mL (including IP) which leads to a residence time of 4.9 seconds before impaction for the smallest particles at 15 L/min. This has been reported by the EPAG [7] who advise to cool the NGI in order to decrease these effects.

NGI measurements were performed both at decreased temperature (storage of NGI in refrigerator for at least 90 minutes prior to measurement) and at room temperature (RT) with air supply at ambient relative humidity (NH). Measurements were also performed at increased relative humidity of the air sucked through the nebuliser (99.9% RH, air at room temperature) with NGI at room temperature as well as with cooled NGI.

The samples were analysed by HPLC using a validated HPLC method (column: RP18 LiChroCart[®] 125-4, LiChrospher[®] 100, Merck KGaA, Darmstadt, Germany; mobile phase: phosphate buffer, methanol, water, 1-heptanesulfonic acid; detection at 280 nm).

3. Reference method II: Laser Diffraction

Particle size distribution was measured by a Sympatec Helos (Sympatec GmbH, Clausthal-Zellerfeld, Germany) using the R2 lens (0.25–87.5 μm) in accordance with the European Standard [1]. PSD data was processed both by the Fraunhofer and the Lorenz-Mie theory (complex refractive index of water for aqueous, colourless, transparent aerosol, $1.33 + 0i$ [8]).

Results and Discussion

Figure 2 shows the comparison of the PSD of the aerosol from the Aeroneb Pro nebuliser measured by NGI, LD and welas[®] as presented before [5]. The PSD measured by NGI was shifted to smaller particles due to evaporation effects that are not accounted for by this method. LD data was processed by the Fraunhofer method which is not suitable for particles in this size range and tends to overestimate fine particle fractions [6].

1. Reference method I: Multistage cascade impaction

Figure 3 shows the PSD measured by NGI. Comparison of the "old" NGI data (RT, ambient humidity (60%)) to the welas[®] data shows the effect of evaporation in the NGI that leads to the measurement of smaller particles. Cooling of the NGI leads to an improved correlation of NGI and welas[®] data. This improvement can also be observed when the air to the nebuliser is humidified to 99.9% relative humidity, at room temperature of air supply and NGI. PSD measured with cooled NGI and ambient condi-

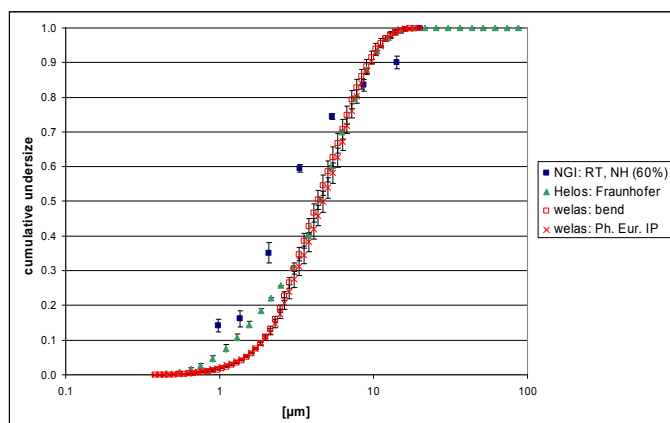


Figure 2: "old" correlation of PSD measured by NGI, Helos and welas[®] [5]

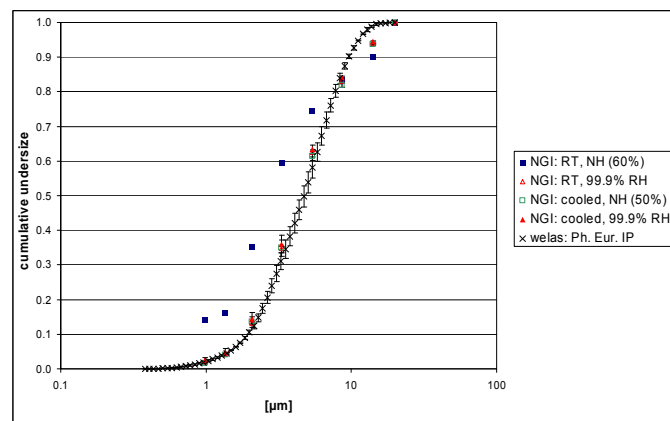


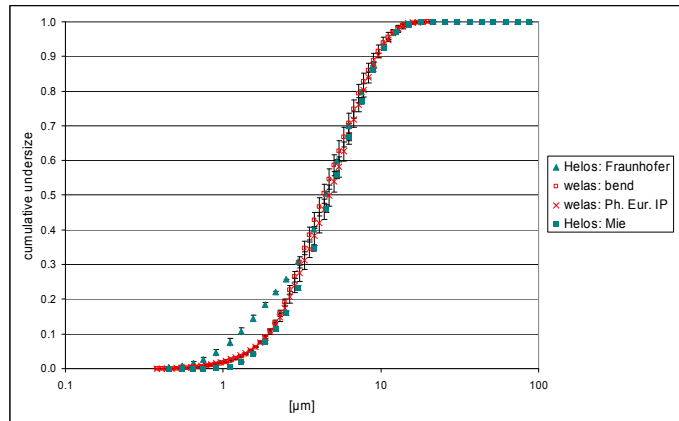
Figure 3: Improved correlation of NGI and welas[®] data

tions for air supply and NGI at room temperature and humidified air supply are identical. No additional change in PSD can be obtained by applying both methods simultaneously: humidification of air supply and cooling of the NGI leads to the same PSD as either of the single methods. Therefore, simultaneous use of both methods leads to no further advantage in PSD measurement.

Either method leads to a PSD similar to that obtained by *welas*[®] measurements. Hence, White Light Aerosol Spectroscopy is a suitable, time saving method to measure PSDs of solution based aerosols from nebulisers.

2. Reference method II: Laser Diffraction

Figure 4 shows the PSDs measured by *welas*[®] and LD. Comparison of the “old” Fraunhofer based data to the *welas*[®] data shows an overestimation of the fine particle fraction by the Fraunhofer method. Analyzing of laser diffraction data by the Lorenz-Mie method using the complex refractive index of water ($1.33 + 0i$ for aqueous, colourless, transparent aerosols [8]) leads to a PSD well comparable to the data from the *welas*[®] system. This supports White Light Spectroscopy as a suitable method in particle size measurement for solution based aerosols from nebulisers.



3. welas[®] measurements with humidified air

Humidification of the air supply leads to minimisation of shrinking of the particles due to evaporation effects in NGI measurements. The residence time of the aerosol particles prior to PSD measurements is shorter for welas[®] than for NGI measurements. Nevertheless, time between leaving the nebuliser and PSD measurement is longer for an individual particle than in open system laser diffraction measurements. Therefore, shrinkage of particles due to evaporation prior to size measurement is possible in welas[®] measurements. In order to quantify this presumable shrinking effect, welas[®] measurements were also performed with humidified air supply (99.9% RH at room temperature) since this procedure led to utilisable results for NGI analysis. Figure 5 shows that PSD measured with humidified air supply does not differ from PSD measured with ambient air supply.

Hence, evaporative effects are negligible when measuring PSDs by the welas[®] system with the aerosol sampling system used in this study.

Conclusion

White Light Aerosol Spectroscopy is an alternative approach in particle size measurements of solution based aerosols from nebulisers. Comparison of the PSD data derived from welas[®] to those from laser diffraction using the Mie theory and those from cascade impaction using a cooled impactor with or without humidification of the air leads to an improved correlation of PSDs (Figure 6). Whereas humidity conditioning of air supply or cooling of the impactor are necessary in NGI measurements in order to avoid bias due to shrinkage of the particles caused by evaporation, welas[®] measurements can be performed at ambient conditions because of the shorter residence time of the particles in the sampling system prior to PSD measurement.

This study confirms that the PSD measured by the welas[®] system in combination with the new aerosol sampling system is well comparable to the PSD measured by the two other methods. The new sampling system for the welas[®] allows the use of white light spectroscopy in the particle sizing of aerosols from pharmaceutical nebulisers.

Figure 4: Improved correlation of Helos and welas[®] data

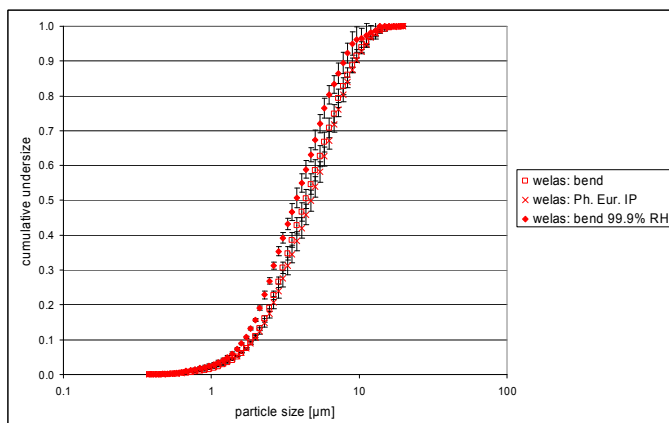


Figure 5: Comparison of ambient conditions and humidified air for PSD from welas[®]

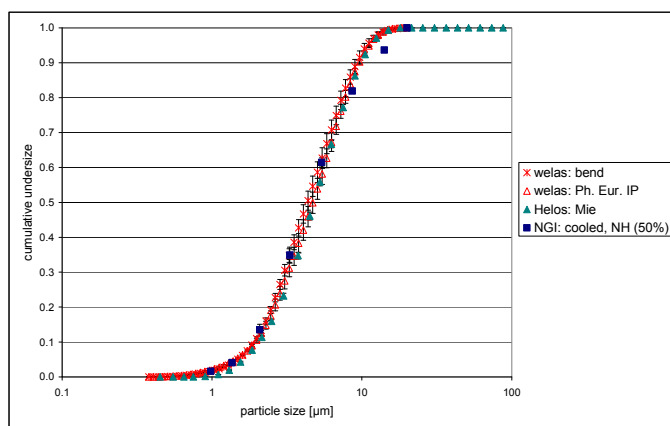


Figure 6: Improved correlation of NGI, Helos and welas[®] data

- [1] European Standard EN 13544-1 (2001): Respiratory therapy equipment – Part 1: Nebulising systems and their components
- [2] L Moelter, P Keßler. (2004) Gefahrstoffe – Reinhaltung der Luft 64(10); 439-447
- [3] M Kuhli, L Moelter, F Munzinger, H Steckel. (2007). Proceedings DPhG joint meeting, Erlangen, Germany
- [4] M Kuhli, L Moelter, F Munzinger, H Steckel. (2007). Proceedings Drug Delivery to the Lungs 18, Edinburgh, UK
- [5] M Kuhli, L Moelter, F Munzinger, H Steckel. (2008). Proceedings 6th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Barcelona, Spain

- [6] R Friehmelt (1999). Aerosol-Messsysteme - Vergleichbarkeit und Kombination ausgewählter online Verfahren.
Dissertation. University of Kaiserslautern, Germany
- [7] E Berg et al. (2007). Proceedings Drug Delivery to the Lungs 18, Edinburgh, UK
- [8] JP Mitchell et al. (2006). J Aerosol Medicine 19; 409-433