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Aerodynamic dose emission characteristics of dry powder inhalers using an Andersen Cascade Impactor with a mixing inlet: The influence of flow and volume

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ABSTRACT

An interaction between device resistance and inhalation flow provides the 'energy' to de-aggregate the metered dose of dry powder inhalers (DPIs). Hence all dry powder inhalers demonstrate flow dependent dose emission but information on this at low flows is not available. We have adapted the compendial method for the Andersen Cascade Impactor (ACI) to include a mixing inlet to determine the aerodynamic dose emission characteristics of a salbutamol Diskus® [DSK], Easyhaler® [EASY] and Clickhaler® [CLICK] and the terbutaline Turbuhaler® [TBH] using flows of 10–60 L/min and inhalation volumes of 2 and 4 L. All DPIs demonstrated flow dependent dose emission ($p < 0.001$) but there was no difference in the measurements between 2 and 4 L. The flow dependent dose emission properties of each DPI started to plateau when the pressure change inside each device, during an inhalation, was between 1 and 1.5 kPa. This corresponds to inhalation flows of 40.1–49.1, 25.4–28.9, 23.6–28.9 and 29.7–36.3 L/min through DSK, CLICK, EASY and TBH. The adapted methodology allows measurements at low flows. The results highlight that the compendial methodology to use an inhaled volume of 4 L with the ACI could be replaced by 2 L and that the recommendation to make measurements using a pressure drop of 4 kPa should be revised.

1. Introduction

The fine particle dose (FPD) is defined as the amount of the emitted drug from a dry powder inhaler (DPI) that contains particles with an aerodynamic particle diameter of <5 μm (Laube et al., 2011). During an inhalation these particles have the greatest potential for deposition on the airway surfaces in the lungs. In vitro studies have reported that this dose emitted from a dry powder inhaler is dependent on the speed of the inhalation used (de Boer et al., 1996; Malton et al., 1996; Ross and Schultz, 1996; Hill and Slater, 1998; Palander et al., 2000; Tarsin et al., 2004, 2006) with links to subsequent changes in lung deposition (Newman et al., 1991; Borgstrom et al., 1994; Chege and Chrystyn, 2000; Abdelrahim, 2010) and clinical effect (Pedersen et al., 1990; Engel et al., 1992; Hirsch et al., 1997). Compendial methods recommend that aerodynamic particle measurements of the emitted dose are determined using an inhalation flow corresponding to a pressure change of 4 kPa inside the inhalation channel of the DPI with an inhalation volume of 4 L (EP, 2012; USP, 2012). During routine practice there are not many patients that can achieve either an inhalation volume of 4 L or a pressure change of 4 kPa during their inhalation manoeuvre (Hawksworth et al., 2000; Broeders et al., 2003; Chrystyn, 2009; Azouz et al., 2013).

The inhalation flow corresponding to a pressure change of 4 kPa will vary due to the resistance of the DPI (Clark and Hollingworth, 1993). However cascade impactors, such as the Andersen Cascade Impactor (ACI), are designed to be operated at set inhalation flows. The cut-off diameter of the stages have, therefore, to be recalculated when using different inhalation flows (Van Oort, 1995) although for the ACI this can be overcome, to some extent, by replacing some of the stage plates and the pre-separator.

We have reported a method that uses a mixing inlet with an ACI that allows the impactor to be used at a set standard flow (60 L/min). The mixing inlet allows supplementary air to be drawn into the ACI at set flow rates of up to 60 L/min (Nadarassan et al., 2010). The difference between the supplementary flow and 60 L/min is drawn through the inhaler when it is in situ in the induction port of the ACI. Using this method we have determined the flow dependent properties of different DPIs and studied the effect of using a 2 and 4 L inhalation volume.

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2. Materials and method

2.1. Chemicals and solvents

Salbutamol suphate, terbutaline suphate and bamathane suphate were all of analytical grade and purchased from Sigma Aldrich (UK). Potassium dihydrogen orthophosphate and orthophosporic acid, obtained from Sigma Aldrich (UK), and acetonitrile from Fisher Scientific (UK) were all of HPLC grade. The water was double distilled for HPLC use.

2.2. Dry powder inhalers (DPIs)

Diskus® [DSK] (Ventolin®, GlaxoSmithKline, UK), Clickhaler® [CLK] (UCB, UK) and Easyhaler® [EASY] (Orion Pharma, Finland) each containing salbutamol (DSK and EASY salbutamol sulphate 200 μg per dose; CLICK 95 μg salbutamol base per dose) and Turbuhaler® [TBH] which contains terbutaline sulphate 500 μg per dose (Bricanyl®, Astra Zeneca, UK).

2.3. Procedure to measure the aerodynamic dose emission characteristics of the DPIs

The ACI and its accessories (pre-separator and induction port) together with the mixing inlet (Copley Scientific Ltd., UK) were washed with methanol/water and dried at a room temperature. To enable determinations at 60 L/min, stages 0 and 7 were replaced by −1 and −0 and the pre-separator designed for use at 60 L/min was used. The collection plates were sprayed with silicone (Dow Corning Limited, UK) and allowed to dry prior to use. The ACI was connected to a vacuum pump (GAST pump Brook Crompton, UK) via the critical flow controller (model TPK Copley Scientific Ltd., UK). The ACI stages were assembled with 10 ml of bamethane (800 μg/L) in distilled water (internal standard) in the pre-separator and a GF50 (Copley Scientific Ltd., UK) filter was placed in the final stage.

The Impactor was initially set up with the arm of the mixing inlet (Copley Scientific Ltd., UK) closed to set the airflow at 60 L/min with an inhalation volume of 4 L. A placebo dry powder inhaler was then encased in an airtight chamber so that inhalation flow could be measured through the inhaler. The side arm of the mixing inlet was then opened to supplementary compressed air. The dry powder flow controller was operated at 60 L/min and the valve of the supplementary air was adjusted until the desired flow, from 10, 20, 30, 40, 50 and 60 L/min, was achieved through the inhaler device whilst maintaining the fixed flow of 60 L/min through the impactor. These settings were used for each respective dose emission determination.

The DPI was detached from the induction port and the casing was discarded. A dose was prepared for discharge from each DPI as recommended in the Patient Information leaflet of the product. This was then fitted into its mouthpiece adapter and a visual check was made that the seal was airtight. The adapter was then fitted into the induction port. A schematic design is described in Fig. 1 (Nadarassan et al., 2010). This figure illustrates how an inhalation flow of 20 L/min is achieved through the DPI when it is in the induction port.

Each dose was discharged into the ACI using the dry powder controller set at 60 L/min with synchronous input of the pre set supplementary air. Separate dose emission determinations were made using flows of 10, 20, 30, 40 and 60 L/min using a 2 and a 4 L inhalation volume through the dry powder inhaler. Hence the dry powder controller was set for 2 and 4 s, respectively. For each set of inhalation conditions (flow and volume, hence 10 in total) five separate determinations were made. Five separate devices were used for each determination. The first 5 doses from each devices was discharged to waste using an inhalation flow of 90 L/min and volume

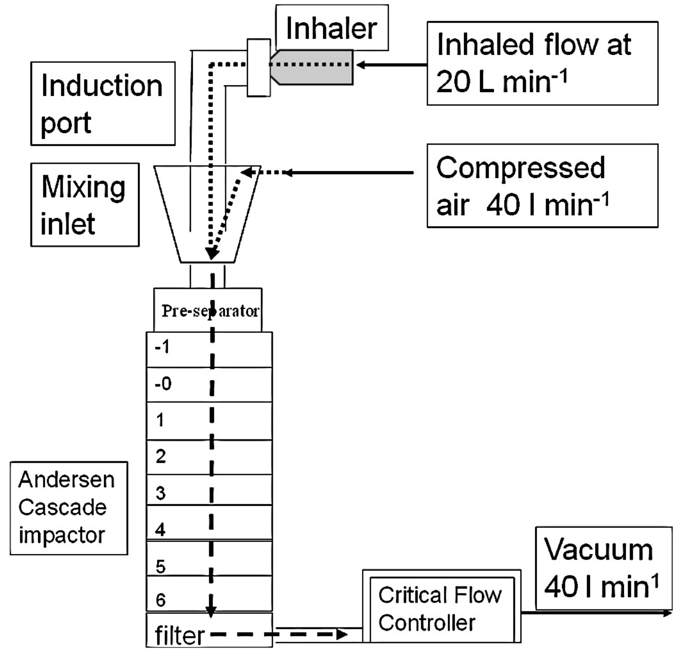

Fig. 1. Schematic design of the modified ACI methodology incorporating the mixing inlet showing how an inhalation flow of 20 L/min through a DPI is achieved.

of 2 L using a dry powder sampling unit (Copley Scientific Ltd., UK). When using the Diskus and the Easyhaler DPIs three doses were discharged from the same device for each determination whilst six doses were used from the Clickhaler. The total amount of salbutamol sulphate discharged into the ACI was, therefore, 600 μg per determination. For the terbutaline Turbuhaler 2 doses from each device were used for each determination. The order of inhalation flow and volume conditions from each device was randomised. After each separate dose emission the residual amount left in each DPI was discharged to waste using an inhalation flow of 90 L/min and volume of 2 L using a dry powder sampling unit (Copley Scientific Ltd., UK).

2.4. HPLC quantification of salbutamol and terbutaline

The induction port, mixing inlet together with the pre-separator, stage-plates and the filter were separately rinsed with various volumes (50–5 ml down to the filter) of standard aqueous bamethane solution 800 μg/L. The amounts of active drug from these washings were determined using high liquid performance chromatography (HPLC). The chromatographic separations for salbutamol, terbutaline and bamathane were carried out at 25 °C using a Phenomenex® (Sphere Clone 5 μ ODS (2) 250 × 4.6 mm) analytical column. The mobile phase was (25:75, v/v%) acetonitrile: 5 mM potassium dihydrogen orthophosphate buffer adjusted to pH 3, with orthophosphoric acid. Before use the mobile phase was filtered through a membrane filter (47 mm diameter, pore size 0.25 μm) and sonicated under vacuum for 10 min. The mobile phase was delivered at a flow of 1.0 mL/min using a Hewlett Packard (HP) 1005 pumping system (Agilent Technologies, GmbH) and the injection volume was 50 μL using a HP 1050 series autosampler with UV detection set at 202 nm (HP 1050 series variable wavelength detector).

The calibration curve was linear ($r^2 = 0.99$) over salbutamol and terbutaline concentrations ranging from 250 to 2000 μg/L ($n = 6$). The method had an accuracy of 100 ± 2% and the intra-day and inter-day precisions had a relative standard deviation (RSD) of 0.89% and 1.68%, respectively, at three different concentrations (400, 800, and 1200 μg/L). The limits of detection (LOD) and