



HAL
open science

Comparative performance study of paperboard disposable spacers versus commercial valved holding chambers for aerosol delivery

Emma Eynaud, Lara Leclerc, Manon Moreau-Neidhardt, Jérémie Pourchez

► **To cite this version:**

Emma Eynaud, Lara Leclerc, Manon Moreau-Neidhardt, Jérémie Pourchez. Comparative performance study of paperboard disposable spacers versus commercial valved holding chambers for aerosol delivery. *International Journal of Pharmaceutics*, 2024, 666, pp.124774. 10.1016/j.ijpharm.2024.124774 . hal-04807084

HAL Id: hal-04807084

<https://hal.science/hal-04807084v1>

Submitted on 27 Nov 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Comparative performance study of paperboard disposable spacers versus commercial valved holding chambers for aerosol delivery

Emma Eynaud, Lara Leclerc, Manon Moreau-Neidhardt, Jérémie Pourchez *

Mines Saint-Etienne, Univ Jean Monnet, INSERM, U 1059 Sainbiose, Centre CIS, F - 42023 Saint-Etienne France

ARTICLE INFO

Keywords:

Spacer
Valved holding chamber
Fluticasone
pMDI
Aerosol delivery
Aerosol particle size
Low-tech
Cost effective

ABSTRACT

Purpose: The aim of this study is to evaluate and compare the performance, for the administration of fluticasone propionate with a pressurized metered-dose inhaler (pMDI), of two low-tech paperboard spacers versus two commercially available valved holding chambers (VHC).

Methods: According to the Canadian standard CAN/CSA-Z264.1-02, total emitted dose (TED) and aerodynamic size distribution were measured for the pMDI in combination with 4 different spacers: a homemade paper cup spacer, the DispozABLE® paperboard spacer, the AeroChamber Plus® plastic VHC, and the Vortex® aluminium VHC.

Results: The two disposable paperboard spacers had a lower TED compared to the aluminium VHC, but delivered more than 2.5 times the dose of fluticasone than the commercial plastic VHC. The 3 antistatic devices (*i.e.* the aluminium VHC, the paperboard DispozABLE® spacer and the paper cup spacer) delivered a significantly higher dose of fine particles than the less antistatic plastic VHC. Their fine particle fraction was statistically similar to that obtained with pMDI without spacer. This respirable fraction ensures an optimal therapeutic effect. All spacers limited the flow of coarse particles, thus avoiding adverse effects on the trachea and oropharynx.

Conclusion: We have shown that inexpensive and low-tech paperboard spacers are interesting alternatives for the administration of aerosols.

1. Introduction

According to the Global Asthma Report, around 339 million people worldwide are affected by asthma, a chronic obstructive airway disease (Global Asthma Report, 2018). It is one of the biggest health problems in the world with high morbidity and mortality in severe cases, both in children and adults (Dharmage et al., 2019). Asthma affects the lungs and causes inflammation of the airways and constriction of the bronchial muscles, leading to breathing difficulties. Common symptoms include persistent coughing, wheezing, shortness of breath and chest tightness (WHO, Asthma, 2024). Various treatment options are available to alleviate daily symptoms and improve patients' quality of life. One approach is the use of inhaled corticosteroids as anti-inflammatory agents or short- and long-acting beta-agonists as bronchodilators (Bush and Saglani, 2010).

Inhalation is the most commonly used method of administering respiratory therapies as it allows a large amount of medication to be delivered directly and quickly to the affected area. This reduces the potential side effects of certain treatments on the body due to minimal

systemic absorption (Moreau-Neidhardt et al., 2023; Pauwels et al., 1997; Saeed et al., 2020; Gachelin et al., 2015). In aerosol therapy, pressurized inhalers are often used to deliver medication, but proper use is difficult (Saeed et al., 2020). This is because it requires excellent hand-mouth coordination as the pMDI is activated and inhaled simultaneously, which is a problem for about a third of patients (Dissanayake and Suggett, 2018), especially those at the extremes ages of life. If the technique is not mastered, the medication cannot reach the bronchi effectively and the therapeutic effect may not be optimal. In addition, some people may experience airway irritation or discomfort due to drug build-up in the trachea and oropharynx (Roland et al., 2004).

Poor control of asthma is often due to incorrect handling of the inhalation system. In these cases, the use of pMDI with an additional device such as a spacer inserted between the inhaler and the mouth is recommended (Saeed et al., 2020; Gachelin et al., 2015; Dissanayake and Suggett, 2018). The spacer including the VHC is a class 1 non-invasive medical device (Gachelin et al., 2015). It was developed to overcome the patient's lack of coordination when using the pMDI. The spacer improves aerosol delivery and thus optimise the pulmonary

* Corresponding author at: École Nationale Supérieure des Mines de Saint-Etienne, 158 cours Fauriel, 42023 Saint-Etienne Cedex 2, FRANCE.
E-mail address: pourchez@emse.fr (J. Pourchez).

distribution of the inhaled medication (Rau, 2006). It serves as a particle retention chamber, which is usually made of plastic (more rarely aluminium) and gives the patient time to inhale as much medicine as possible (Saeed et al., 2020). In addition, this device allows the selection of a larger number of fine particles $< 5 \mu\text{m}$ likely to be deposited in the lungs and ensuring an optimal therapeutic effect, and, conversely, to reduce between 80 and 90 % the impaction of large particles $> 5 \mu\text{m}$ in the oropharynx (Gachelin et al., 2015; Dissanayake and Suggett, 2018) by retaining them in the chamber.

Multiple situations arise where the use of commercial spacers is non-viable. Firstly, the high cost and the fact that commercial spacers are not available in some countries are factors that affect their use (Zar et al., 1999). The price and reimbursement vary by brand, model and country. In some parts of the world, particularly in developing countries, there is no reimbursement, making access to expensive spacers difficult for patients who are prone to inhaler handling errors (Zar et al., 1999). On the other hand, there are some emergencies, e.g. at school, where medication needs to be administered very quickly and children do not have a pMDI or a VHC with them. This has led to the emergence of inventive and cost-effective homemade alternatives: plastic drink bottles, paper cups, paper towel rolls or aluminum cans (Pauwels et al., 1997; Dissanayake and Suggett, 2018; Willemse et al., 2003). For example, an asthma emergency bag has been developed in London schools. It contains a pMDI with disposable paperboard spacers for first aid in the event of an asthma attack (Sanders and Bruin, 2015; Chavasse et al., 2021). Paperboard has the advantage of being antistatic, inexpensive, and recyclable.

The aim of the study was therefore to characterise and compare the performance of two commercial VHCs (made of plastic and aluminium) with two low-cost and home-made alternative spacers (made from paperboard) according to the Canadian standard. In particular, we compared the total emitted dose (TED) and the particle size distribution emitted by a pMDI alone or with the spacers analysed. Manufacturers in the industry generally consider this standard as a benchmark for establishing normative procedures that ensure the efficiency and safety of commercially available spacers.

2. Materials and Methods

2.1. Study design

The active ingredient used in this study was fluticasone propionate delivered in a pMDI (Flixotide® 250 $\mu\text{g}/\text{dose}$, suspension for oral inhalation, pressurized bottle with 120 doses, GlaxoSmithKline laboratory, lot: WS4P). Fluticasone propionate is a corticosteroid with an anti-inflammatory effect, particularly on the bronchial mucosa. It is used as an anti-asthmatic agent in the basic treatment of asthma (VIDAL, 2024). Measurements were performed for pMDI alone and for pMDI in combination with four different devices. Two types of VHCs were investigated: AeroChamber Plus® (150 mL, Trudell Medical International Europe Limited, Canada) and Vortex® (193 mL, PARI GmbH, Germany). In comparison, two cost-effective disposable alternatives were analysed:

DispozABLE® paperboard spacer (250 mL, Clement Clarke International, Harlow, United Kingdom) and a spacer made from an empty paper cup (250 mL, Ref: 1000802, Sincère, France). A hole was cut into the bottom of each paper cup with a cutter to match the size and shape of the pMDI. The plastic part of the DispozABLE® was used to cover the open end of the handmade spacer to simulate a mouthpiece. The Vortex® aluminium VHC (Al_{VHC}), the DispozABLE® spacer (DPs) and the paper cup spacer (PCs) were characterised as antistatic devices, while the AeroChamber Plus® plastic VHC (Pl_{VHC}) was characterised as a non-antistatic chamber. A summary of the characteristics of each accessory can be found in Table 1.

For the AeroChamber Plus® and Vortex® VHCs and for pMDI alone, the values reported by Moreau et al. in their comparative study of plastic and aluminium spacers were used (Moreau-Neidhardt et al., 2023). These data were selected as they originate from the same laboratory, using the same equipment and following exactly the same standardized operating procedures. Additionally, some data were partially repeated to verify the validity of the comparison. This consistency ensures a robust comparison, enabling the performance of the paperboard devices to be accurately placed in relation to the others.

The TED and aerodynamic size distribution were measured to determine the performances of each device according to the Canadian standard CAN/CSA-Z264.1-02 – Spacers and Inhalation Chambers for Metered-Dose Inhalers (CAN/CSA-Z264.1-F02 (C2016)). The study follows the A5, B1, B2 and B3 normative procedures described in this standard.

2.2. Measurement of the total emitted dose

The Canadian standard Section A5 describes the experimental procedure for measuring the emitted dose by filter collection (CAN/CSA-Z264.1-F02 (C2016)). Fig. 1 shows the experimental setup. A vacuum pump (High-Capacity Pump – HCP5, Copley Scientific, Nottingham United Kingdom) was connected to the setup to simulate the inhalation air flow of 28.3 L/min. The continuous flow was set with an electronic digital flow meter (DFM4 Copley Scientific, Nottingham United Kingdom). The setup includes the pMDI with spacer connected to a holder containing a filter (Filters Pads, PARI GmbH, Germany). The pMDI was preloaded before dosing (5 s shaking followed by 3 activations in a vacuum arm). The actuator was then replaced with a clean one

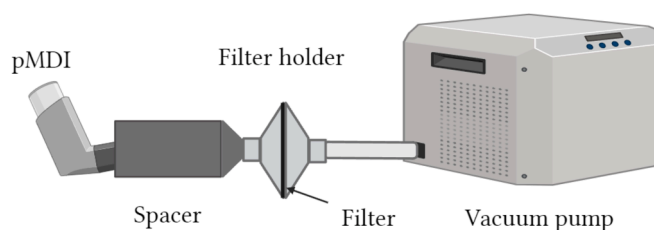


Fig. 1. Scheme of the experimental set-up for the measurement of total emitted dose by filter collection with the standard section A5.

Table 1

Characteristics of valved holding chambers and spacers used in this study.

Types	AeroChamber Plus®	VORTEX®	DispozABLE®	Paper cup
Picture				
Material	Plastic	Aluminium	Paperboard	Paperboard
Volume	150 mL	193 mL	230 mL	250 mL
Property	Non antistatic	Antistatic	Antistatic	Antistatic
Valve	Yes	Yes	No	No

for the test. During the evaluation of each spacer, the dose released from the pMDI was measured by collecting 5 activations at 28.3 L/min on the filter inside the holder. The pMDI was shaken for 5 s between each activation. After the last dose, 20 s were waited before switching off the flow. At the end of the experiment, the filter was collected and transferred to 20 mL of 80:20 (v:v) methanol:water (Methanol HiPerSolv CHROMANORM, CAS 67-56-1, VWR, France). The sample is then sonicated for 5 min in normal mode at 130 KHz in an ultrasonic bath (TI-H15 MF3, VWR, Germany) to desorb the filter and extract the active ingredient. Experiments were repeated 9 times for each disposable spacer, as the previous VHC experiments were performed in triplicate for three devices of each type.

2.3. Characterization of particle size distribution

An Andersen Cascade Impactor (ACI, Copley Scientific, Nottingham United Kingdom) was used to determine the aerosol mass and particle size distribution emitted from a pMDI with a spacer compared to a pMDI alone in accordance with clauses B1, B2 and B3 of the standard. The test setup is shown in Fig. 2. The same vacuum pump as described above was connected to the impactor to simulate a constant inhalation air flow of 28.3 L/min. The pMDI with a spacer (B1) or alone (B2) was placed at the inlet of the induction port. Before the experiment, the pMDI was pre-loaded as previously described (5 s shaking followed by 3 activations in a vacuum arm) and the actuator was replaced with a clean one. The particle size distribution was determined by collecting 5 activations delivered at 28.3 L/min through the ACI. The pMDI was shaken for 5 s between each activation. After the last dose, a 20 s wait was performed before the flow was switched off. The fluticasone particles were collected on the actuator, the spacer, the induction port of the impactor and the collection plates of stages 1 to 8, depending on their aerodynamic size. The components were rinsed with 80:20 (v:v) methanol:water to collect the drug particles. 20 mL was used for the spacer and induction port, and 5 mL for all collection plates. The volumes were transferred to 50 mL (Centrifuge Tube, Corning Incorporated – Life Science, Reynosa, Mexico) or 15 mL tubes (Centrifuge Tube, Thermo Fisher Scientific, Mexico). Experiments were repeated 6 times for each disposable spacer, as the previous VHC experiments were performed in triplicate for two devices of each type.

Various parameters were determined from the mass of fluticasone

collected in the induction port and the collection plates 1–8: Emitted Dose (ED), Fine Particle Dose (FPD), Fine Particle Fraction (FPF), Extra Fine Particle Dose (EPD), Extra Fine Particle Fraction (EPF), Coarse Particle Dose (CPD) and Coarse Particle Fraction (CPF). The R-value is the ratio of FPD to CPD. The parameters measured with the ACI are shown in Fig. 2. The particle fractions are calculated as % of the emitted fluticasone dose.

To compare the administration of the aerosol with and without the spacer, the F value was calculated in relation to the extra-fine fraction (Fe), the fine fraction (Ff) and the coarse fraction (Fc). This represents the fraction of the extra-fine, fine and coarse dose emitted by the spacer compared to the dose emitted by the pMDI alone. These values were used to calculate the index of aerosol quality (I_{S-VHC} : Ratio Ff/Fc), a measure of the *in vitro* performance of the spacer in terms of the removal of coarse drug particles and the increase or decrease of fine particles compared to the pMDI alone. The mean mass aerodynamic diameter (MMAD) and geometric standard deviation (GSD) are also determined.

2.4. Quantification

The quantification of the fluticasone was determined by UV spectroscopy at a wavelength of 236 nm (spectrophotometer UV-vis, GENESYS 150, Thermo Scientific, USA).

To prepare the standard curve for the measurement of the TED, a calibration range was established on filters with the following concentrations: 12.5, 25, 37.5, 50, and 62.5 $\mu\text{g/mL}$ of fluticasone propionate. The procedure involved assembling the setup with two PARI filters in a filter holder. The vacuum pump was calibrated to 28.3 ± 0.5 L/min using the flowmeter. After shaking the pressurized aerosol for 5 s, it was primed with three sprays into a vacuum arm. The required number of sprays for each concentration was then applied. Filters were collected, desorbed in 20 mL of 80:20 methanol and processed in an ultrasonic bath. Data from the absorbance values were used to generate the calibration curve in Excel, ensuring linearity with an r^2 of at least 0.96.

To characterize particle size distribution, a stock solution was prepared and used to create the calibration range. A series of dilutions was made from this stock solution. The calibration range included the following concentrations: 75, 37.5, 3.75, 1.875, 0.1875 and 0.09375 $\mu\text{g/mL}$. This dilution process ensures that the calibration curve covers the concentration range required for accurate analysis.

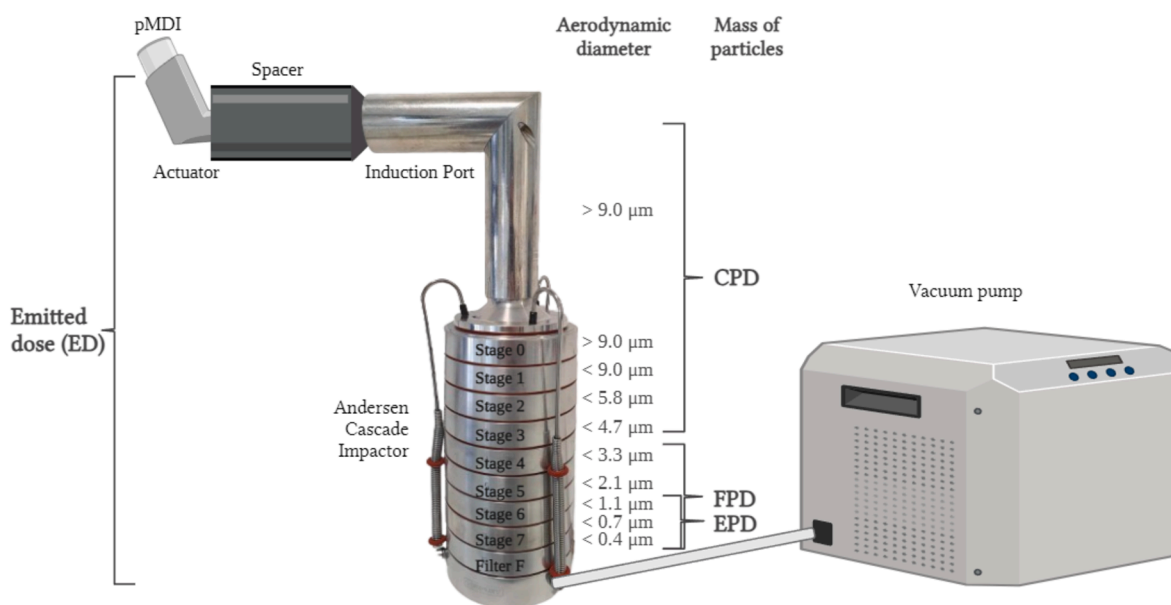


Fig. 2. Scheme of the set-up for the measurement of particle size distribution delivered from a pMDI with the spacer at constant flow (28.3 ± 0.5 L/min) with the standard section B1.

2.5. Statistical analysis

Statistical analyses were performed with the Software Prism® 10 (GraphPad Prism Software, San Diego, USA). The total emitted dose and particle size distribution characterization for the different combinations pMDI/spacer and pMDI alone were expressed in mean \pm SD. Data were compared using a two-sample *t*-test for normally distributed variables and a Mann-Whitney non-parametric test for non-normally distributed variables. A *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Total emitted dose

The average TED of fluticasone pMDI with each spacer are shown in Fig. 3. The results are expressed as a percentage of the label claim dose (LCD); 250 μ g/dose. No significant difference was observed between the TEDs of the two disposable paperboard spacers ($p = 0.2104$, Fig. 3). However, the highest TED value was observed with the Vortex® aluminium VHC and was significantly higher than with the AeroChamber Plus® plastic VHC ($p < 0.0001$, Fig. 3), the DispozABLE® spacer ($p = 0.0069$, Fig. 3) and the homemade paper cup spacer ($p = 0.0946$, Fig. 3). The pMDI with plastic VHC had the lowest TED compared to the other three pMDI/device combinations ($p < 0.0001$, Fig. 3). Although the two disposable paperboard spacers had a lower TED compared to the aluminium VHC, they emitted more than 2.5 times the dose of fluticasone than the AeroChamber Plus® plastic VHC.

3.2. Particle size distribution

According to the Canadian standard, the total mass of drug collected on all components of the assembly divided by the total number of actuations of the pMDI should be within $\pm 25\%$ of the LCD (Zar et al., 1999) to obtain reliable results. Depending on the method, 5 activations of 250 μ g were triggered, corresponding to a mass of 1250 μ g. The total mass of the drug collected and shown in Table 2 therefore had to be between 937.5 μ g and 1562.5 μ g. The results obtained vary between 80 and 88 % of the LCD.

The Fluticasone drug was captured and collected from the trigger, the spacer, the induction port and the collection plates from stage 1 to 8. The particle size distributions and aerodynamic characteristics of fluticasone are shown in Table S.1 (Supplementary Data), Table 3, Figure S.1

Table 2

Total mass of drug collected for pMDI alone and in combination with the four spacers studied. Data for pMDI, Pl_{VHC}, and Al_{VHC} (reproduced from reference Moreau-Neidhardt et al., 2023).

	pMDI	Plastic VHC	Aluminium VHC	DispozABLE® Spacer	Paper Cup Spacer
LCD (μ g)	1250				
Emitted Dose (μ g)	1101 \pm 83	1062 \pm 154	1046 \pm 75	1005 \pm 39	1001 \pm 57
Total mass of drug collected (% of LCD)	88 \pm 7	85 \pm 12	84 \pm 6	80 \pm 3	80 \pm 5

Table 3

Aerodynamic Characteristics of Fluticasone dose delivered via pMDI alone or with VHCs or spacers. NC: Not Calculated. Data for pMDI, Pl_{VHC}, and Al_{VHC} (reproduced from reference Moreau-Neidhardt et al., 2023).

	pMDI	Plastic VHC	Aluminium VHC	DispozABLE® Spacer	Paper Cup Spacer
CPD (μ g)	128 \pm 14	3.9 \pm 2.9	18 \pm 11	29.2 \pm 3.1	42 \pm 7
FPD (μ g)	74 \pm 11	27.0 \pm 5.3	87.6 \pm 12.9	71.4 \pm 8.3	66.2 \pm 2.5
EPD (μ g)	1.2 \pm 0.5	0.3 \pm 0.4	2.0 \pm 2.8	1.9 \pm 0.5	1.8 \pm 0.2
CPF (% of the ED)	57.1 \pm 4.2	1.8 \pm 1.0	8.6 \pm 4.6	14.5 \pm 1.7	21.0 \pm 3.8
FPF (% of the ED)	32.7 \pm 3.6	12.7 \pm 2.9	41.9 \pm 7.6	35.5 \pm 3.8	33.1 \pm 1.3
EPF (% of the ED)	0.5 \pm 0.2	0.1 \pm 0.2	1.0 \pm 1.2	0.9 \pm 0.2	0.9 \pm 0.1
R (FPD/CPD)	0.57	6.90	4.85	2.45	1.57
MMAD (μ m)	NC	3.2 \pm 0.1	3.4 \pm 0.2	3.5 \pm 0.2	3.9 \pm 0.2
GSD	NC	1.5 \pm 0.1	1.5 \pm 0.2	NC	NC

(Supplementary Data) and Fig. 4.

The highest retention within the spacer was observed for the AeroChamber Plus® plastic VHC and was significantly greater than the Vortex® aluminium VHC, the DispozABLE® spacer and the homemade

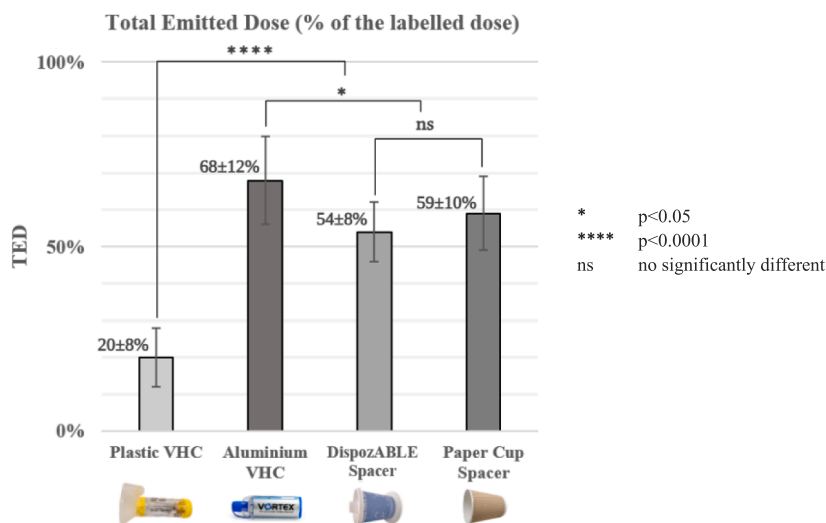


Fig. 3. Results of TED expressed in percentage of the labelled dose by filter collection with pMDI using the 4 types of spacers investigated. Data for Pl_{VHC} and Al_{VHC} (reproduced from reference Moreau-Neidhardt et al., 2023).

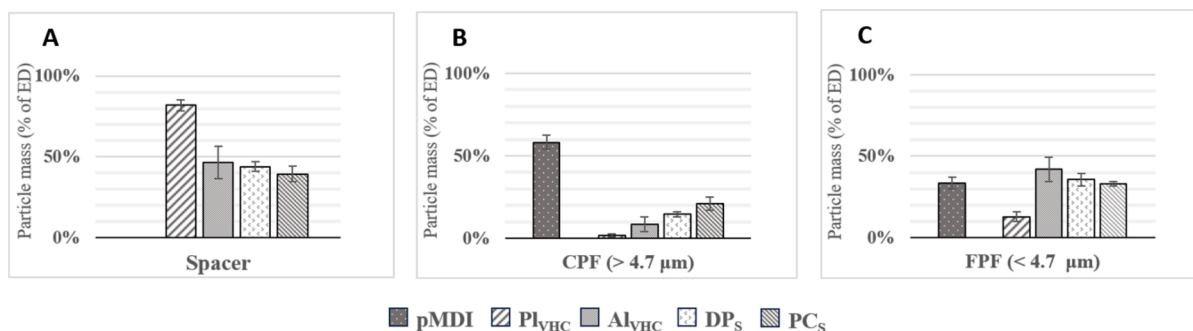


Fig. 4. A) Mass of particles collected in the spacer (in % of ED). B) CPF. C) FPF. Data for pMDI, Pl_{VHC}, and Al_{VHC} (reproduced from reference Moreau-Neidhardt et al., 2023).

paper cup spacer ($p = 0.0022$, Table 3, Fig. 4, Table S1, Fig. S1). No significant difference was found between the antistatic devices (Al_{VHC} vs. DP_S: $p = 0.6991$, DP_S vs. PC_S: $p = 0.2403$, PC_S vs. Al_{VHC}: $p = 0.0946$, Table 3, Fig. 4).

With the pMDI alone, an average of $46.9 \pm 5.1\%$ (Table S1) of the fluticasone dose was collected in the induction port of the impactor, the equivalent of the patient's pharynx. All spacers restricted the flow of large particles in the oropharyngeal tract. Indeed, the coarse particle fraction was significantly lower with the combinations of pMDI and spacer than with pMDI alone ($p < 0.0001$, Table 3, Fig. 4, Fig. S1). More specifically, a lower amount of large particles passed through the plastic VHC compared to the disposable paperboard spacers ($p < 0.0001$, Table 3, Fig. 4, Fig. S1). The same applies to the aluminium VHC compared to the disposable paperboard spacers. In addition, a significant difference was found between the CPF of the two disposable paperboard spacers (PC_S vs. DP_S: $p = 0.0068$, Table 3, Fig. 4).

The FPF was statistically similar between the pMDI without spacer and with the DispozABLE® spacer or the homemade paper cup spacer (pMDI vs. DP_S: $p = 0.2861$, DP_S vs. PC_S: $p = 0.1868$, pMDI vs. PC_S: $p = 0.8701$, Table 3, Fig. 4) and it was significantly higher than that of the plastic VHC ($p < 0.0001$, Table 3, Fig. 4). The R-ratio (FPD/CPD) was lowest for pMDI without spacer and was less than one (0.57, Table 3). A larger fraction of coarse particles was inhaled than the fraction of fine particles. However, in combination with the other spacers, the R-ratio was higher than 1. Commercial VHCs had the highest FPD/CPD ratio (Pl_{VHC}: 6.90, Al_{VHC}: 4.85, Table 3). The extra-fine fraction (Fe), the fine fraction (Ff), the coarse fraction (Fc) and the index of aerosol quality (I_{S-VHC}) are listed in Table 4.

A value greater than 0.8 for Fe and Ff is desired, because it indicated that the spacer is not retaining the small particles needed for delivery to the lung. An Fc value below 0.20 indicates that the spacer or VHC delivers less than 20% of the coarse particle dose that would have been delivered without the device. To minimise the unwanted dose reaching the upper respiratory tract, the I_{S-VHC} value should be greater than 1 and closer to 10 (CAN/CSA-Z264.1-F02 (C2016)).

The Vortex® aluminium VHC, the DispozABLE® spacer and the homemade paper cup spacer had Fe and Ff values greater than 0.80 (Table 4), indicating that there was no significant loss of extra and fine particles. In contrast, the AeroChamber Plus® plastic VHC had Fe and Ff values below 0.80 (Table 4). The Fc values were only below 0.20 for the

Table 4

Comparison of Aerosol delivery via pMDI with and without VHCs or spacers at constant flow. Data for pMDI, Pl_{VHC}, and Al_{VHC} (reproduced from reference Moreau-Neidhardt et al., 2023).

	Fe	Ff	Fc	I_{S-VHC}
Plastic VHC	0.22	0.37	0.03	12.05
Aluminium VHC	1.72	1.16	0.14	8.47
DispozABLE® Spacer	1.57	0.90	0.33	2.74
Paper Cup Spacer	1.61	0.97	0.23	4.27

two commercial VHCs. These results show that the DispozABLE® spacer and the paper cup spacer are less effective at retaining coarse particles in the chambers than the VHCs, which can lead to side effects. This is confirmed by the I_{S-VHC} values, which are greater than one but less than ten for the two paperboard spacers (2.74 for DP_S and 4.27 for PC_S, Table 4).

4. Discussion

The objective of the paper is not solely to present new data on the paperboard device but also to position its performance in relation to other spacers, providing a more comprehensive assessment of its effectiveness compared to established plastic and aluminium devices. Thus, the values reported by Moreau et al. for the AeroChamber Plus® and Vortex® VHCs, generated from the same laboratory and partially repeated simultaneously with cardboard spacers tests, were utilized.

The purpose of a VHC or spacer is to deliver the same dose as a properly inserted pMDI to ensure its efficacy and safety. However, the shape of the spacer, the material, the volume and the design of the valves influence the aerosol delivery and thus the efficacy of these medical devices (Liu et al., 2017). Measuring the total dose delivered makes it possible to quantify the performance of the spacer or VHC in relation to the mass of drug potentially inhaled by the patient. A higher inhaled dose ensures an optimal therapeutic effect. In this study, the antistatic devices (Vortex® aluminium VHC, DispozABLE® paperboard spacer and the paper cup spacer) have a higher TED than the plastic VHC (AeroChamber Plus®). As the plastic is a low antistatic material, the charged particles released by pMDI interact with the inner walls of the plastic device. The negatively charged drug particles are pressed against the wall of the VHC reservoir due to their mutual repulsion. The polymers used in the manufacture of inhalers are positively charged (Mitchell et al., 2007). As a result, the attractive forces between the charged particles and the oppositely charged surfaces keep the particles in the chamber despite the patient's inhalation, leading to a reduction in the delivered dose. This explains why some VHC have been designed with electrically conductive metal, such as the Vortex® aluminium VHC, to prevent loss of medication (Dissanayake and Suggett, 2018). However, when considering the pharmacoeconomic aspects of these devices, it should be noticed that metal is more expensive to manufacture than plastic and paperboard. Indeed, the efficacy of the inhalation chamber influences the patient's choice, but its availability and cost are also important factors.

Although the total dose emitted gives a good indication of the efficacy of the device, it is not sufficient to characterise the performance of the spacer. The fluticasone pMDI contains particles of different sizes, but the TED does not distinguish between coarse and fine particles. Depending on their size, the particles are deposited in different places. The finest particles, $< 4.7 \mu\text{m}$, are deposited in the bronchopulmonary system. It is this respirable fraction that is responsible for the desired therapeutic effect while the coarse particles $> 4.7 \mu\text{m}$, are deposited in

the trachea and oropharynx. These deposits can cause irritation or breathing difficulties. The antistatic devices (the Vortex® aluminium VHC, the DispozABLE® spacer and the homemade spacer made from paper cup) not only delivered a higher total emission dose, but also a significantly higher proportion of fine particles than the non-antistatic device. However, the plastic VHC enabled better elimination of coarse particles originally contained in the fluticasone pMDI. This phenomenon of particle size selection was caused by the deposition of particles in the chamber by electrostatic interaction, but also by impaction, for example on the valve. Indeed, the valve of the VHC can accommodate more aerosol particles before inhalation than the spacer. However, the resistance of the valve can be an obstacle for small children and patients with narrowed airways. The cardboard alternatives do not contain a valve.

In addition, a disposable paper cup has the advantage of being readily available and inexpensive. And because it is a single-use product, the risk of cross-infection is eliminated (Willemse et al., 2003). Emergency situations can occur anywhere and at any time. Disposable products can therefore be the solution when patients do not have access to a disinfected commercial spacer. However, there are some factors to consider with the spacer made from an empty paper cup. Although this device showed similar results in terms of TED and FPF compared to the DispozABLE® medical device, the bottom of the paper cup had to be cut to fit the pMDI actuator using appropriate tools. In addition, in this study, the open end of the paper cup was covered with the plastic part of the DispozABLE® to simulate a mouthpiece. Without this part and depending on the morphology and size of the patient's face, the medication may leak out.

In terms of cost, the two paperboard spacers are considerably cheaper than VHCs: a few centimes versus between 15 and 30 euros or more. However, long-term use with a chronic disease raises the question of the viability of single-use products. In a recent study, the durability of the DispozABLE® paperboard spacer was tested. The results indicate that the DispozABLE® can be used several times without its effectiveness diminishing, but as it cannot be washed, its lifespan remains limited (Saeed et al., 2020).

4.1. Limitations of the study

Furthermore, this study is limited to an *in vitro* model, which is suitable for comparing pMDI and the add-on spacer devices tested, but cannot reflect the clinical response. Moreover, the continuous flow rate of 28.3 L/min does not reflect the inhalation flow rates of the paediatric population and even less the reality of a crying child with breathing difficulties, although this is probably the largest user group besides the elderly. Indeed, this study is based on a standard protocol, but one of the limitations is the representativeness of this protocol in order to mimic a suction flow that perfectly correspond to a natural or forced children or adult air supply. Further studies with an *in vivo* component would provide additional evidence for the evaluation of aerosol delivery with cardboard spacers. Another limitation of the study was that only a single commercial pMDI was tested. The results may not reflect the performance when paired with a different device.

5. Conclusion

In summary, the two paperboard spacers were shown to be effective compared to the use of pMDI alone or with VHCs when administering inhaled medications such as fluticasone propionate. This study has shown that the disposable paperboard spacers, which are inexpensive and technically easy to handle, can be used as an alternative for the administration of aerosols in an emergency or without storage of commercial VHCs.

CRedit authorship contribution statement

Emma Eynaud: Writing – review & editing, Writing – original draft,

Visualization, Validation, Methodology, Investigation, Formal analysis. **Lara Leclerc:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Data curation, Conceptualization. **Manon Moreau-Neidhardt:** Writing – review & editing, Validation, Investigation. **Jérémy Pourchez:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpharm.2024.124774>.

References

- Bush, A., Saglani, S., 2010. Management of severe asthma in children. *Lancet* 376 (9743), 814–825.
- CAN/CSA-Z264.1-F02 (C2016): Tubes espaceurs et chambres d'inhalation pour les aérosols doseurs. www.ShopCSA.ca.
- Chavasse, R.J.P.G., Coffey, T., Brown-Bampoe, O., Adebayo, I., Kumar, V., 2021. Implementation of a school emergency asthma bag. *Arch. Dis. Child.* 106 (6), 619.
- Dharmage SC, Perret JL, Custovic A. Epidemiology of Asthma in Children and Adults. *Frontiers in Pediatrics* [Internet]. 2019 [cité 4 mars 2024];7. Disponible sur: <https://www.frontiersin.org/articles/10.3389/fped.2019.00246>.
- Dissanayake, S. and Suggett, J., 2018. A review of the *in vitro* and *in vivo* valved holding chamber (VHC) literature with a focus on the AeroChamber Plus Flow-Vu Anti-static VHC. *Therapeutic Advances in Respiratory Disease*, 12, 1753465817751346. <https://journals.sagepub.com/doi/epub/10.1177/1753465817751346>.
- Gachelin, E., Vecellio, L., Dubus, J.C., 2015. Évaluation critique des chambres d'inhalation commercialisées en France. *Revue Des Maladies Respiratoires* 32 (7), 672–681.
- Global_Asthma_Report_2018.pdf [Internet]. [cité 4 mars 2024]. Disponible sur: http://globalasthma-report.org/2018/resources/Global_Asthma_Report_2018.pdf.
- Liu, X., Guo, C., Chowdhury, B., Starke, P., Limb, S., Peri, P., et al., 2017. Valved holding chambers and *in vitro* metered dose inhaler performance: effects of flow rate and inhalation delay. *J. Aerosol Medicine and Pulmonary Drug Delivery* 30 (6), 399–410.
- Mitchell, J.P., Coppolo, D.P. and Nagel, M.W., 2007. Electrostatics and inhaled medications: influence on delivery via pressurized metered-dose inhalers and add-on devices. *Respiratory care*, 52(3), pp.283-300.
- Moreau-Neidhardt, M., Leclerc, L., Grange, J., Périnel, S., Pourchez, J., 2023. Assessing of low-tech solutions for aerosol delivery: Comparative performance study of manufactured versus homemade spacers. *Int. J. Pharm.* 633, 122652.
- Pauwels, R., Newman, S., Borgstrom, L., 1997. Airway deposition and airway effects of antiasthma drugs delivered from metered-dose inhalers. *Eur Respir J* 10 (9), 2127–2138.
- Rau, J.L., 2006. Practical problems with aerosol therapy in COPD. *Respiratory care* 51 (2).
- Roland, N.J., Bhalla, R.K., Earis, J., 2004. The Local Side Effects of Inhaled Corticosteroids: Current Understanding and Review of the Literature. *Chest* 126 (1), 213–219.
- Saeed, H., Abdelrahim, M.E., Rabea, H., Salem, H.F., 2020. Evaluation of disposable and traditional accessory devices for use with a pressurized metered-dose inhaler. *Respir Care* 65 (3), 320–325.
- Sanders, M., Bruin, R., 2015. A rationale for going back to the future: use of disposable spacers for pressurized metered dose inhalers. *Pulmonary Medicine*. 1–6.
- VIDAL [Internet]. [cité 22 janv 2024]. FLIXOTIDE. Disponible sur: <https://www.vidal.fr/medicaments/gammes/flixotide-3768.html>.
- Asthma [Internet]. [cité 4 mars 2024]. Disponible sur: <https://www.who.int/news-room/fact-sheets/detail/asthma>.
- Willemse, B.W., Toelle, B.G., Li, J.S.M., Shah, S. and Peat, J.K., 2003. Use of a paper disposable cup as a spacer is effective for the first-aid management of asthma. *Respiratory medicine*, 97(1), pp.86-89.
- Zar, H.J., Brown, G., Donson, H., Brathwaite, N., Mann, M.D., Weinberg, E.G., 1999. Home-made spacers for bronchodilator therapy in children with acute asthma: a randomised trial. *Lancet* 354 (9183), 979–982.