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The on-line analysis of aerosol-delivered pharmaceuticals via single particle aerosol mass spectrometry

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ABSTRACT

The use of single particle aerosol mass spectrometry (SPAMS) was evaluated for the analysis of inhaled pharmaceuticals to determine the mass distribution of the individual active pharmaceutical ingredients (API) in both single ingredient and combination drug products. SPAMS is an analytical technique where the individual aerodynamic diameters and chemical compositions of many aerosol particles are determined in real-time. The analysis was performed using a Livermore Instruments SPAMS 3.0, which allowed the efficient analysis of aerosol particles with broad size distributions and can acquire data even under a very large particle load. Data similar to what would normally require roughly three days of experimentation and analysis was collected in a five minute period and analyzed automatically. The results were computed to be comparable to those returned by a typical Next Generation Impactor (NGI) particle size distribution experiment.

1. Introduction

Pharmaceutical aerosols are used for the delivery of drugs directly to the human lung for both local and systemic treatment. The fraction of the aerosol that is deposited in different locations of the respiratory tract is a function of the distribution of the aerodynamic size of the particles, the mode of inhalation and the morphology of the respiratory tract (Dolovich, 2000; Martonen et al., 2000). The aerodynamic diameter is the most appropriate measure of aerosol particle size because it correlates most directly to the efficiency of lung delivery and ultimate therapeutic effect (Telko and Hickey, 2005).

Practically all pharmaceutical aerosols are polydisperse systems that contain drug particles distributed across sizes ranging from 0.5 μm up to 10 μm in aerodynamic diameter, depending on the specific formulation. The aerodynamic particle size distribution of a polydisperse aerosol can be described in terms of number of particles, particle volume or particle mass as a function of this aerodynamic diameter. Because physiological and therapeutic effects of active pharmaceutical ingredients (APIs) are most directly related to the mass of the API delivered, the mass versus aerodynamic diameter distribution for the APIs of interest is the most useful value.

The FDA Draft Guidance for Industry on Chemistry Materials and Controls for inhaled products (Draft 13 November, 1998), as well as the respective monographs of the United States and European Pharmacopeias, give methods for aerodynamic particle size distribution analysis of pressurized metered dose inhalers (pMDIs) and dry powder inhalers (DPIs) in terms of the mass of API collected on the various stages of a cascade impactor (FDA, 1998). The advantages of cascade impaction are its direct measurement of aerodynamic diameter while preserving the size-segregated fractions for subsequent determination of API mass (Mitchell and Nagel, 2003). The Next Generation Impactor (NGI, MSP Corporation, http://www.mspcorp.com) is widely considered to be the most convenient and suitable cascade impactor for pMDI and DPI analysis.

NGIs have a number of advantages over previous cascade impactors, such as expedient setup and drug recovery (Marple et al., 2003), but in general suffer from the inefficiencies of any cascade impaction/offline analysis approach. Each NGI analysis requires the disassembly of the impactor and the washing of the impaction plates or cups followed by high-performance liquid chromatography (HPLC) or other suitable analytical method. This results in a large demand on resources in terms of laboratory personnel and solvents, and results are typically returned days

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later only. In addition, it has been observed in combination products that the addition of another API can affect the performance of one or both APIs (Taki et al., 2011; Gordon and Panos, 2010; Traini et al., 2007; Nelson et al., 2003), but the NGI/HPLC technique does not give any information regarding the relationships among the various APIs and excipients in the formulation on the level of the individual particles and, for example, cannot reveal if and what co-associations exist between an API and excipient or between multiple APIs, if there are more than one. That co-association is one postulated reason for a possible increased pharmacological efficacy (Haghi et al., 2013).

An alternative for aerosol characterization is single particle aerosol mass spectrometry (SPAMS), which determines both the aerodynamic diameter and the chemical composition of many individual particles in real-time. SPAMS is descended from other single particle characterization techniques and a brief discussion of its antecedents appears here.

Rapid single-particle mass spectrometry (RSMS) (McKeown et al., 1991; Garson et al., 1995) could determine the chemical composition of each particle at a rate of one per second but only determined the particle size very inaccurately by measuring the light scattering intensity collected by a relative large diameter fiber optic perpendicular to the scattering laser.

In 1994, Prather et al. improved upon the RSMS design using a system that they termed aerosol time-of-flight mass spectrometry (ATOFMS), which was the first analytical technique capable of the in-situ simultaneous characterization of both the chemical composition and aerodynamic diameter of individual aerosol particles in real time (Prather et al., 1994). In 1997 the first portable ATOFMS was constructed (Gard et al., 1997) and commercialized three years later by TSI Corporation (http://www.tsi.com). The system was primarily developed for environmental air sampling and monitoring but its capabilities for characterizing pMDIs aerosols have been demonstrated (Noble and Prather, 1998; New et al., 2008).

Unfortunately, while promising, the limitations the ATOFMS instrumentation limited the effectiveness of the technique as demonstrated by their specific analytical methods. First, the tendency of the ATOFMS light scattering detection system to saturate at particle concentrations common to pMDIs prevented quantitation of the particle concentrations. Second, the ATOFMS instruments were unable to efficiently analyze particles across the therapeutically relevant size range. Thus, in our opinion, while the overall approach of using on-line single particle mass spectrometry was innovative and remains robust, the experiments failed to demonstrate its utility.

Therefore, there was the need for a real time identifier of individual aerosol particles with a higher total particle analysis throughput and that would degrade progressively once the level of saturation is reached at very high particle concentrations. The SPAMS system developed by Lawrence Livermore National Laboratory prevented the light scattering system saturation and added high speed mass spectral acquisition and analysis in real time Frank et al., 2009. The SPAMS was unique in its ability to acquire mass spectra rapidly and analyze data within seconds. The SPAMS technology was subsequently commercialized, with revisions, by Livermore Instruments (http://www.livermoreinstruments.com). We also propose that a simpler and more comprehensible method of data analysis than principal component analysis would be more suitable to the determination of API concentrations in individual aerosol particles, particularly in relatively simple formulations where all components are known or when only a dry powder excipient is present.

In the current study, a Livermore Instruments SPAMS 3.0 system was used to determine the size and chemical composition of individual aerosol particles generated from commercial pharmaceutical pMDIs. The SPAMS 3.0 system's operating principles, described in the experimental section, are a hybrid of the RSMS and ATOFMS, allowing the determination of the aerodynamic diameter of the particles being analyzed while saturating the detection system at far higher concentrations of particles than the previous generation ATOFMS systems and degrading gracefully as these particle concentration limits are approached. Because the components of a pharmaceutical pMDI are known in their entirety, the mass balance can be determined; co-associations between components can be characterized; and variations of the performance between combination and single API component products can be justified. The purpose of this study was to demonstrate the capabilities of the SPAMS 3.0 for analyzing pharmaceutical pMDIs.

2. Experimental

2.1. Aerosol analysis instrumentation

An overview of the instrumental setup, as applied to the analysis of pMDIs, appears in Fig. 1. Aerosol particles are introduced into the SPAMS 3.0 through the port in the top of the instrument. The aerosol interface of the SPAMS 3.0 was designed with a pressure flow reducer and a unique aerodynamic focusing lens stack for the transmission of a wide range of aerodynamic diameters (Gard et al., 2008). While the transmission efficiency of the SPAMS interface remains to be formally measured, informal observations made during the process of acquiring the size calibration show transmission for particles from 0.1 to at least 8 μm in aerodynamic diameter and a calibration curve for those particles appears in Fig. 2. In addition, particles clearly far larger have been observed incidentally during instrumental operation, though no attempt was made to formally characterize the interface for those larger particles during this study. Like most single particle mass spectrometers, the SPAMS 3.0 is capable of acquiring both positive and negative mass spectra simultaneously.

2.2. Materials

For the calibration of the instrument's sizing region, polystyrene (PLS) microspheres (Thermo-Fisher Scientific, http://www.thermoscientific.com/content/tfs/en/products/particle-technology.html) and SiO_2 spheres (Microspheres, GMBH, http://www.microspheres.de) with physical diameters of 0.1–8.0 μm (std. deviation of 5–10%) were used. Spheres were suspended in water and nebulized through Livermore Instruments' disposable nebulizer and conducted through a series of two diffusion dryers filled

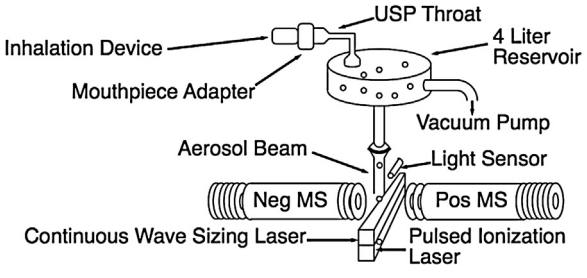

Fig. 1. Schematic depicting the experimental setup including the SPAMS 3.0. Particles to be analyzed are introduced into the 4 L reservoir through a standard USP throat. The SPAMS 3.0 draws particles from the reservoir and focuses them into an aerosol beam using an aerodynamic focusing lens stack. The particles continue across a square profile continuous wave laser where their transit time is used to compute their velocity and thus their aerodynamic diameter. As a particle leaves the sizing laser, it is ionized by the pulse of an excimer laser and the ions are measured using a dual polarity time-of-flight mass spectrometer.