Calibration of the Andersen Cascade Impactor for the Characterization of Nasal Products

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ABSTRACT: Current cascade impactor protocols do not completely rule out nasal preparations entering the lower respiratory tract. A modified cascade impactor (MCI) was developed to characterize the particle size fraction capable of deposition in the lower respiratory tract. This is an important measure of the potential for delivery to a site which is not the route of administration, and which could lead to potential toxicity. Monodisperse aerosols were utilized to calibrate the Stage -2 and Stage -0 of an Andersen Mk II nonviable cascade impactor at 15 L per minute flow rate. While these sampling conditions are beyond the normal working range of impactor theory in practice the instrument was shown to discriminate the designated particle sizes sampled. This novel setup extended the upper limit of the range of particle sizes that the cascade impactor can characterize from 8.7 to 16.5 μm. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:3462–3466, 2008

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INTRODUCTION

Current methods to determine *in vitro* deposition of nasal sprays utilizing the cascade impactor involve using a "short stack" (stages 0, 1, 2, and filter) with a 2 L expansion chamber.[1,2] However, there is no method to characterize deposition of particles greater than about 10 μm. At aerodynamic diameters of up to 20 μm, as much as 10% of the particles could potentially enter the respiratory tract, an undesirable outcome for a nasal product.[3] Significant pulmonary deposition can occur for nasal preparations that have a large quantity of particles with small aerodynamic diameters (<5 μm). The Food and Drug Administration (FDA) requires evidence that a nasal preparation does not penetrate the lungs.[4] However, *in vitro* approaches to characterizing respirable particles are limited and do not account for the full range of sizes that might potentially deposit in the lungs. Radionuclide imaging is commonly performed to satisfy this requirement by showing deposition in the nasal cavity, and absence from the lungs.[5] This technique is costly. An *in vitro* system, using an appropriate particle size cut-off, for penetration to the lungs, might be as effective as imaging in characterizing nasal product performance.

The theoretical cut-off diameter of each stage of an impactor can be calculated by the formula:

$$d_{50}\sqrt{C_c} = \left[\frac{9\eta\pi D_j^3(Stk_{50})}{4\rho_p Q}\right]^{1/2} \quad (1)$$

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where d_{50} is the cut-off diameter, C_c is the Cunningham correction factor, η is the viscosity, D_j is the diameter of the jet, Stk_{50} is the Stokes number at 50% collection efficiency, ρ_p is the density of the particle, and Q is the flow rate of air.[6] To modify the cut-off diameters of the stages of the cascade impactor, the most direct way is to change the flow rate of the air through the system, without changing any of the other factors. However, in order for the cascade impactor stage cut-off diameter to be relevant, the airflow must be turbulent. The Reynolds number (*Re*) is a dimensionless number that characterizes fluid flow through a pipe or around and obstacle. It is mathematically determined by the equation:

$$\mathrm{Re} = \frac{\rho V d}{\eta} \tag{2}$$

where ρ is the density of air, V the relative velocity, d the particle diameter, and η the viscosity of air. For a cascade impactor, the *Re* must be between 500 and 3000.

The original Andersen Mk II nonviable impactor consisted of eight stages (0–7) operated at a flow rate of 28.3 L/min, with particle size cut-offs, in the respirable range, between 9 and 0.22 μm.[7] If the flow rate is increased (to 60 or 90 L/min) the cut-off diameters for the collection efficiency curves on each stage become smaller and consequently, the impactor becomes less useful in sizing aerosols in respirable size ranges. Additional stages (-2, -1, and -0) were designed for insertion at higher flow rates to enable the respirable size range to be covered. It is fortuitous that if the impactor is operated at a low flow rate (e.g., 15 L/min) these additional stages will have particle size cut-off efficiencies that are higher than those of the conventional impactor. This is a desirable situation for evaluation of nasal products where a fraction of the particles that might deposit in the nose can potentially enter the lungs (in the range 10–20 μm). However, the Andersen has not been calibrated at low flow rates with the supplementary stages inserted that would allow determination of particles in this size range.

A modified Andersen Mk II nonviable cascade impactor was calibrated and used to characterize a product for the full range of particles having a probability of entering the lungs.

MATERIALS AND METHODS

The Vibrating Orifice Aerosol Generator (VOAG, model 3450, TSI, Inc. Shoreview, MN) was used to produce monodisperse aerosol particles in the 9–22 μm particle size range. Solutions of oleic acid and fluorescein dissolved in methanol flowed through a 35 μm orifice in an inverted apparatus at a flow rate of 15 L/min (Fig. 1). The aerosol passed a Polonium-210 radioactive source (Nuclespot Static Eliminator, NRD LLC, Grand Island, NY) to reduce the surface charge on the formed droplets. Due to fluctuations in the fluid pressure seen in the syringe pump provided with the VOAG, a high-pressure liquid chromatography (HPLC) pump (Model 510, Waters, Corp. Milford, MA) was used. Droplet sizes were based on the

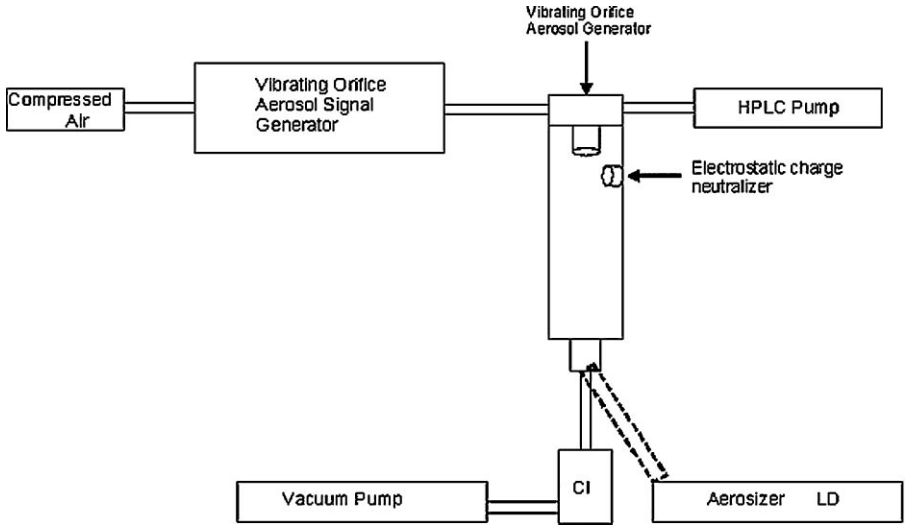

Figure 1. Experimental setup for the calibration of the cascade impactor (CI) at 15 L/min.