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COMPARATIVE ANALYSIS OF THE EFFICACY OF TWO ANTI-STATIC VALVED HOLDING CHAMBER DEVICES

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1. SUMMARY

This report describes a comparative analysis of the efficacy of two anti-static valved holding chamber (VHC) devices: DosiVent® (Palex Medical) and the AeroChamber Plus® Flow-Vu® (Sandoz). For the study, salbutamol (Ventolin®), an inhaled drug formulation used to relieve symptoms of asthma and chronic obstructive pulmonary disease (COPD) such as coughing, wheezing and feeling breathless, was used as model drug. The comparative analysis was performed based on the quantification of the retained and delivered doses of salbutamol during the use of the devices, and through the characterisation of particle size distribution in the aerosolised drug. According to the results, DosiVent and AeroChamber VHCs showed similar drug retention and delivery in terms of quantification of salbutamol. Concerning particle size distribution, the two devices did not retain any specific size fraction of salbutamol. The DosiVent and AeroChamber devices showed similar efficacy, however the rubber valve present in the AeroChamber VHC retained a considerable higher amount of the tested drug, indicating a possible inferior performance of the later device compared to the former one.

2. OBJECTIVE

To compare the efficacy of two anti-static valved holding chamber (VHC) devices used for administration of aerosolised drugs, based on the quantification of the retained and delivered doses of salbutamol and on the analysis of particle size distribution in the aerosolised drug dispersion.

3. MATERIALS & METHODS

3.1. MODEL DRUG AND TESTED DEVICES

For the study, the commercial formulation Ventolin® Salbutamol 100 micrograms/inhalation (lot nº JB8L and UM8F) was used as model drug. Salbutamol is used to relieve symptoms of asthma and chronic obstructive pulmonary disease (COPD) such as coughing, wheezing and feeling breathless. It works by relaxing the muscles of the airways into the lungs, which makes easier to breathe. Salbutamol comes in an inhaler (puffer) presentation. According to the Spanish Agency of Medicines and Medical Devices ("*Agencia Española de Medicamentos y Productos Sanitarios*", AEMPS)[1] the recommended dosis of salbutamol for an adult is 1 or 2 puffs to relief mild symptoms or allergenic reaction up to a maximum of 8 puffs in more extreme cases.

For the comparative study, two anti-static valved holding chamber (VHC) devices were tested: DosiVent® (Palex) and AeroChamber Plus Flow-Vu™ (Sandoz, lot nº 210245). VHC devices are a type of spacer that includes a one-way rubber valve at the mouthpiece. These devices provide "space" between user's mouth and the inhaler and trap and hold the drug, which gives the user time to slowly inhale the drug. The VHC devices are made of three main pieces connected each other: 1) an inhaler adaptor to connect the drug flask to the device, 2) an anti-static holding chamber and 3) a unidirectional rubber valve closer to the mouthpiece to aid drug administration and to prevent medication loss (Figure 1).

Figure 1 Anti-static VHC devices tested: AeroChamber Plus Flow-Vu™ (A) and DosiVent® (Palex Medical) (B). 1) indicates the inhaler adaptor, 2) the VHC and 3) the rubber valve close to the mouthpiece.

[1] https://cima.aemps.es/cima/dochtml/p/70869/Prospecto_70869.html.

3.2. EXPERIMENTAL DESIGN

The experiment was set up according to Oliveira et al.[2]. Two approaches were adopted depending on the parameter evaluated. The two approaches are detailed below.

3.2.1. QUANTIFICATION OF SALBUTAMOL THROUGH UPLC ANALYSIS

For the quantification of Salbutamol through high-performance liquid chromatography (UPLC) analysis, the salbutamol flask was connected to inhaler adaptor of the VHC device, and a face mask was connected to the mouthpiece at the opposite site of the device. The face mask was then coupled to a two pieces plastic chamber containing a cellulose filter in the first chamber and a vacuum pump (PB0004B Busch, Germany) connected to the second chamber. The vacuum pump (4m^3/h, 230V 0.1kW 50Hz) was used to generate negative pressure in the whole system simulating breathing. Figure 2 shows the system design adopted for the quantification of retained and delivered doses of Sabutamol. To perform the experiment, once the negative pressure was stablished (10 seconds after turning on the vacuum pump), 8 puffs were administered (keeping 5 seconds between each puff) into the system. After that, the system was carefully disassembled, and the different parts of the system (VHC, rubber valve, face mask and cellulose filter) were gently washed with distilled water to recover the salbutamol accumulated at these different sites of the system. Samples were analysed in a ACQUITY Ultra Performance Liquid Chromatography (UPLC) H-CLASS PLUS of Waters equipment coupled to Waters TQSCronos (UPLC/MS/MS) mass detector (Malvern Instruments, Malvern, UK). The experiment was repeated three times to guarantee the robustness of the results.

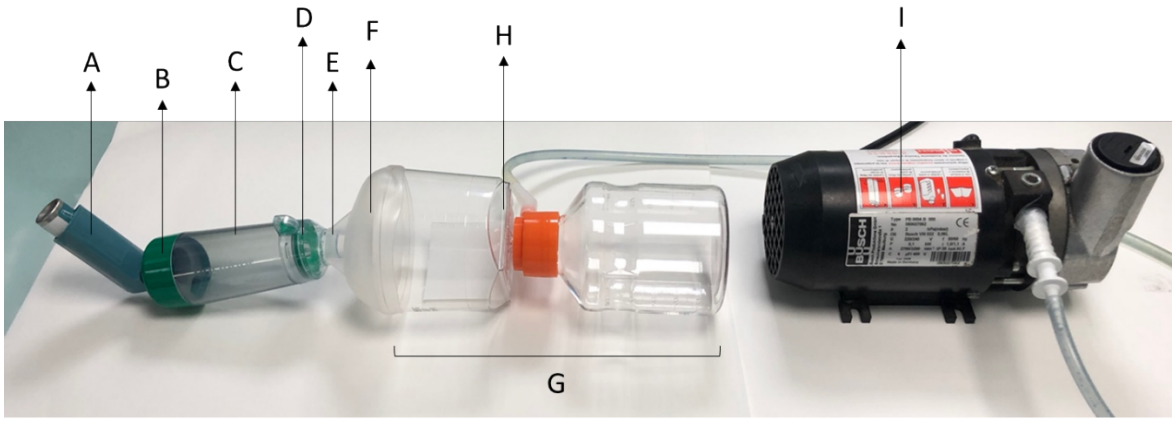

Figure 2. Design of the experimental system used to quantify the inhalation of Salbutamol. The figure indicates the Salbutamol inhaler (A) connected to the inhaler adaptor (B) of the VHC (C) containing a rubber valve (D) at the opposite site close to the mouthpiece (E). The face mask (F) was then connected to the two pieces plastic chamber (G) with a cellulose filter in the first chamber (G) to traps the inhaled Salbutamol. The system was connected to a vacuum pump (I) that simulates breathing.

[2] Oliveira, R.F. et al. 2015. Efficiency of valved Holding Chambers: Experimental Full Dose Assessment. Journal of Aerosol Medicine and Pulmonary Drug Delivery.A-1-A-25. doi: http://doi.org/10.1089/jamp.2015.ab02.abstracts.

3.2.2. PARTICLE SIZE DISTRIBUTION THROUGH LASER DIFFRACTION ANALYSIS

For the assessment of particle dispersion, the salbutamol flask was connected to the inhaler adaptor of the VHC device, and the laser diffraction unit connected to the mouthpiece of the VHC device at the opposite site. The laser diffraction unit counts with an incorporated vacuum pump that generates the negative pressure to simulate breathing (Figure 3). For the experiment, 1 puff was administered in each assay and the size of the particles that crossed the VHC devices reaching the mouthpiece (inhaler user mouth) was measured by laser diffraction (Spraytec®, Malvern Instruments, Malvern, UK). The experiment was repeated three times to guarantee the robustness of the results.

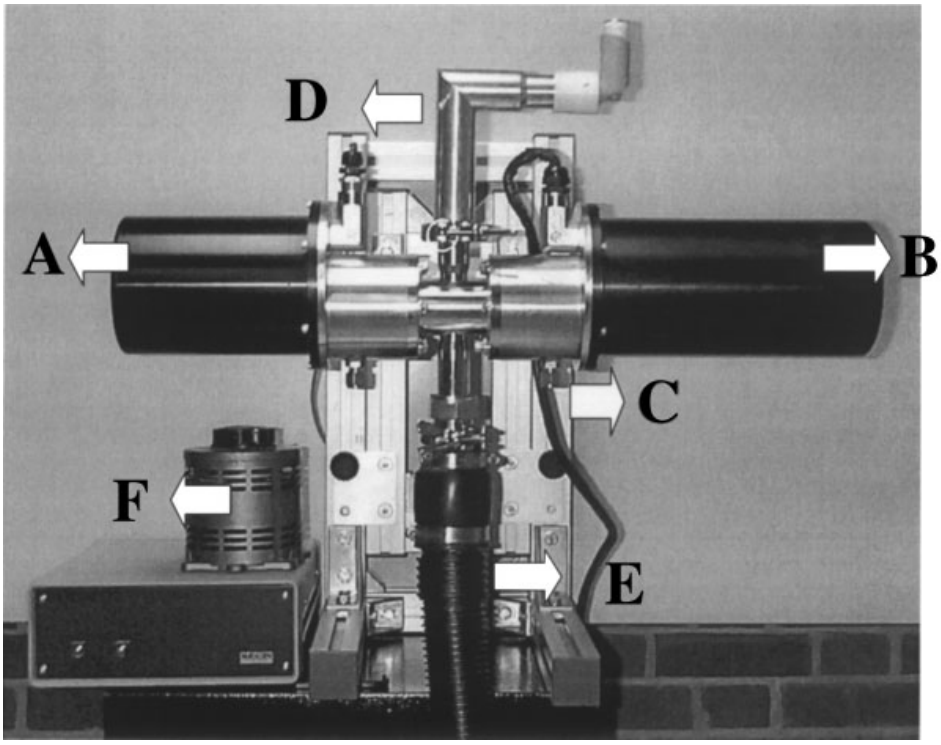

Figure 3. Spraytec® unit used for the particle size determination. The figure indicates the Spraytec® laser source (A) and the detector (B) held in a closed inhalation system (C). The USP throat(D) connect the VHC device to the Spaytec unit and the coupled vacuum pump (E) simulates breathing. The airflow through the unit is by a vacuum source (2.0HP) through the voltage regulator (F). Image taken from Haynes et al.[3].

[3] Haynes, A., et al. 2004. Evaluation of the Malvern Spraytec with inhalation cell for the measurement of particle size distribution from metered dose inhalers. Journal of Pharmaceutical Science. 93(2):349-63. doi: http://doi.org/10.1002/jps.10558.

4. RESULTS

4.1. QUANTIFICATION OF SALBUTAMOL

According to the UPLC analysis, high doses of Salbutamol were accumulated in the VHC and rubber valve of both DosiVent and AeroChamber devices (Figure 4). A smaller fraction of Salbutamol reached out the cellulose paper (inhaler user mouth), and a minor fraction was retained in the face masks (Figure 4). Comparing the two devices, AeroChamber rubber valves retained higher amounts of Salbutamol during the breathing simulation (Figure 4). Figure 5 shows evidence of the higher deposition of Salbutamol in the AeroChamber rubber valve compared to the valve in the DosiVent device.

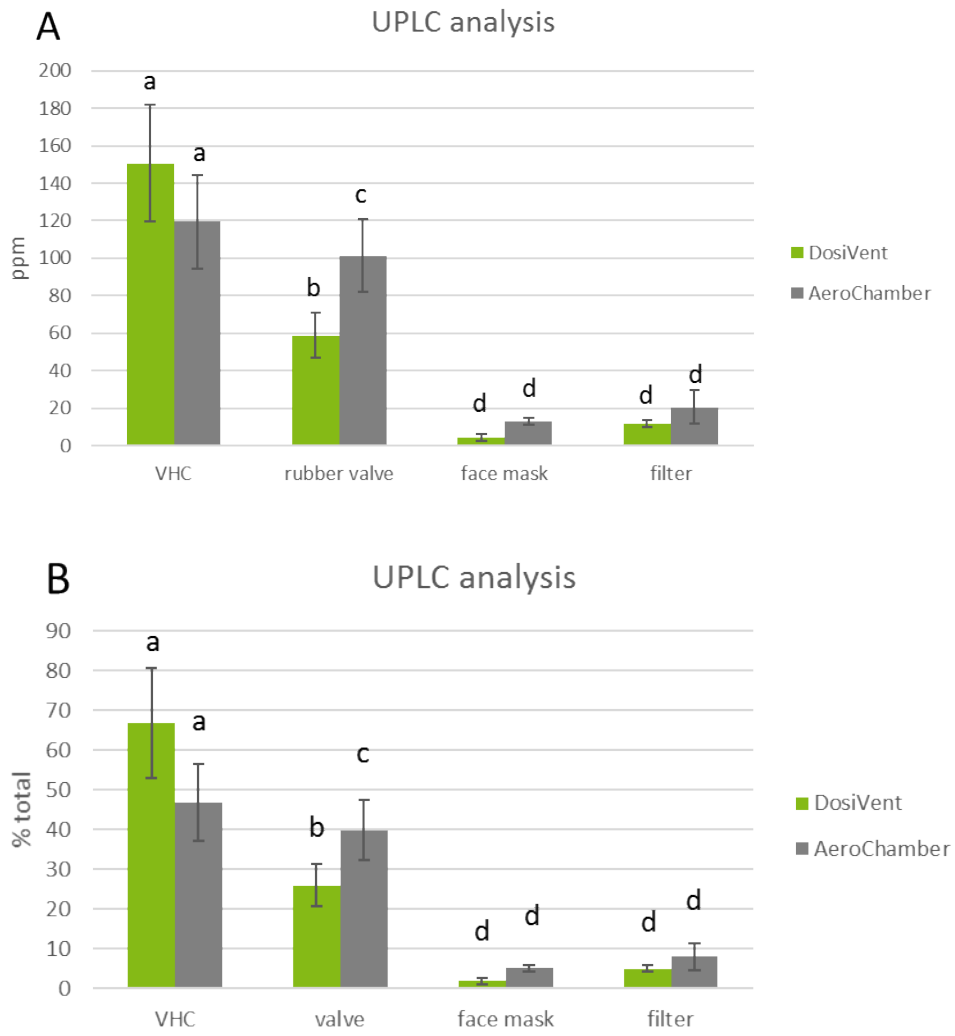

Figure 4. Salbutamol concentration as ppm (A) and as % total (B) at the different parts of the system (VHC, rubber valve, face mask and cellulose filter) measured by UPLC. Different letters indicate significant differences according to the Kruskal-Wallis followed by the Mann-Whitney U-test (p>0.05).

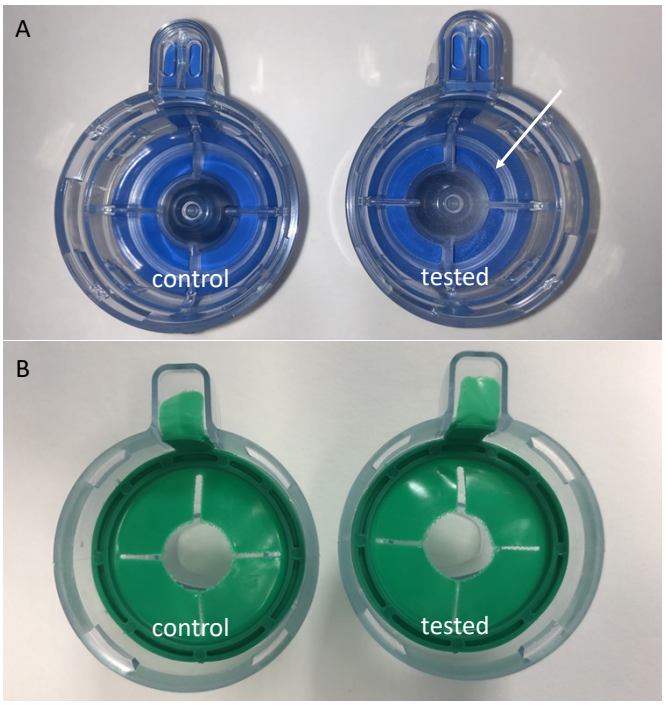

Figure 5. Drug deposition on the AeroChamber (A) and the DosiVent (B) rubber valves after breathing simulation of salbutamol. The image shows control (unused/new) and tested (used in the breathing simulation test) devices. The white arrow highlights the deposition of Salbutamol on the rubber valve.

4.2. PARTICLE SIZE DISTRIBUTION

Results of laser diffraction analysis are presented as follows:

Dv(10), Dv(50) and Dv(90) represent the size (in µm) of the largest particles, in the 10%, 50% and 90% fractions, respectively (e.g. Dv(10): 10% of the particles shows a size equal or below this number).

Vol(%) <10µm is the percentage of the particles that are below 10 µm.

Span is an additional parameter that represents the bandwidth of the particle size distribution. It reflects how wide or narrow is the variability of particle size.

D[4][3] or D[4,3] is the size to volume ratio of the particles and reflects the diameter of the particles.

According to the laser diffraction analysis, salbutamol particles showed a size distribution below 10 µm (Figure 6) with a relatively narrow bandwidth (Figure 7), meaning that particles showed small size variability. Particles varied from 1.7 to 7.75 µm in size, but the great majority of particles (Dv(90)) showed a size distribution between 6.57 to 7.75 µm (Table 1). Comparing size distribution of salbutamol aerosolised via VHC devices and salbutamol aerosolised directly into the Spraytec unit, small differences were found at the Dv(10) (Ventolin ~ Ventolin+DosiVent >

Ventolin+AeroChamber) (Table 1, Figure 8) and at Dv(50) (Ventolin > Ventolin+DosiVent > Ventolin+AeroChamber) (Table 1, Figure 9), but these differences are not considered clinically relevant as in the major fraction (Dv(90)), particles showed a similar size distribution (Table 1, Figure 10). Taken together, VHC devices showed a similar performance and did not retain any specific particle size fraction (Figure 11).

Table 1. Particle size distribution of Salbutamol (Ventolin®), salbutamol aerosolised in a Dosivent VHC (Ventolin + DosiVent) and in a AeroChamber VHC (Ventolin + AeroChamber).

	Ventolin		Ventolin+DosiVent		Ventolin+AeroChamber	
	Mean	SD	Mean	SD	Mean	SD
Dv(10) µm	1.76	0.01	1.76	0.01	1.70	0.01
Dv(50) µm	3.44	0.11	3.22	0.04	3.19	0.04
Dv(90) µm	7.75	0.72	6.57	0.05	7.47	0.81
Vol(%) <10µm	93.62	1.15	95.30	0.30	92.99	1.93
Span	1.74	0.16	1.50	0.01	1.81	0.23
D[4][3] µm	5.86	0.47	5.48	0.21	6.31	0.93

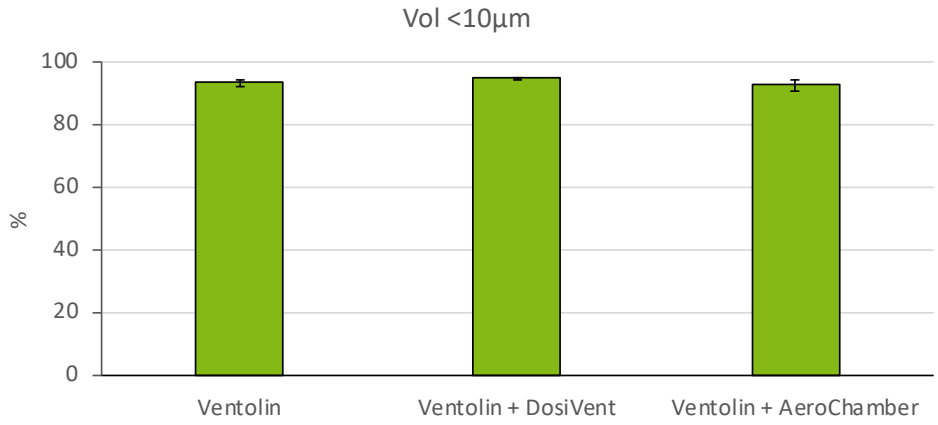

Figure 6. Percentage of particles below 10 µm measured by laser diffraction.

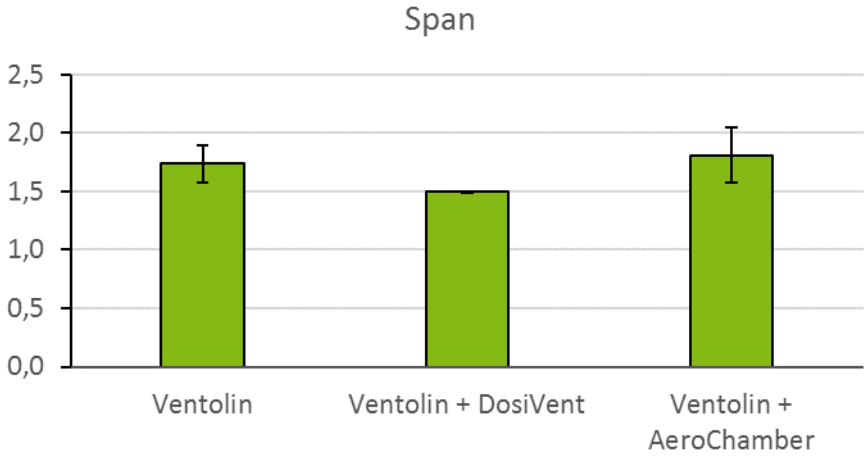

Figure 7. Bandwidth of the particle size distribution measured by laser diffraction.

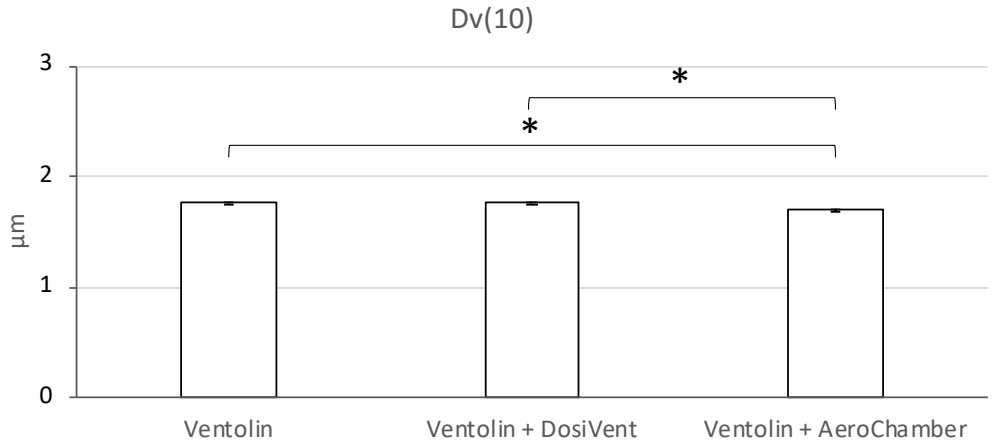

Figure 8. Particle size distribution in the Dv(10) fraction (10% of the particles) measured by laser diffraction. * Significant differences according to the Kruskal-Wallis followed by the Mann-Whitney U-test (p>0.05).

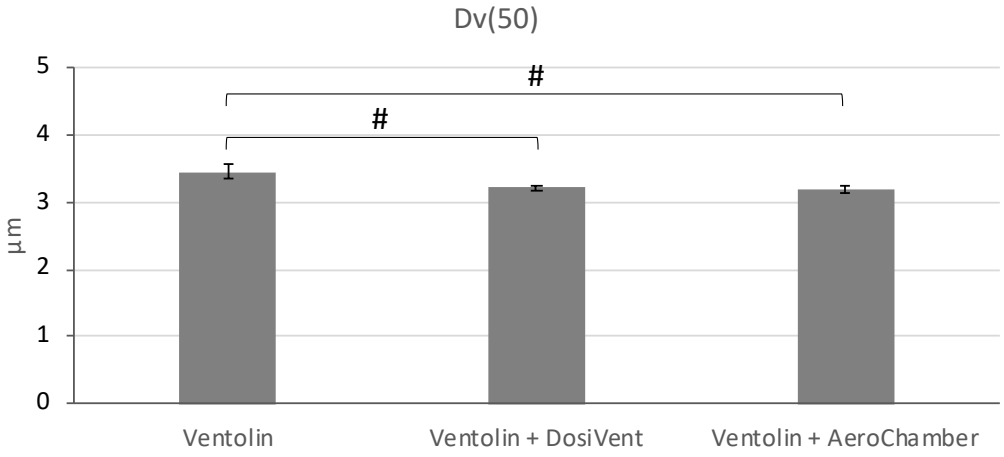

Figure 9. Particle size distribution in the Dv(50) fraction (50% of the particles) measured by laser diffraction. # Significant differences according to the Kruskal-Wallis followed by the Mann-Whitney U-test (p>0.05).

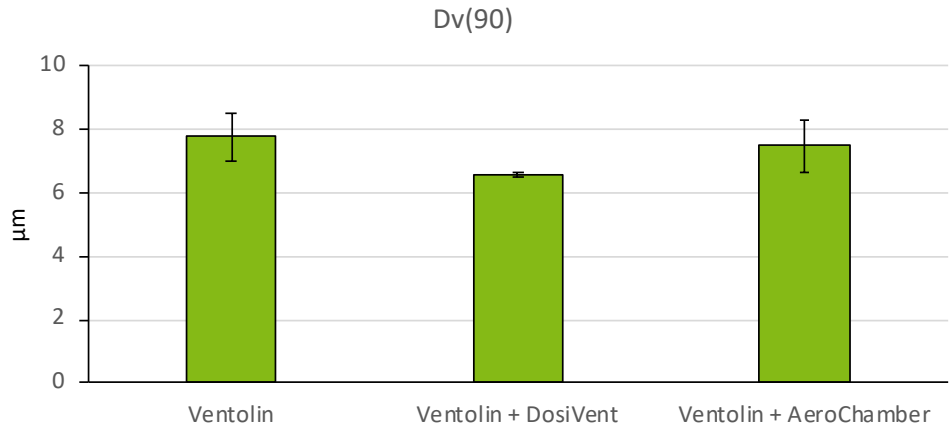

Figure 10. Particle size distribution in the Dv(90) fraction (90% of the particles) measured by laser diffraction.

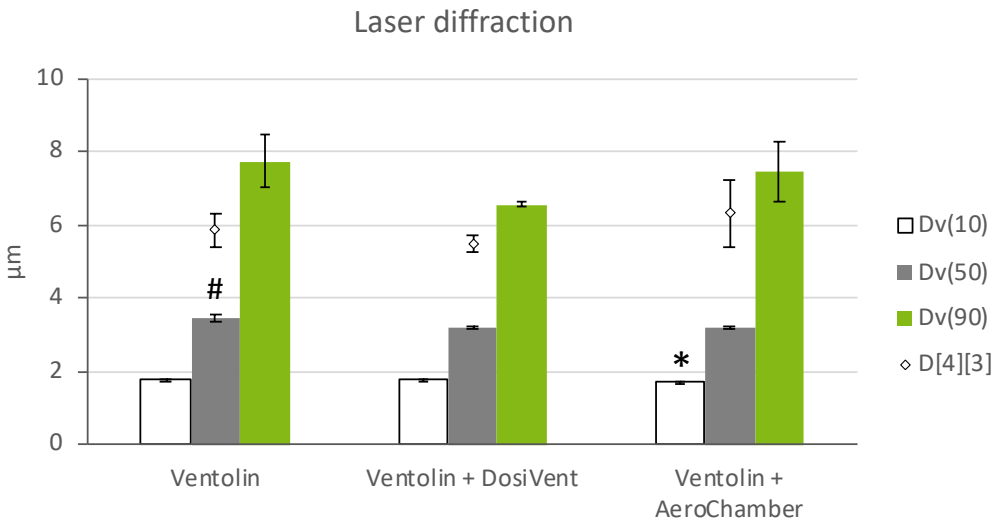

Figure 11. Particle size distribution in the Dv (10), Dv(50) and Dv(90) fractions and average particle diameter expressed in relation to particles volume measured by laser diffraction.

5. CONCLUSIONS

- DosiVent and AeroChamber VHCs showed similar drug retention and delivery in terms of quantification of salbutamol, however a higher concentration of salbutamol particles was observed on the rubber valve of the AeroChamber device, indicating drug retention on this part of the device.

- Concerning particle size distribution, both VHC devices showed a similar performance and did not retain any specific particle size fraction of salbutamol.

- Both devices presented similar efficacy, however the accumulation of salbutamol on the rubber valve of the VHCs was higher in the AeroChamber device compared to the Dosivent.