Aerosol Science 40 (2009) 523 – 533

Contents lists available at ScienceDirect

Aerosol Science

journal homepage: www.elsevier.com/locate/jaerosci

A sampling and dilution system for droplet aerosols from medical nebulisers developed for use with an optical particle counter

Maren Kuhli[a], Maximilian Weiss[b], Hartwig Steckel[a,*]

[a] Christian Albrecht University of Kiel, Department of Pharmaceutics and Biopharmaceutics, Gutenbergstr. 76, 24118 Kiel, Germany

[b] Palas® GmbH, Greschbachstr. 3b, 76229 Karlsruhe, Germany

ARTICLE INFO

Article history:
Received 21 November 2008
Received in revised form
17 February 2009
Accepted 18 February 2009

Keywords:
Nebuliser
Cascade impaction
Laser diffraction
Humidity conditioning
Light-scattering aerosol spectrometer

ABSTRACT

An in-line sampling and dilution system for droplet aerosols from medical nebulisers is described. The device has been designed to interface with a white light aerosol spectrometer (welas® 2070, Palas® GmbH, Germany) that allows measurements of highly concentrated aerosols. The performance of the sampling system in terms of the measured particle size distribution (PSD) is compared to EN 13544-1 approved measurement techniques as well as to techniques proposed for the European Pharmacopoeia (2.9.44). The measured PSD compares favourably to the ones measured by a Next Generation Impactor, cooled prior to measurement, and by laser diffraction analysed by the Mie theory. This study included three nebulisers (Pari LC Plus, Aeroneb Pro, Omron MicroAIR). The measuring system presented in this study offers a time saving alternative for the measurement of PSD as well as quantity of aerosols from medical nebulisers that is of interest for quality control in the pharmaceutical industry.

1. Introduction

In the development of formulations for pulmonary delivery and in the characterisation of different nebulisers, the particle size distribution (PSD) of aerosol exiting a nebuliser as well as the delivered dose are of significant importance. Therefore, this paper introduces an alternative method for the measurement of PSDs of pharmaceutical aerosols. The European Standard for respiratory therapy equipment suggests two separate methods for aerosol characterisation: the multistage cascade impactor and laser diffraction for particle sizing and an additional method for testing the aerosol output rate (CEN, 2001). Following the successful development of the Next Generation Impactor (NGI), the extension of the calibration to 15 L/min allowed the use of this impactor in the characterisation of aerosols from nebulisers (Marple et al., 2004). The new monograph 2.9.44 proposed for the European Pharmacopoeia (Ph. Eur.) defines new test methods for assessing delivered dose, delivery rate and PSD. The method for the aerodynamic assessment of nebulised aerosols is based on the NGI (Copley, 2008b). Since cascade impaction is very time consuming, de Boer et al. (2002b) developed a modular aerosol sampling system for laser diffraction. While laser diffraction is less time consuming, it shows the substantial disadvantage of being unable to determine particle quantity.

Optical particle counters (OPC) are an interesting alternative to cascade impaction and laser diffraction, due to their accuracy and resolution in obtaining PSDs. However, exit concentrations from a medical nebuliser are generally too high for direct measurement with an OPC. The challenge is to dilute aqueous aerosol droplets and sample the aerosol into the OPC.

Abbreviations: HPLC, high performance liquid chromatography; NGI, Next Generation Impactor; OPC, optical particle counter; Ph. Eur., European Pharmacopoeia; PSD, particle size distribution.

* Corresponding author. Tel.: +49 431 880 1330; fax: +49 431 880 1352.
E-mail addresses: mkuhli@pharmazie.uni-kiel.de (M. Kuhli), mail@palas.de (M. Weiss), hsteckel@pharmazie.uni-kiel.de (H. Steckel).

0021-8502/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jaerosci.2009.02.007

In the current paper, a new sampling and dilution system for nebuliser aerosols is described. The system is designed for use with a white light aerosol spectrometer (welas®) 2070 optical spectrometer (Palas® GmbH, Karlsruhe, Germany; formerly known as welas® 2100S sensor) which has been described in the literature before (Moelter, 2006; Moelter & Kessler, 2004). This system has considerable advantages for aerosols in higher concentrations, because the welas® 2070 sensor allows single particle measurements in concentrations higher than 10^5 particles per cm^3 in a particle size range of 0.3–40 μm due to its custom T-aperture-technique (Moelter, 1999). The second advantage is the geometry of the aerosol inlet, which greatly reduces interface problems with a dilution system. 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. Optical aerosol spectrometers are described in the VDI guideline 3867 part 1 and 4 as well as in ISO/FDIS 21501-1. In this study, we first describe the sampling and dilution system, followed by a performance comparison with existing, approved techniques.

Pharmaceutical aerosols can be delivered by basically three types of inhalers: metered dose inhalers, dry powder inhalers and nebulisers. In this study, only aerosols from nebulisers are considered. Requirements for an aerosol sampling system for the welas® system are similar to those for an aerosol sampling system for laser diffraction. The modular aerosol sampling system for laser diffraction developed by de Boer et al. (2002b) features a connection of the inhaler to a closed system with a vacuum control unit to ensure the specific flow rate that is necessary for the type of inhaler in order to meet the pharmacopoeial standards (15 L/min for nebulisers). However, there is also a need to dilute the aerosol in order to allow single particle measurement when using an OPC for high concentrated aerosols. Isokinetic sampling into the dilution system is important to consider, both to avoid bias in the measured PSD (Helsper, 1995) and to be able to quantify the aerosol amount based on the dilution factor. Also, minimal particle losses on the inner walls of the measuring system are necessary in order to quantify the aerosol amount.

As the welas® 2070 system is so far limited in its use to the measurement of environmental aerosols or to filter efficiency testing, pharmaceutical aerosol characterisation could be a potential application. This type of aerosol characterisation benefits from the advantages of white light spectroscopy, namely single particle measurements which allow fast quality and quantity control of pharmaceutical aerosols.

The purpose of this study was the development and optimisation of a new sampling system for aerosols from pharmaceutical nebulisers for the welas® 2070 system. PSDs measured with the welas® system at ambient conditions were compared to welas® measurements with humidified air supply, NGI measurements at ambient conditions, humidified air supply and cooled conditions and laser diffraction measurements.

2. Materials and methods

2.1. Nebulisers in the study

The nebulisers presented on the pharmaceutical market employ different principles of aerosol generation. The most established systems are jet and ultrasonic nebulisers (Seemann & Weinstein, 2006).

Three nebulisers were included in this study, a Pari LC Plus nebuliser (Pari GmbH, Munich, Germany) as an example for a jet type nebuliser, an ultrasonic nebuliser (Omron MicroAIR, U22, Omron Medizintechnik Handelsgesellschaft mbH, Mannheim, Germany) and a mesh nebuliser (Aeroneb® Pro, Aerogen Inspirational Medical, Bochum, Germany). All nebulisers were used according to the user instructions as given in the manual of the devices.

2.2. Drug assay

Salbutamol sulphate solutions (0.12% in isotonic solution) were used as model drug for this study. The quantification of samples from welas® and NGI measurements was performed using a validated high performance liquid chromatography (HPLC) method with a RP18 column (LiChroCart® 125-4, LiChrospher® 100, Merck KGaA, Darmstadt, Germany). A mobile phase (pH 3) was composed of phosphate buffer (0.2 mM, 61.5 mL), methanol (400 mL), water (538.5 mL) and 1-heptanesulfonic acid (1.1 g). Salbutamol sulphate was detected at 280 nm after a retention time of 3.5 min at a flow rate of 1.2 mL/min. Calibration was performed with an external standard in the range of 1–25 μg/mL.

2.3. White light aerosol spectrometer (welas®)

2.3.1. Aerosol sampling systems

The aerosol sampling system incorporates a variable inlet, a dilution unit and a pump to ensure aerosol sampling at 15 L/min (Fig. 1). The dilution unit in such a system is necessary to avoid coincidence in the single particle measurements. A variable air flow of 0.2–1.0 L/min was transmitted isokinetically into the dilution unit, the other 14.0–14.8 L/min were drawn by the extra pump. The variable air flow was diluted to 5.0 L/min in the dilution unit and measured by the welas® 2070 detector. Welas® was operated for the particular nebulisation time plus an extra 10 s to ensure the measurement of all the particles that left the nebuliser.

An experimental design was set up to develop an optimal inlet for the aerosol sampling system for the welas®. This experimental design (3^{2-0}, 2 centre points, Statistica 6.0, StatSoft GmbH, Hamburg, Germany) included three different tubing lengths