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RESEARCH

Long-Term In-Vitro Aerosol Performance and Drug Retention of a Cardboard-Based Spacer (MDI PLUS®) Compared with Conventional Spacer Designs

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Abstract

Background Spacers and valved holding chambers improve drug delivery. However, plastic versions are bulky, costly, and susceptible to electrostatic effects. Newer cardboard or portable designs are affordable and convenient, though evidence regarding long-term aerosol performance remains limited.

Methods This study assessed the durability, drug retention, and aerosol emission performance of a cardboard-based spacer (MDI PLUS®) over 200 repeated actuations. Aerosol emission of salbutamol (Ventolin®, 100 µg/actuation) and beclometasone (Clenil Forte®, 250 µg/actuation) was measured at set intervals using an Andersen cascade impactor (28.3 L/min), determining total emitted dose (TED) and aerodynamic particle size characteristics. Single-puff deposition within the MDI PLUS®, on the pressurized metered dose inhaler (pMDI), and on a user's hand was also compared with two commercial plastic spacers, AeroChamber Plus® and AeroChamber2go™.

Results Over 200 uses, MDI PLUS® maintained a stable delivered dose for salbutamol (TED 221–198 µg) and beclometasone (506–532 µg), without significant change in mass median aerodynamic diameter (≈3.97–4.45 µm). Salbutamol fine particle dose (FPD) and fraction (FPF) declined non-significantly, from 165 µg/75% to 119 µg/60%, while beclometasone FPD (307–393 µg) and FPF (61–75%) remained largely unchanged. Drug retention within the spacer increased with repeated use across all devices but was significantly lower for MDI PLUS® ($p<0.05$) than for either AeroChamber device. Deposition on the pMDI and on the hand was negligible for all devices.

Conclusion MDI PLUS® showed durable, consistent aerosol performance across repeated use, with lower drug retention supporting its suitability as a reliable long-term spacer.

Keywords Long-term · In-vitro · Aerosol performance · Drug retention · MDI PLUS · AeroChamber Plus, AeroChamber2go

Introduction

Inhaled aerosol therapy continues to be the backbone for treatment of chronic respiratory conditions such as asthma and chronic obstructive pulmonary disease (COPD), allowing pulmonary delivery of medications with immediate effect after inhalation, avoiding the systemic route [1, 2]. Pressurized metered dose inhalers (pMDIs) are predominantly used in the market because they are portable, convenient, and economical g [3, 4]. However, an accurate pMDI technique is vital to ensure appropriate pulmonary drug deposition [3]. One significant drawback of pMDIs is the requirement for proper timing and synchronization between actuation and inhalation processes [5, 6]. Research indicates that a significant number

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of patients, particularly children and the elderly, do not properly synchronize these steps, resulting in higher oropharyngeal deposition, less therapeutic efficacy, and possible systemic side effects [7, 8]. o address coordination errors and improve lung deposition, the Global Initiative for Asthma (GINA) guidelines strongly recommend the routine use of spacers with pMDIs [9].

Spacers and valved holding chambers (VHCs) are accessory devices that are used to help solve these problems. These devices slow down the aerosol, let the propellant evaporate, and give patients more time to breathe in the medicine [10, 11]. Hence, spacers help asthmatic patients inhale the small particles into the lungs and decrease the portion of the aerosol deposited early in the mouth and throat [12, 13]. Many traditional plastic spacers, like the AeroChamber Plus®(Trudell Medical, Canada), are bulky and expensive [14, 15]. Hence, their size and cost often make them hard to carry around and decrease patient adherence, especially when needed in an emergency situation [16].

To address these challenges, several new designs have been developed to ease use and improve accessibility. The MDI PLUS® (MDI PLUS Ltd., Athy, Ireland) is a disposable spacer made of cardboard that also serves as the inhaler's outer packaging [17]. It is a cost-effective, eco-friendly, and convenient alternative to traditional plastic devices [16]. In the meantime, the AeroChamber2go™ (Trudell Medical, Canada) offers a compact, portable spacer option with a built-in protective case for the pMDI for use on the go. Figure 1 shows the three

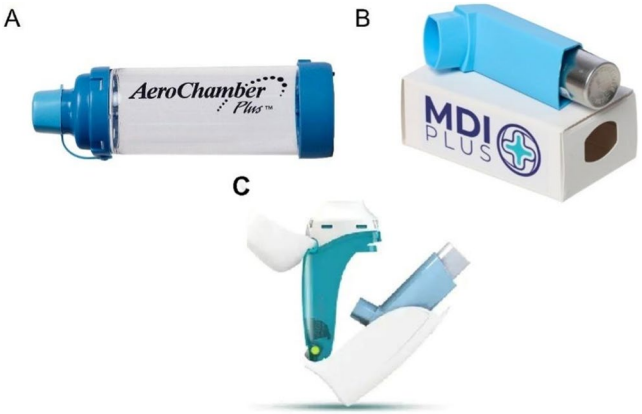

Fig. 1 Spacer devices evaluated in the study: (**A**) AeroChamber Plus®, (**B**) MDI PLUS® with pMDI, and (**C**) AeroChamber2go™ with pMDI

described spacers. Nonetheless, direct evidence comparing the performance, durability, and aerosol deposition characteristics of these emerging devices is still scarce [18].

This study aimed to evaluate the durability, aerosol delivery performance, and drug deposition behavior of the MDI PLUS® cardboard-based spacer during repeated use, and to compare the amount of aerosol retained within the spacer, on the pMDI, and on the simulated user's hand represented in the investigator's hand after several uses with those of traditional spacer devices (AeroChamber Plus® and AeroChamber2go™) using two common pMDI formulations.

Methods

Mimicking the typical use of MDI PLUS with pMDI

To mimic the patient use of the pMDI with MDI PLUS, the pMDI was given to the investigator placed within the MDI PLUS as a storage box. The investigator then opened the MDI PLUS and took the pMDI out of it, turned the MDI PLUS into a spacer, and connected the pMDI to it as in Fig. 2. One puff from the pMDI was discharged into the MDI PLUS® with a simulated inhalation to a waste filter (Pall Corporation, USA) using a vacuum pump (Brook Crompton, UK) set at a flow rate of 28.3 L/min at a breathing volume of 4 L (adult simulation). The pMDI was placed back within the MDI PLUS after that. This process was repeated at 4 different times per day (about 6 h apart) over 5, 12.5, 30, and 50 days to mimic 20, 50, 120, and 200 typical patient uses, respectively.

In-Vitro Durability and Aerosol Emission Performance of the MDI PLUS®

Two different pMDIs were used for evaluation: Ventolin Evohaler® (salbutamol sulfate, 100 µg/puff; GlaxoSmithKline, Cairo, Egypt) and Clenil Forte® (beclomethasone dipropionate, 250 µg/puff; Chiesi Limited, Manchester, UK). For each type of pMDI, five separate groups of 8 pMDIs and MDI PLUS were set for 5 different testing intervals: at first use and after 20, 50, 120, and 200 uses. At each

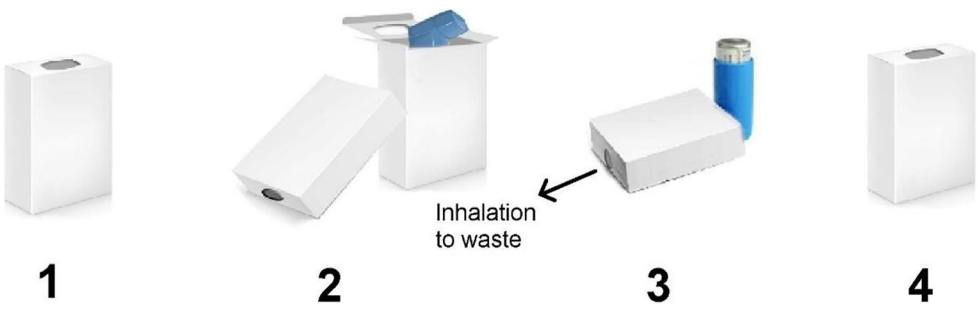

Fig. 2 Typical use of MDI PLUS with the pMDI

testing interval, five puffs were actuated for analytical evaluation. An Andersen MKII Cascade Impactor (ACI, Copley Scientific, Nottingham, UK) was used to study the aerodynamic characterization ($n=3$) of the pMDI aerosolized drug that came out of the MDI PLUS® spacer. The total emitted dose (TED, $n=5$) was determined using a pMDI sampling apparatus (Huironghe Technology, Beijing, China). Both were equipped with A/E fiberglass filters (Pall Corporation, USA) within the sampling unit and the final stage of the ACI. Inhalation was simulated using a vacuum pump and a critical flow controller, set at a flow rate of 28.3 L/min at a breathing volume of 4 L (adult simulation) [19]. Flow rates were determined using an electronic digital flow meter (MKS Instruments, USA), and all apparatus connections were sealed with Parafilm M (Pechiney Plastic Packaging, USA). The inhaler was shaken well and primed with two actuations before each measurement to make sure that the dose was consistent. The five test puffs were released into the MDI PLUS® spacer and drawn through the ACI and the pMDI sampling apparatus within one second of actuation. The MDI PLUS®, the pMDI sampling apparatus, and the ACI collection plates and filters were rinsed with 90% (v/v) acetonitrile for salbutamol (Ventolin) samples, and with acetonitrile-10 mM ammonium acetate (70:30% v/v), adjusted to pH 5 with orthophosphoric acid for beclomethasone dipropionate (Clenil Forte) samples. The MDI PLUS® and the filters' samples were then sonicated for 3 min, filtered to remove any particulates, and stored at 4 °C until further analysis.

Deposition After Several Uses

Another part of the study was to determine the amount of pMDI's aerosol deposited within the spacer after several uses of the MDI PLUS®, AeroChamber Plus®, and AeroChamber2go™spacers. Ventolin Evohaler® (salbutamol sulfate, 100 µg/puff) and Clenil Forte® (beclomethasone dipropionate, 250 µg/puff). For each type of the pMDI, five separate group 5pMDIs and each set for 5 different testing interval, at first use and after 20, 50, 120, and 200 uses. After each interval, one puff was discharged into the spacer as described previously and the amount of aerosol deposited in the spacer, on the pMDI and on the user's hand were collected using similar aliquot as described above and stored at 4 °C until further analysis.

Detection Methods

The method applied for the quantification of both salbutamol and beclomethasone was a validated high-performance liquid chromatography (HPLC) method. For salbutamol sulfate, the detection was made using an ultraviolet detector wavelength set at 225 nm (Agilent 1260 Infinity system, USA). Using a mobile phase of acetonitrile-water (90:10 v/v) with 0.1% phosphoric acid and a flow rate of 1 mL/min, chromatographic separation was done on a ZORBAX Eclipse Plus C18 column (4.6 × 250 mm, 5 µm; Agilent, USA). The volume of the sample injection was 100 µL. The HPLC method showed a lower limit of detection (LOD) of 0.35 µg/mL and a lower limit of quantification (LOQ) of 2.55 µg/mL. Salbutamol had linear calibration curves between 2 and 100 µg/mL [20].

While the detection of beclomethasone dipropionate was made using a mobile phase of acetonitrile-10 mM ammonium acetate (70:30% v/v) adjusted to pH 5 with orthophosphoric acid and a flow rate of 1 mL/min. The chromatographic separation of the analyte was performed at 40 °C using a ZORBAX Eclipse Plus C18 column (4.6 × 250 mm, 5 µm) analytical column. The analysis was conducted at a flow rate of 1 mL/min at an ultraviolet detection wavelength of 254 nm. The injection volume was 50 µL. The LOD and LOQ were found to be 0.01 mg/mL and 0.03 mg/mL, respectively. Beclomethasone had linear calibration curves between 0.03 and 62.50 µg/mL [21].

The following aerosol performance parameters were calculated using Copley Inhaler Testing Data Analysis Software (CITDAS, Copley Scientific, UK): Fine Particle Dose (FPD), Fine Particle Fraction (FPF), and Mass Median Aerodynamic Diameter (MMAD).

Statistical Analysis

Results are presented as mean and standard deviation (SD). Differences in MDI PLUS® aerosol performance across usage intervals were evaluated using one-way ANOVA with Tukey's HSD post-hoc test. Spacer drug deposition across devices and time points was analyzed using two-way ANOVA with Tukey's post-hoc correction for multiple pairwise comparisons. Statistical analysis was performed using SPSS software (v25) (SPSS Inc., Chicago, IL, USA). A p-value ≤ 0.05 was considered statistically significant.

Results

The aerosol delivery performance of the MDI PLUS® spacer was evaluated after 0, 20, 50, 120, and 200 uses using Ventolin® (salbutamol sulfate, 100 µg per actuation). As shown in Table 1, the TED remained consistent across all usage intervals, ranging from 220.99 (12.24) µg at baseline (0 use) to 198.71 (46.71) µg after 200 uses, with no statistically significant differences observed.

The FPD showed only a decrease from 165.07 (20.97) µg at baseline to 119.67 (20.83) µg after 200 uses. However,