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A new approach to characterise pharmaceutical aerosols: Measurement of aerosol from a single dose aqueous inhaler with an optical particle counter

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ABSTRACT

An in-line sampling system with dilution units for aqueous droplet aerosols from single dose inhalers (Berodual Respimat®, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany) for an optical particle counter is described. The device has been designed to interface with a white light aerosol spectrometer (welas® digital 2100, Palas® GmbH, Germany) that allows the time-resolved measurement of highly concentrated aerosols. Performance of the sampling system with regard to the measured particle size distribution (PSD) is compared to Next Generation Impactor (NGI) and to laser diffraction measurements (Sympatec Inhaler and open bench). Optimal settings of the sampling system lead to PSDs that correspond well to those measured by the evaporation minimising NGI approach (15 L/min, cooled) and laser diffraction. The better accuracy of the new dilution unit in presence of an additional aerosol sampling filter in comparison to a previously described aerosol sampling system is shown for different settings of the sampling system. This allows a more precise quantification of the delivered drug amount which is also well correlated to the aerosol volume measured by the welas® system. In addition, using time-resolved welas® measurements provides insight into droplet size, evaporation and size changes of aerosol clouds delivered by liquid inhalers.

1. Introduction

The particle size distribution (PSD) as well as the delivered dose of a pharmaceutical aerosol are of significant importance in the development of formulations for pulmonary delivery and in the quality control of pharmaceutical aerosols. This paper focuses on alternative method for the characterisation of the PSD and mass output of a single dose aqueous solution-based pharmaceutical aerosol (Respimat® Soft Mist™ inhaler, Boehringer Ingelheim, Germany) and the time-resolved characterisation of its single doses. The European Pharmacopoeia describes cascade impaction methods for the characterisation of PSD of aerosols (Ph. Eur, 2008). de Boer et al. (2002) developed a modular aerosol sampling system for laser diffraction to minimise the use of the time consuming cascade impaction. A disadvantage of laser diffraction measurements is, however, the method's inability to determine particle quantity.

Therefore, optical particle counters (OPC) are an interesting alternative to cascade impaction and laser diffraction, due to their accuracy and resolution in obtaining PSDs. A sampling and dilution system for the PSD measurement of droplet aerosols from medical nebulisers for a welas® 2070 system (Palas® GmbH, Karlsruhe, Germany) has been described before for solution-based aerosols (Kuhli et al., 2009a) and suspension aerosols from continuously operating nebulisers with different PSDs of the suspended particles (Kuhli et al., 2009b). The welas® system has been described in the literature before (Moelter, 2006; Moelter and Kessler, 2004). The system has considerable advantages for aerosols in higher concentrations, because the welas® system allows single particle measurements in concentrations higher than 10^5 particles per cm^3 in a particle size range from 0.3 to 40 μm due to its custom-built T-aperture-technique (Moelter, 1999). The welas® calibration curve for this study is based on the refractive index of water because the aerosol consists of an aqueous, transparent and colourless solution (Mitchell et al., 2006). In this study, a new welas® digital 2100 system was used that allows coincidence correction and time-resolved measurements. 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 (Kuhli et al., 2009a).

Pharmaceutical aerosols can be delivered by three types of inhalers: dry powder inhalers, metered dose inhalers and nebulisers. Soft Mist™ inhalers such as the Respimat® device are a specific

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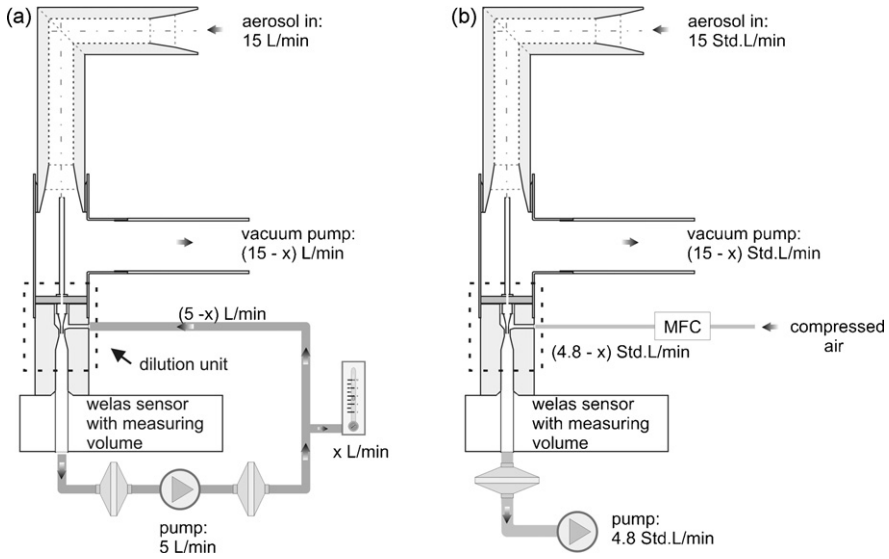

Fig. 1. Aerosol sampling system for welas® with dilution unit I (a) and II (b).

subgroup of aqueous drop inhalers that deliver single spray doses of aqueous solutions without propellant.

The purpose of this study was to adapt the aerosol sampling system for aerosols from continuously operating pharmaceutical nebulisers for the welas® 2070 system described by Kuhli et al. (2009a) to allow measurement of PSD and quantification of aerosol amount delivered by an aqueous solution-based single dose aerosol generator (Respimat® Soft Mist™ inhaler) with a new welas® digital 2100 system. In order to allow a precise quantification of the delivered aerosol amount, a new dilution unit was introduced and accuracy of the dilution system was to be shown in presence of an additional aerosol sampling filter for different settings of the dilution unit and different flow rates. The amount of drug sampled on the aerosol sampling filter behind the welas® sensor was to be correlated to both the aerosol volume measured by the welas® system (with the new dilution unit II) and the amount theoretically to be expected at this point of the measuring setup for different amounts of aerosol administered into the sampling system. The aim of this approach was to allow quantification of the aerosol amount from the Respimat®. Time-resolved measurements were to be undertaken to gain insight into aerosol PSD and concentration changes over time.

2. Materials and methods

2.1. Aerosol in the study: Respimat

Aerosols from Berodual® Respimat® Soft Mist™ inhalers (Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany) were characterised in this study. Respimat® Soft Mist™ inhalers are new generation, propellant-free, multi-dose inhalers that use mechanical energy from a spring to pass a metered volume at pressures around 250 bar through a dedicated nozzle system to generate a slow-moving aerosol of inhalable particles (Hochrainer et al., 2005).

Wachtel and Ziegler (2002) used an Andersen Mark II cascade impactor at a flow rate of 28.3 L/min in order to measure the PSD emitted from a Respimat® Soft Mist™ inhaler. They emphasize the importance of suppressing evaporation by using supply air with nearly 100% relative humidity to show a tight correlation between the PSD determined by laser diffraction and by impaction. Hubrath and Kumb (2008) compared the effect of impactor cooling and supply air conditioning to 100% relative humidity on evaporation prevention and concluded that the resulting PSDs are slightly different, nevertheless either method to be suitable for Andersen Mark II cascade impactor measurements of the Respimat® Soft Mist™ inhaler at 28.3 L/min. According to Ziegler and Wachtel (2005), flow rate influence on the measured PSD is negligible for an induction port-based laser diffraction measurement. The influence of flow rate on PSD for Andersen Mark II cascade impaction was not part of their study but is to be expected.

2.2. Drug assay

Berodual® Respimat® contains ipratropium bromide and fenoterol hydrobromide as active ingredients in an aqueous solution. The quantification of ipratropium bromide in the samples from welas® and NGI measurements was performed using a validated high performance liquid chromatography (HPLC) method with a RP8 column (LiChroCART® 125-4, LiChrospher® 100 CN (5 μm), Merck KGaA, Darmstadt, Germany). Calibration was performed with an external standard in the range of 1–25 μg/mL and the ipratropium bromide concentration of the samples was calculated. The mobile phase (pH 3.2) was composed of water (750 mL), acetonitrile (305 mL) and 1-heptanesulfonic acid (1.5 g). Ipratropium bromide was detected at 220 nm with a retention time of 4.1 min at a flow rate of 1.2 mL/min. Samples were dissolved in water.

2.3. Aerosol sampling systems for a white light aerosol spectrometer (welas®)

2.3.1. Dilution unit I

The aerosol sampling system incorporates an induction port as described for cascade impaction by Ph. Eur (2008), a pump to ensure the desired aerosol sampling flow rate and an internal dilution unit (Fig. 1a). A dilution unit in the system is necessary to avoid coincidence in the single particle measurement. This dilution unit I works with a recirculation of the volume flow of 5.0 L/min of the welas® pump in combination with a rotameter to let a variable air flow *x* of 0.2–1.0 L/min leave the system. From this follows that a variable air flow *x* of 0.2–1.0 L/min was sucked isokinetically into the dilution unit. The variable air flow was diluted to 5.0 L/min in the dilution unit and measured by the welas® 2100 detector. Aerosol sampling