Aerosol Tribocharging and its Relation to the Deposition of Oxis™ Turbuhaler® in the Electrical Next Generation Impactor

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Received 21 February 2011; revised 4 July 2011; accepted 11 July 2011

Published online 17 August 2011 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.22721

ABSTRACT: Although there have been published electrostatic characterisation studies of drug-only Turbuhaler® and lactose carrier–drug formulations, there has not been an investigation into spheronised agglomerates containing micronised lactose and eformoterol, such as in Oxis® Turbuhaler®. Ten doses of Oxis® (12 μg eformoterol) were dispersed into an electrical next generation impactor (eNGI) in a single run, and runs were conducted in triplicate to determine the aerosol performance and aerosol charge distribution at flow rates of 30, 60 and 90 L/min. Eformoterol fine particle fraction (FPF) reached a maximum of 50%–60% at 60 and 90 L/min, whereas lactose FPF increased from 31% to 42% when flow rate was increased from 30 to 90 L/min. Specific net charge (C/μg) within the eNGI stages increased from 30 to 60 L/min, but then decreased at 90 L/min. These results were attributed to the shift in balance between surface charging after interparticle and particle–surface collision (dominant at 30 and 60 L/min) and charge separation after impact fragmentation of agglomerates (dominant at 90 L/min). However, the aerosol charge profiles do not suggest that electrostatic forces play a major role in the deposition of Oxis® Turbuhaler® dry powder formulation. © 2011 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:5270–5280, 2011

Keywords: particle size; pulmonary drug delivery; static charge; aerosol; materials science; dry powder inhaler; turbuhaler; eformoterol; lactose; eNGI

INTRODUCTION

Development of Dry Powder Formulations

As a general rule, aerosol particles need to have an aerodynamic diameter between 1 and 5 μm to reach the lower airways. Micronised drug particles are highly cohesive as a result of interparticulate forces, and the dosage is usually in the microgram range, which is difficult to reproduce.[1] For this reason, dry powder formulations may be blended with carrier particles to reduce cohesion and add bulk to the powder. Early dry powder inhalers (DPIs), such as Spinhaler® (Sanofi-Aventis, Guildford, Surrey, UK), Rotahaler® (GlaxoSmithKline, Research Triangle Park, NC, USA) and Cyclohaler® (N.V. Medicopharma, Zaandam, the Netherlands), were single-unit systems using capsules filled with micronised drug and sugar carrier particles (usually α-lactose monohydrate).

Some of the more recent commercial DPI formulations have instead employed a multi-dose system. One example is Turbuhaler® (Astra Aktiebolag, Sodertalje, Sweden), which contains a reservoir from which bulk powder is scraped into a metering cavity.[2] This enables reproducible dosing of small doses of active drug–for instance, Pulmicort™ Turbuhaler® (AstraZeneca, Sodertalje, Sweden) contains 400 μg budesonide per dose with no excipients. In order to overcome the issue of strong particle cohesion between micronised drug particles, the powder is spheronised into aggregates, which are loose enough to break up in turbulent air flow, but strong enough to improve flow properties of the powder.

However, where the required dosage is extremely low, micronised carrier particles may be blended with the drug to provide sufficient bulk to the metered dose. Oxis™ Turbuhaler® (AstraZeneca, Sodertalje, Sweden) is formulated to deliver 6 or 12 μg eformoterol, with 600 μg lactose monohydrate per dose used as a bulking agent. As with other Turbuhaler® formulations, the powder blend is then spheronised into aggregates to aid dispersion.[3]

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Journal of Pharmaceutical Sciences, Vol. 100, 5270–5280 (2011)

Tribocharging Studies with DPIs

Although electrostatic charge forces (attraction and repulsion) have been considered to be a potential contributor to aerosol deposition in the lung,[4–6] studies of tribocharging (electrostatic charge generated by contact between surfaces) in pharmaceutical aerosols remain few and far between. Of these published studies, even less have looked at the triboelectrification of carrier–drug formulations.[7–10]

The electrical next generation impactor (eNGI) was developed by the authors to allow the measurement of electrostatic charge contained in the size fractions of a dispersed pharmaceutical aerosol, in addition to the measurement of particle size distribution in a manner equivalent to the standard NGI, which is a pharmacopoeia methodology.[11,12] Up until now, eNGI has been used to study commercial pressurised metered dose inhalers,[13,14] commercial drug-only Turbuhaler® formulations,[15] and experimental lactose carrier (63–90 μm)–drug formulations in a Cyclohaler®[8] at vacuum air flow rates ranging from 30 to 90 L/min.

However, the Oxis® Turbuhaler® formulation (micronised lactose and salbutamol sulphate in spheronised agglomerates) sits in a knowledge gap between the drug-only Turbuhaler® study and the coarse lactose carrier–drug study. In this paper, the authors intend to investigate the electrostatic charge characteristics and *in vitro* aerosol performance of Oxis® Turbuhaler®.

MATERIALS AND METHODS

Materials

Oxis® Turbuhalers® (12 μg eformoterol and 600 μg lactose monohydrate per dose) were acquired from AstraZeneca (North Ryde, NSW, Australia). Raw eformoterol was obtained from Sigma–Aldrich (Castle Hill, NSW, Australia) and Lactochem® α-lactose monohydrate from Friesland Foods Domo (Zwolle, the Netherlands). Trifluoroacetic acid (Sigma–Aldrich), acetonitrile (Lomb Scientific, Taren Point, NSW, Australia) and methanol (Sigma–Aldrich) were of analytical grade and used as received.

Electrical Next Generation Impactor

For a brief overview, Figure 1 describes the basic design and operation of the eNGI. The eNGI is essentially constructed from non-permanent modifications to an existing NGI. The United States Pharmacopoeia (USP) induction port (2), pre-separator (3) and NGI body are separated with polypropylene adaptors. The impaction plates (4) are insulated from the eNGI body, and from each other, with PTFE foam (8). With the apparatus separated into 10 regions with dielectric material, electrometer probes (5) in contact with each region conduct electric current from the eNGI.

The entire eNGI structure is enclosed within an earthed metal cage, thus completing a Faraday well construction (consisting of an earthed outer conductive layer, inner conducting layer and electrically insulating material in between) for each of the 10 measurement regions. This ensures that the current measured from each probe is the result of the electrical charge within a single region and not influenced by environmental interference or circuit leakage between regions.

Each of the 10 probes are connected to Model 6517A electrometer, which has been installed with a Model 6521 10-channel scanner card (both from Keithley Instruments, Cleveland, Ohio, USA). Each probe corresponds to a single measurement channel. The

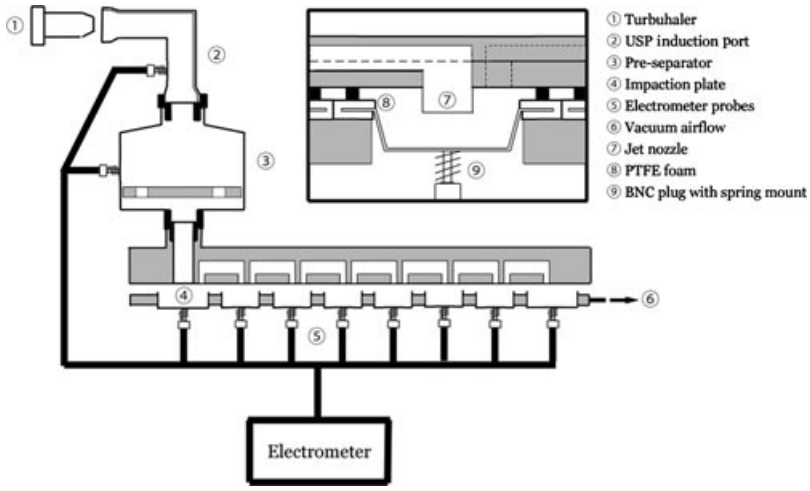

Figure 1. Schematic diagram of the electrical next generation impactor (eNGI) setup. For the current experiment, the pre-separator was omitted from the setup. (Insert) Cross-section of a single eNGI impaction stage.