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Inhaler Testing

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Summary

In the following assignment IVL has performed inhaler testing. An experimental set-up was developed, including an optical particle counter (Grimm 1.108) for determining the particle mass size distribution of the generated aerosol in the size range of 0.3-20 μm. Five different inhalers were tested including an inhaler that is under development and not yet on the market (here called the Prototype), using two different medical substances (Salbutamol sulphate (SS) and Ipratropium (IP)). For comparative purposes, the mass size distribution using an 8- stage Andersen Cascade Impactor (ACI) and an OPC were also derived.

The different inhalers were tested by analysing five actuations for each inhaler and compound tested. Prior testing an inhaler, 5 actuations were actuated to the vent. In all the tests also Ventolin was analysed in order to see the stability of the set-up.

Three different types of inhalers were tested: Pressurised metered-dose inhalers (pMDI), Aqueous droplet inhalers (ADI) and Nebulisers (Neb).

For salbutamol sulphate larger particle sizes were observed for the Ventolin inhaler compared to the Prototype, Nebulizer and Respimat inhalers. The mass median diameter (MMD_1, calculated assuming a lognormal distribution, and [MMD_2], calculated interpolating the points before and after the 50% cumulative mass (the method commonly used for cascade impactors)) was 3.16±0.05 [2.78±0.04], 0.57±0.02 [0.50±0.01], 0.62±0.07 [0.48±0.02] and 0.89±0.08 [0.75±0.08] μm for Ventolin, Respimat, the Nebulizer and the Prototype, respectively. One reason for larger particle sizes measured for Ventolin may be that Ventolin gives micronized drug particles suspended in the propellant, whereas aqueous solutions were used in the other inhalers. Important to note is that the Respimat inhaler is designed specifically for Spiriva inhalation fluid. Using another medical substance can give the wrong dosage.

To be able to better investigate the performance of the Prototype, tests with IP were also conducted. Here all the inhalers were using solution formulations, so the Prototype could readily be compared with another pMDI that is available on the market (Atrovent). Both Atrovent and the Prototype showed a bimodal size distribution with one mode peaking below 1 μm and another mode around 2 μm. Respimat yielded a more unimodal size distribution with one mode peaking below 1 μm. The MMD_1 and [MMD_2] of Atrovent, Prototype and Respimat were 0.72±0.02 [0.64±0.01], 1.13±0.28 [1.03±0.43] and 0.43±0.01 [0.37±0.01] μm, respectively.

In order to compare the mass size distributions measured with the 8-stage ACI and the OPC, three sets of actuations were conducted, each containing 10 actuations in order to get enough mass for the successive filter weighing. However, the results showed that the number of actuations per filter was not enough to get a representative mass size distribution. Instead, 52 actuations were conducted. The mass size distribution obtained using the ACI is similar to literature data, showing that the set-up developed is well suited for inhaler testing. The MMD_2 using the OPC is somewhat larger (2.56±0.11 vs 2.36 μm) which probably is due to non-spherical particle sizes of the micronized drug particles.

Introduction

In the following assignment IVL has performed inhaler testing. The purpose of the testing was to determine the particle mass size distribution generated by the different inhalers. An experimental set-up was developed, including an optical particle counter (Grimm 1.108) for determining the particle mass size distribution in the size range 0.3-20 µm. Five different inhalers were tested including an inhaler that is under development and not yet on the market (here called the Prototype) and two different medical substances (salbutamol sulphate and Ipratropium). For comparative purposes the mass size distribution using an 8-stage Andersen Cascade Impactor (ACI) and an OPC were measured. The different inhalers were tested by analysing five actuations for each inhaler and compound tested. Prior testing an inhaler, 5 actuations were actuated to the vent. In all the tests also Ventolin was analysed in order to see the stability of the set-up. When doing the ACI and OPC comparison, 52 actuations were conducted to overcome mass limitations of the subsequent filter weighing.

Experimental

The experimental set-up developed and used is shown in Figure 1. For particle characterisation an Optical Particle Counter (OPC) was used (Grimm, Model 1.108), measuring particles in the size range 0.3-20 µm. The set-up consisted of one inlet part, where the inhaler was attached, that was positioned 90 ° towards the main flow, simulating the human throat.

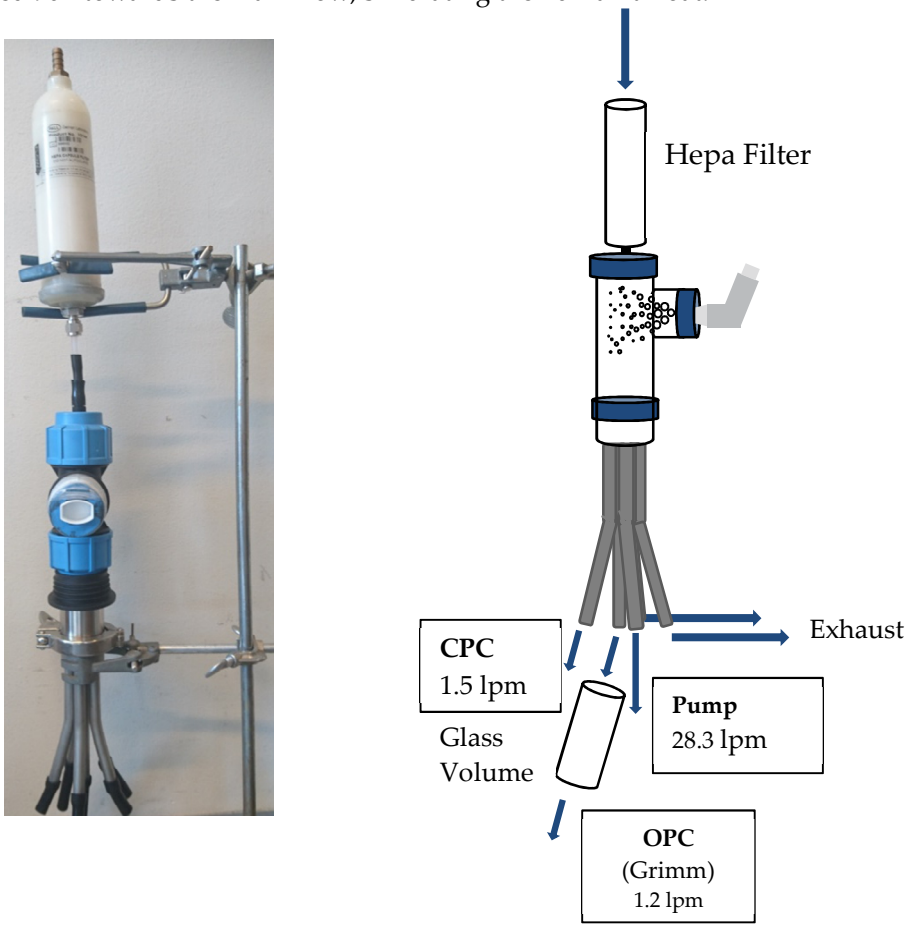


Fig. 1 *To the left a picture and to the right a schematic of the set-up used.*

The actuated dose was diluted with cleaned room air using a Hepa-filter. The total flow was ~31 litres per minute (lpm). A CPC (condensation particle counter, TSI 3775) was used for rapid detection of the total number of particles (time resolution 1 Hz). This was used as a guide for knowing when to actuate and when to take the inhaler away from the inlet. When adding the inhaler to the set-up the flow is distorted for a small period of time and the signal from the CPC gives a good indication of when the system is constant again.

Prior testing of all the inhalers, five actuations were performed to the vent. To prevent too high concentrations for the OPC, a glass volume was used to smear out the signal in time. The system was optimised for testing Ventolin, and when testing some of the other inhalers only a part of the dose could be added to the set-up in order to get the correct concertation range. The total flow was measured both before and after the tests.

Optical Particle Counter (Grimm 1.108)

With this on-line instrument particles are detected by light scattering, where each pulse is giving number of particles and the size of the particles is retrieved by the intensity of the scattered light. The light source is a laser diode (780 nm). The size range measured is 0.3 to 20 µm in 15 size channels and with a time resolution of 6 s. Mass is calculated by assuming spherical particles with unit density. In order to be able to detect the scattered light from each particle, the particle concentration cannot be too high in the air sample. The concentration range possible to measure with this instrument is $0\text{-}2\times10^6$ particles per litre (Grimm 1.108 Manual).

Andersen Cascade Impactor (ACI)

The Andersen Cascade Impactor (ACI) is an 8-stage cascade impactor where particles are separated depending on their aerodynamic size. Each stage contains progressively finer nozzles, where larger particles are impacted on a collection plate due to inertia and smaller particles follow the air stream to the following stage. The cut-off sizes for the eight stages at a flow rate of 28.3 lpm are shown in Table 1. In this work, glass fibre filters were used and the weighing before and after exposure was performed in an accredited laboratory for filter weighing (stable temperature and humidity).

Table 1. The size range and midpoint diameter of the eight stages in the ACI

Stage	Size range (µm)	Midpoint Diameter (µm)
0	9.0-10[a]	9.50
1	5.8-9.0	7.40
2	4.7-5.8	5.25
3	3.3-4.7	4.00
4	2.2-3.3	2.75
5	1.1-2.2	1.65
6	0.7-1.1	0.90
7	0.4-0.7	0.55

[a] *If a pre-separator is used, otherwise no upper limit*

Inhalers and substances analysed

In this assignment four different inhalers, available on the market, were tested (including three different types of inhalers) as well as a new inhaler that is under development and not yet on the market, here called the **Prototype**. In the tests, the medical substances salbutamol sulphate (SS) and Ipratropium (IP) were used.

The inhalers included in this assignment were:

Pressurised metered-dose inhalers (pMDI) that use a propellant to deliver a fixed aerosol volume (liquid solution or suspension) to the patient (Ventolin, Atrovent, Prototype).

Aqueous droplet inhalers (ADI) that deliver a pre-metered dose of solution formulation without using a propellant (Respimat).

Nebulisers (Neb), are similar to ADI, but generally operate continuously once loaded.

In Table 2, a summary of the different inhalers and the medical substances tested is shown.

Table 2. Summary of the inhaler types and medical substances tested and their properties

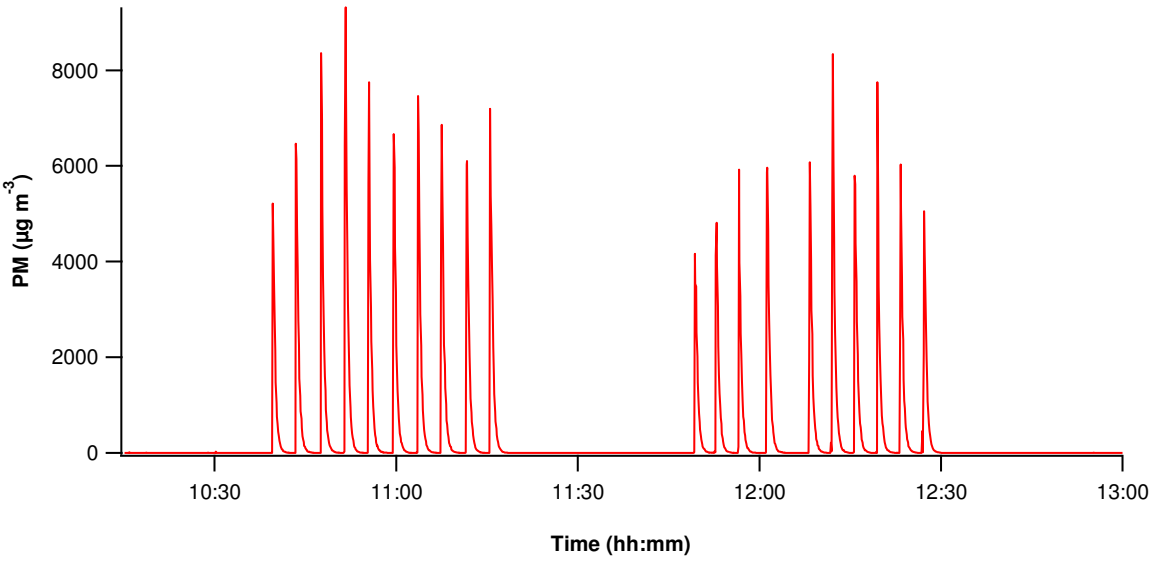
Trade Name	Inhaler type	Propellant	Medical Substance	Formulation
Ventolin	pMDI	HFA-134a	Salbutamol sulphate	Suspension
Atrovent	pMDI	HFA-134a	Ipratropium	Solution
Prototype	pMDI	CO_2	Salbutamol sulphate & Ipratropium	Solution
Respimat[a]	ADI	-	Salbutamol sulphate & Ipratropium	Solution
-	Neb	-	Salbutamol sulphate	Solution

[a] *Respimat is designed specifically for Spiriva inhalation fluid. Using another medical substance can give the wrong dosage.*

Results and Discussion

Reproducibility between different actuations

In Figure 2, an example of the reproducibility of 10×2 actuations of Ventolin as measured by the OPC is illustrated. In this figure also the total mass of the particles are shown as integrated particle mass per actuation.



Actuation	Integrated PM (µg)
1	71
2	96
3	106
4	136
5	103
6	101
7	102
8	100
9	92
10	98
Average	**100±16**
MMD_1	**2.94±0.09**
MMD_2	**2.64±0.09**

Actuation	Integrated PM (µg)
1	64
2	74
3	70
4	94
5	86
6	111
7	90
8	81
9	85
10	75
Average	**83±13**
MMD_1	**2.90±0.10**
MMD_2	**2.59±0.10**

Fig. 2 *Example of the reproducibility of 10×2 actuations of Ventolin. The top graph displays the mass of particles measured using the OPC in µg m^{-3}. The infolded tables give the total mass of each actuation in µg and the mass median diameter (MMD_1 and MMD_2). Stated errors are standard deviation*

According to the medical labelling each dose is 100 µg. The average mass per actuation was 100±16 for the first set and 83±13 for the second set of actuations. Also the mass size distribution was similar between the actuations and sets of actuations (Figure 3 and Tables in Figure 2). The mass median diameter (MMD) has here been calculated both by assuming a lognormal distribution (MMD_1), and by interpolating the points before and after the 50% cumulative mass (the method commonly used for cascade impactors) [MMD_2].

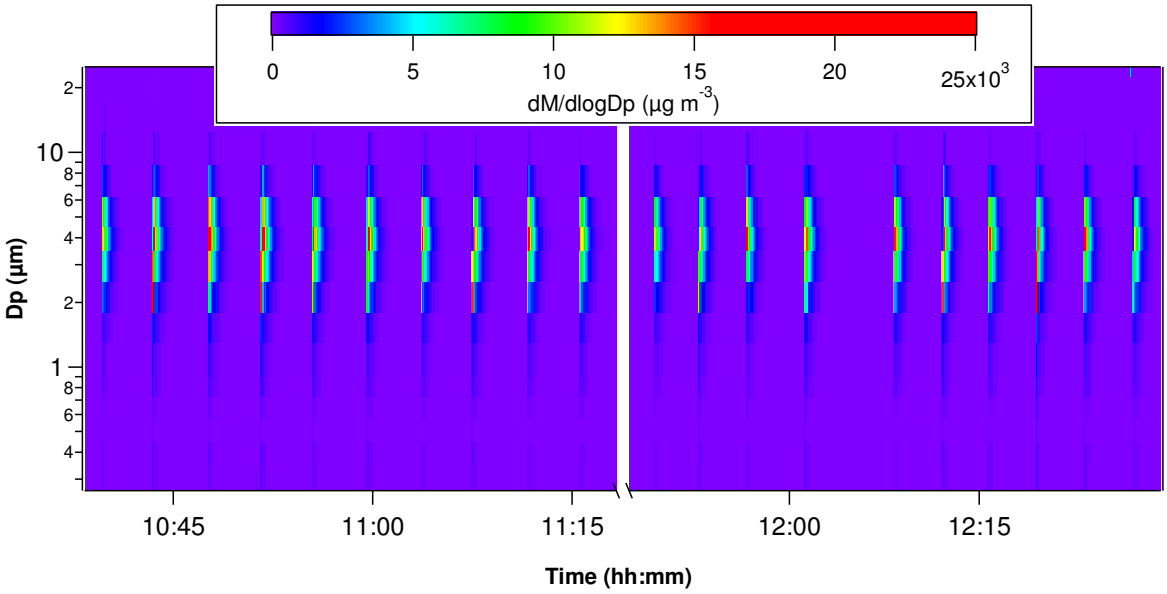


Fig. 3 *The normalised mass size distribution measured for 10×2 actuations of Ventolin.*

Salbutamol sulphate (SS) testing

In Figure 4 the average particle mass size distributions measured for salbutamol sulphate (SS) are shown and as can be seen all inhalers except for Ventolin were giving one particle mode that was peaking below 1 µm. The size distribution of the Nebulizer and the Prototype were bimodal with one mode peaking below 1 µm and another around 2 µm. For Ventolin the mass size distribution was peaking at larger particle sizes, the mass median diameter, MMD_1 [MMD_2] was 3.16±0.05 [2.78±0.04] µm. The MMD_1 [MMD_2] for Respimat, the Nebulizer and the Prototype were 0.57±0.02 [0.50±0.01], 0.62±0.07 [0.48±0.02] and 0.89±0.08 [0.75±0.08], respectively. One reason for larger particle sizes measured for Ventolin may be that Ventolin gives micronized drug particles suspended in the propellant, whereas aqueous solutions were used in the other inhalers.

During the different testing days, the MMD_1 [MMD_2] of Ventolin was in the range 2.88-3.16 [2.41-2.78] µm which is somewhat higher than literature data: 2.34 µm (Berlinski and Pennington, 2017), 2.4 µm (Cripps et al., 2000 and Cruz McCabe et al., 2012). However, important to note is that these data are mass median aerodynamic diameter (MMAD), whereas the diameter measured with the OPC is the optical diameter or volume diameter which for suspended formulation may not be the same thing.

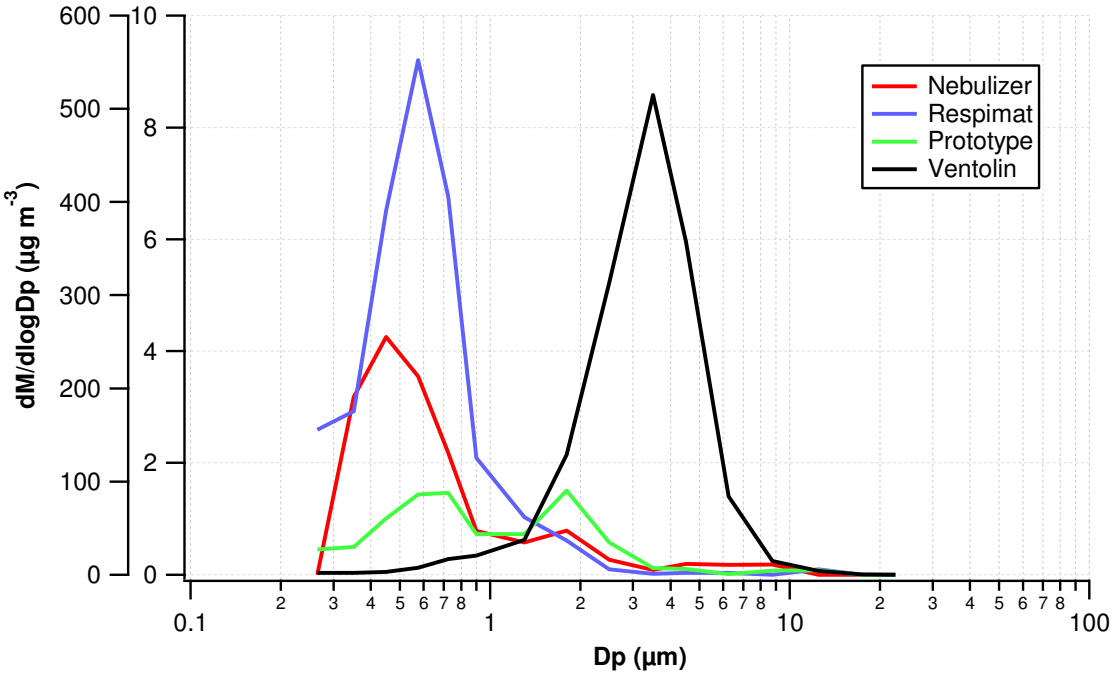


Fig. 4 *The average particle mass size distribution measured for the inhalers Nebulizer (red), Respimat (blue), Prototype (green) and Ventolin (black) using salbutamol sulphate. The y-axis most to the left is the axis for Ventolin.*

Ipratropium (IP) testing

For the SS testing both suspensions and aqueous solutions were measured which may be problematic when using the OPC technology as the assumption is spherical particles with unit density. For this reason tests were also conducted using the medical substance Ipratropium. In Figure 5 the average particle mass size distributions are shown. During these tests also Ventolin was tested, acting like an internal standard in order to check the performance of the experimental set-up between different tests and days. Atrovent is a pMDI that is available on the market for Ipratropium, which is a solution formulation. Due to the upper concertation limits of the OPC instrument, only a fraction of the total dose was added to the experimental set-up. Atrovent was actuated into a spacer and after 5s the spacer was added to the mouth piece of the experimental set-up (see Fig. 1).

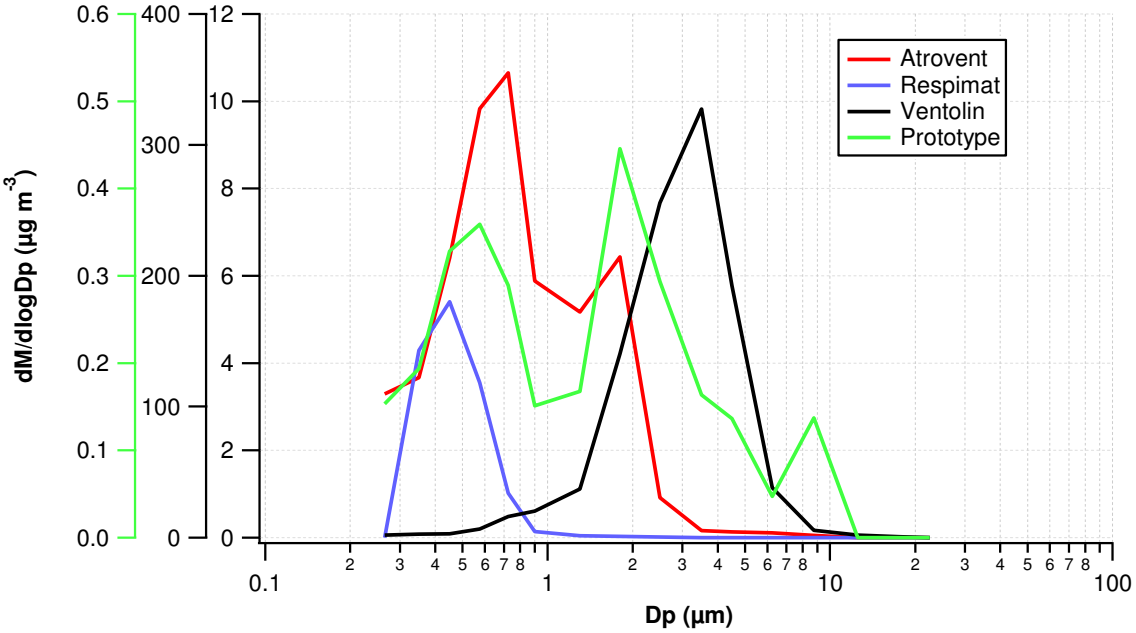


Fig. 5 *The average mass size distribution of the different inhalers tested using solution formulation of Ipratropium. Atrovent (red), Respimat (blue), Prototype (green). For comparative purposes of the status of the experimental set-up also Ventolin (using suspension formulation of SS) is shown (black). The y-axis most to the left is for the Prototype and the axis second to the left is for Ventolin.*

Both Atrovent and the Prototype were showing a bimodal size distribution with one mode peaking below 1 µm and another mode around 2 µm. Respimat is giving a more unimodal size distribution with one mode peaking below 1 µm. The MMD_1 [MMD_2] of Atrovent, Prototype and Respimat were 0.72±0.02 [0.64±0.01], 1.13±0.28 [1.03±0.43] and 0.43±0.018 [0.37±0.01] µm, respectively. The MMD_1 of Atrovent is similar to literature MMAD data 0.87±0.05 (Nikander et al., 2011), 0.9±0.0 (Adi et al., 2012) and 0.7±0.1 (Dennis et al., 2015).

The impact of using a spacer before the inlet of the experimental set-up was tested using the Respimat inhaler. In Figure 6, the average mass size distribution with and without utilizing a spacer before the inlet is shown and as can be seen there is little influence on the mass size distribution observed (MMD_1 0.46 vs 0.43). Hence, the mass size distribution of Atrovent can be compared with size distributions not using a spacer before the inlet.

The IP tests started by testing Ventolin and ended by testing Ventolin, just to make sure that the experimental set-up is stable with time, and as can be seen in Figure 7, the average mass size distribution is very similar throughout the day (MMD_1 2.90±0.08 vs 2.82±0.05 µm, respectively).

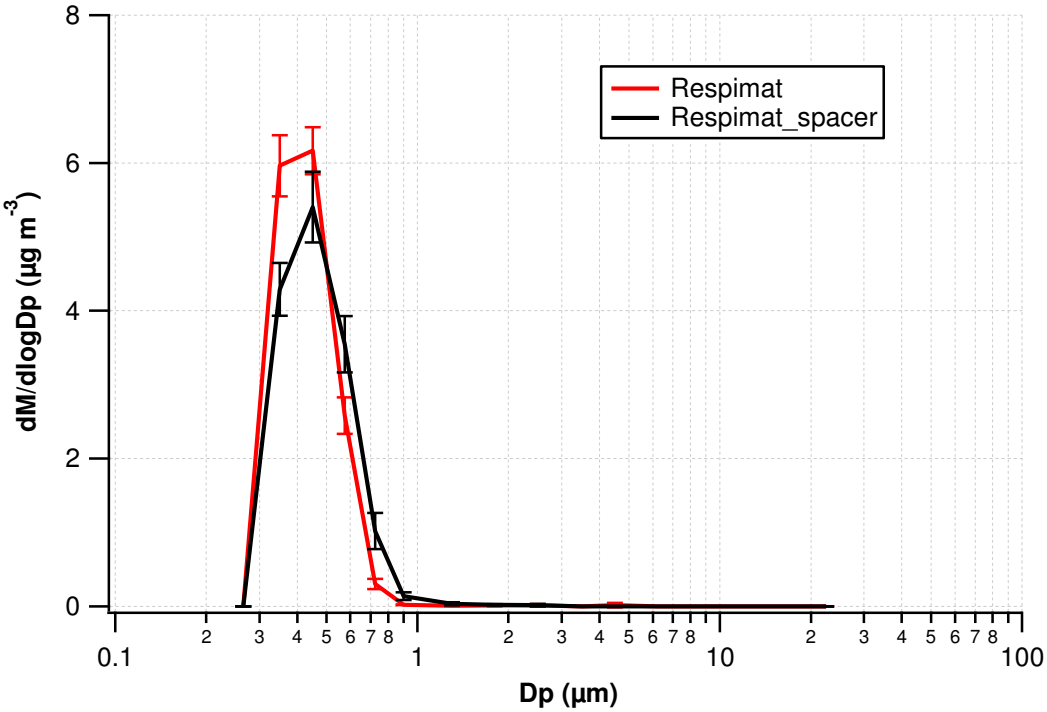


Fig. 6 *The average mass size distribution with (black) and without (red) a spacer before the inlet of the experimental set-up.*

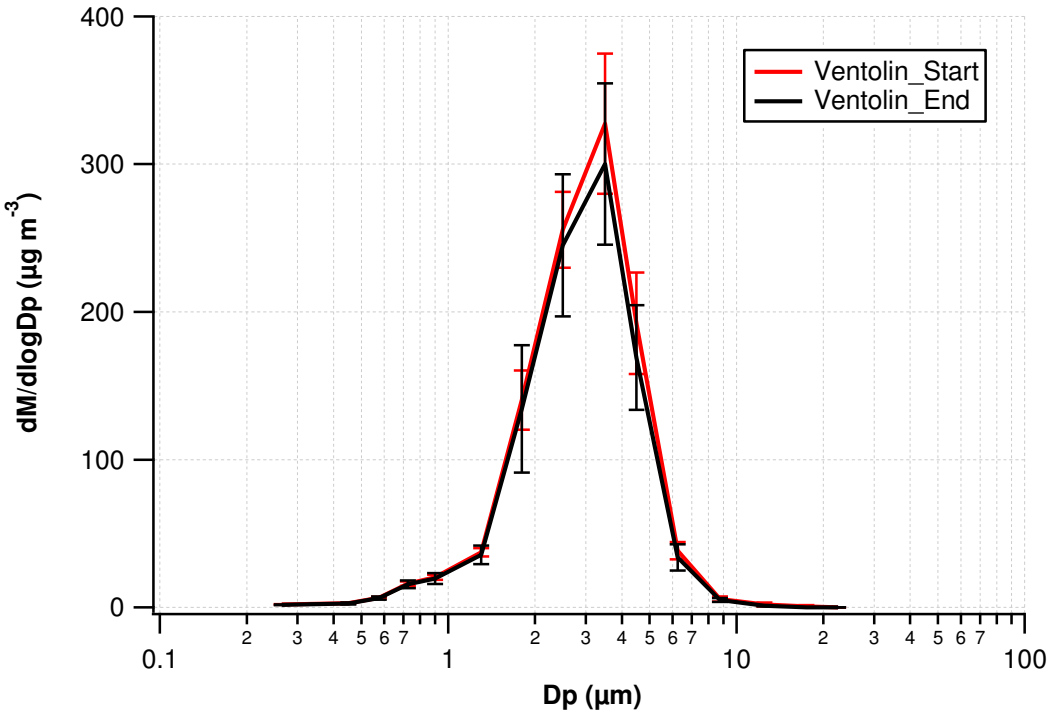


Fig. 7 *The average mass size distribution of Ventolin in the beginning of the tests (red) and at the end of the tests (black).*

Andersen Cascade Impactor (ACI) and Optical Particle Counter (OPC)

In order to compare the mass size distributions measured with the 8-stage ACI and the OPC, three sets of actuations were conducted, each containing 10 actuations in order to get enough mass for the successive filter weighing. The Ventolin inhaler was used. During these actuations both the OPC and the ACI were sampling simultaneously. The ACI was positioned just before the pump shown in Figure 1. The flow through the ACI was 28.3 lpm. Prior the tests, 5 actuations were actuated to vent. Additional 8 filters were taken when only measuring the background, i.e., Hepa-filtered air with no actuations. The analysis of the filters revealed that the number of actuations per filter was not enough to get a representative mass size distribution. When analysing the background filters the mass difference was generally negative, hence suggesting there is some material/contamination that is cleaned when exposed to an air flow (the filters used were newly bought glass fibre filters 81 mm). An additional test was therefore developed where the filters first were exposed to 45 min of Hepa-filtered air before weighing and these filters were thereafter exposed to 52 actuations of Ventolin. It was a new inhaler so prior the tests 50 actuations were actuated to vent. The time between actuations was ~60 s. For the last five actuations the time between actuations was 3-4 min in order to also get valid OPC data. The mass size distribution measured using the ACI and the OPC is shown in Figure 8. As can be seen the mass size distributions measured using the two instruments are similar. The $MMAD_2$, calculated by interpolating the points before and after the 50% cumulative mass (the method commonly used for cascade impactors), was 2.36 µm which is in accordance with literature. However, calculating assuming a lognormal size distribution the $MMAD_1$ will be 2.93 µm. The MMD_1 and MMD_2 calculated from the OPC data were 2.89±0.15 and 2.56±0.11, respectively.

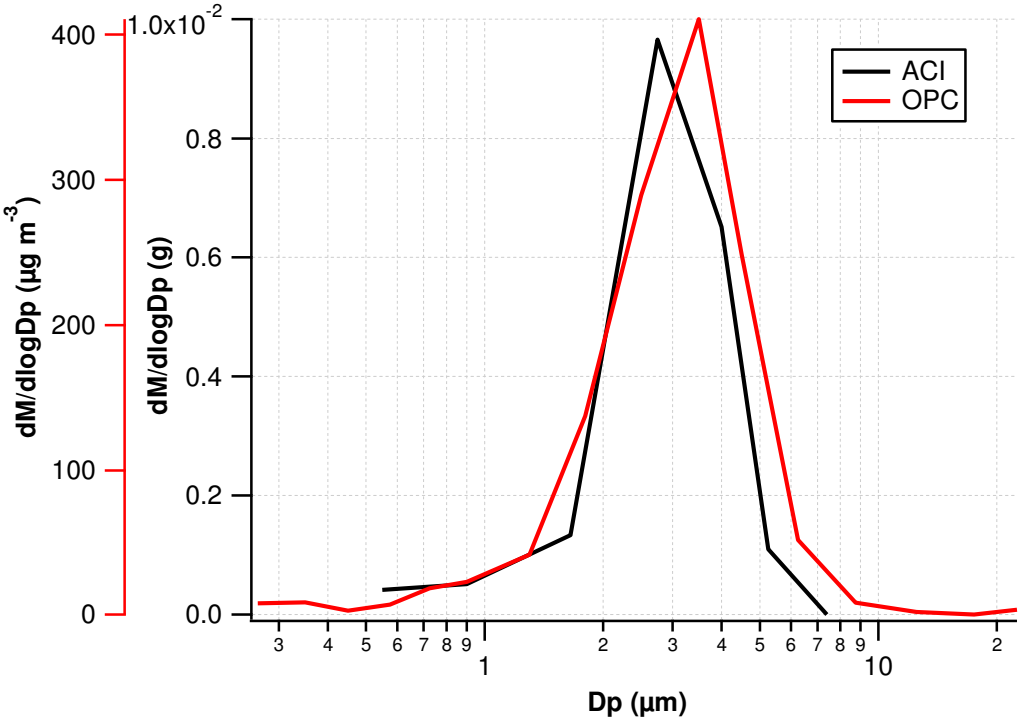


Fig. 8 *In red the average mass size distribution (52 actuations) using an 8-stage ACI and the average mass size distribution of the last five actuations using an OPC (Grimm, Model 1.108).*

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