Available online www.jsaer.com

***Journal of Scientific and Engineering Research*, 2020, 7(3):107-121**

Research Article

ISSN: 2394-2630
CODEN(USA): JSERBR

Numerical Study of a Modified Valved Holding Chamber for Spray Inhalation

Agustina Ravettino, Ana Scarabino , Federico Bacchi

Computational Fluid Dynamics Group – GFC. School of Engineering, National University of La Plata, Argentina

Abstract Pressurized measure-dose inhalers (pMDIs) administer medication to patients suffering from chronic diseases of the lower respiratory tract, particularly asthma. The drug released from the pMDI can be difficult to inhale directly, which explains the different chamber designs available, which contribute to the correct dose inhalation.

In this paper we study, through numerical simulation, the behavior of medication microdrops injected into two different devices known as “Valved Holding Chambers” or “Spacers”. ANSYS CFX software is used to model a multiphase flow, in which the continuous phase (air) replicates the breathing cycles of a child and an adult, while the discrete phase (medication microdrops) is modeled by a Lagrangean particle formulation. Two different designs are studied: A cylindrical standard model, and a modified grooved design, with a geometry that induces a swirling motion when the patient breathes in. The particle flow is studied, and the total amount of inhaled medication is compared for both systems, finding quantifiable increases in the modified design.

Keywords spray, puff, inhalers, CFD, particle injection, spacers, PMDIs

1. Introduction

The World Health Organization (WHO) reports that chronic diseases of the lower respiratory tract ranked third in the 10 causes of global death between 2000 and 2016 [1]. Inhalation therapy is the first-line treatment of asthma, a disease characterized by episodes of wheezing, breathing difficulties, chest tightness, and coughing. Asthma is the result of chronic inflammation of the conducting zone of the airways, which subsequently results in increased contractility of the surrounding smooth muscles. This disease affects more than 300 million people in the world, growing at a rate of 50% per decade and causing the death of 220,000 people per year [2].

Inhalation therapy is a cornerstone in the treatment of airway diseases. Anti-inflammatory and bronchodilator drugs are used with the objective of reducing the inflammation of the pulmonary tissue, which causes a reduction in the diameter of the bronchus [3].

Asthma drugs are divided into either quick-relief or long-term medications. The most effective long-term medications reduce airway inflammation, which helps prevent symptoms from starting. These medications do not give quick relief from symptoms. Inhaled corticosteroids are the preferred medication for the long-term control of asthma. They are the most effective option for the long-term relief of the inflammation and swelling that makes airways sensitive to certain inhaled substances. Quick-relief, or “rescue” medications, instead, relieve asthma symptoms that may flare up. These medications act quickly to relax tight muscles around the airways when the patient is having a flareup. They allow the airways to open up, so air can flow through them. Inhaled short-acting beta2-agonists (such as salbutamol or terbutaline) are the first choice for quick relief [4].

Nowadays, inhalation therapy is the most common and effective way to deliver asthma drugs to the lungs, regardless of age. Compared to oral tablets, inhaled medications are delivered directly to the airways and allow a smaller dose to be administered leading to a quicker onset of action and fewer side-effects.

In this paper the pressurized metered dose inhaler (pMDI) with a spacer will be considered as the main drug delivery treatment for asthma. A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medication that is usually self-administered by the patient via inhalation. Pressurized metered-dose inhalers (pMDIs, **Error! Reference source not found.**) are among the major aerosol generating devices used for aerosol delivery of bronchodilators in ambulatory patients. The pMDI is a small, cost-effective and very portable device containing between 100 and 400 doses. This device comprises a disposable canister with a pressurized mixture of propellants, surfactants, preservatives, flavoring agents and active drugs. This mixture is released from the canister through a metering valve.

A propellant is a compressed inert gas that acts as a vehicle for discharging the contents of an aerosol container. For years, chlorofluorocarbon (CFC) was the propellant used to move the albuterol medication out of the inhaler, so the patient can inhale the medication, but because this propellant has been shown to deplete the ozone layer, new asthma inhalers using hydrofluoroalkane (HFA) are now being used [5].

Figure 1: Pressure Metered Dose Inhaler PMDI

Drug dose effectiveness in inhaled delivery is difficult to measure due to the fact that only a small fraction of the pMDI nominal dose reaches the lower respiratory tract.

Spacer devices are an extension attachment to the pMDI device and simply provide a “space”, distance between the patient’s mouth and the inhaler device, to slow down the high velocity of the emitted aerosol cloud. This slowing down leads to reduced throat deposition and allows time for greater evaporation of the propellant, producing relatively smaller drug particles that have greater potential to deposit within the lungs.

The application of Computational Fluid Dynamics (CFD) in the design of aerosol drug delivery technologies has been proved to be a valuable tool when inhaler performance is investigated. The pMDI actuation is a complex phenomenon which involves turbulent flow, multiple phases, and heat mass and momentum transfer between the droplets and the environment. Several studies have been developed in order to model numerically pharmaceutical aerosols as a multi-phase flow, in which the inhaled air is the continuous phase and the particles or droplets, the discrete phase [6]. The combination of complex physical processes, transient effects, small length and time scales and limited knowledge of initial conditions, all complicate the CFD modeling of pMDI aerosol formation and delivery. Perhaps because of these complications, there have been relatively few CFD studies performed on pMDI inhalers, especially on the process of aerosol formation in the production region of these devices. Studies have primarily focused on modeling spray physics in post-nozzle flow, often comparing numerical predictions with *in vitro* experimental measurements of droplet velocity, size and deposition [7]. Dunbar et al., performed a theoretical investigation of a pMDI spray by a CFD study consisting of the modeling of an actuator flow from the metered chamber to the nozzle, which was based on a quasi-steady-state for flow analysis during a single actuation [8]. The objective was to examine droplet formation and trajectories during the inhaler actuation. The predicted results were validated against experimental data obtained using “phase Doppler particle analysis” (PDPA). Comparing the numerical results with the experimental data, it was observed that for a distance of 25 mm from the spray orifice, the droplet velocity and size distributions were in agreement, although such a correlation did not hold further downstream. Versteeg *et al* [9], used CFD to examine steady-

state airflow and aerosol plume behavior in two pMDI models. Simulated flow fields through an experimental pMDI and the "AstraZeneca Pulmicort" pMDI were found to be similar and highly complex; multiple regions of recirculation with high levels of turbulence were observed inside the inhaler. Smyth *et al* [10], also performed a spray pattern analysis for pMDIs, studying the influence of orifice size, particle size, and droplet motion correlations. Ruzycki *et al* [7], presented a comprehensive review of the use of CFD in inhaler design. These authors showed that the application of CFD modeling techniques for pMDIs, nebulizers and DPIs improved the understanding of aerosol transport and deposition and allowed saving time and resources for the optimization of inhaler technologies.

The study by Kleinstreuer *et al* [11], demonstrated the effect of spacer use on deposition rates for pMDIs. Inserting a spacer between the pMDI and upper airway provided a sudden expansion in volume that decreased flow velocity and increased droplet residence time and evaporation. A subsequent reduction in droplet speed and size resulted in significantly reduced deposition in the oral cavity, while simultaneously increased drug delivery to the lungs. Performance of both the CFC and HFA pMDIs improved with spacer use, with lung deposition increasing from 5.2 to 52.9% for the CFC-pMDI and from 46.6 to 74.6% for the HFA-pMDI. Nevertheless, while the simulations by Kleinstreuer *et al* suggested that spacer use increased lung deposition considerably, Leach and Colice [12], observed *in vivo* that lung deposition was relatively unaffected using small particle aerosols (HFA) and either the same or less using large particle aerosols (CFC). They also found a higher proportion of deposition in the spacer compared with the simulations by Kleinstreuer *et al*. The discrepancy in deposition measurements may arise from nozzle diameter or formulation differences between the *in vivo* pMDI of Leach and Colice and the simulated pMDI of Kleinstreuer *et al*., which could lead to significant variations in droplet size and velocity and subsequently influence deposition. These differences also highlight the difficulties of modeling this problem. Despite the observed differences in deposition, both studies demonstrated the general trend of decreased oropharyngeal deposition with spacer use, a trend further observed in an *in vitro* study of HFA-pMDIs by Cheng *et al* [13]. With this in mind, the differences in deposition between the Kleinstreuer *et al.* simulations and *in vivo* measurements by Leach and Colice suggest that this is an area requiring further exploration.

While the study by Kleinstreuer *et al*. suggested that spacer use could increase lung deposition and decrease oropharyngeal deposition, the effects of spacer design were not considered. Oliveira *et al* [14], used CFD to optimize the design of the "Volumatic" spacer for improved deposition performance. It was proposed that modifications to the spacer body and valve could reduce the large areas of recirculation observed in the "Volumatic" spacer. An optimized spacer was designed by combining the best-performing body and valve geometries following simulations of several prototypes. Noticeable improvements in flow features were observed in the optimized spacer. Reduced regions of recirculation and decreased levels of turbulence kinetic energy suggested that the improved design would increase drug delivery to the patient while reducing deposition inside the device. The design process employed by Oliveira *et al.* allowed for the evaluation of several concepts using CFD prior to physical prototyping [7]. We thus decided to explore further modifications of the spacer geometry which can potentially improve the medication inhalation efficiency.

The hypothesis proposed in the present work is: The helical geometry of the modified grooved valved holding chamber design (here called "SwirlChamber") induces a rotating movement in the air flow when the patient inhales, which causes an improvement in the device inhalation efficiency.

The overall objective is to verify the effect of the axial rotation caused by the helical geometry of the "SwirlChamber" and analyze the percentage of the injected dose of medication effectively inhaled by the patient (inhalation efficiency) in comparison with a standard cylindrical spacer.

Specific objectives are:

- Simulate the fluid´s behavior inside the different valved holding chambers, taking into account two main breathing conditions: One average adult and one average child,
- Verify the efficiency of both devices through numerical simulation, for an adult and for a child.

In this model, the fluid´s behavior through the oropharyngeal tract is not examined. Only the trajectory from the injection up to the total length of the spacer chambers is taken into account.

2. Methodology

The different stages of this work include:

- Bibliographic research to determine the breathing patterns of children and adults, drug dosage, spray characteristics, size of drops produced by inhalers and technical characteristics of spacers, especially for pediatric use. The breathing profiles were reproduced from Grotberg [15]. The mass flow evolution was fitted in each case by analytical expressions.
- Theoretical study of different CFD models of liquid injection in air, selection of the most suitable for the problem, and definition of injection parameters based on the information about sprayers found in the bibliography [16].
- Geometrical survey and CAD development of a standard spacer available in the market, as well as a new grooved design ("SwirlChamber"), which induces a rotational motion in the air.
- Setting of the different model configurations for the problem in ANSYS-CFX software.
- Computation, analysis of results, and conclusions.

2.1 Geometry

The difference between the two studied devices can be seen in the aerodynamic chamber geometry, where the drug particles are suspended before and during the inspiration phase. The different geometries are shown in Figure and Error! Reference source not found.. The inhalation valve model has the same geometric characteristics for both devices as shown in Figure 4.

Figure 2: standard chamber geometry

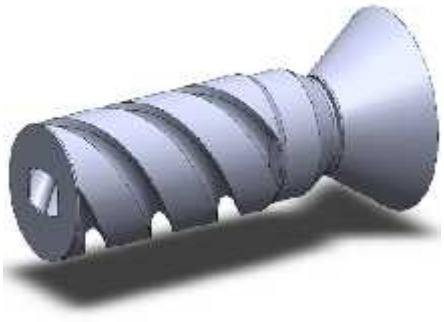

Figure 3: "SwirlChamber" geometry

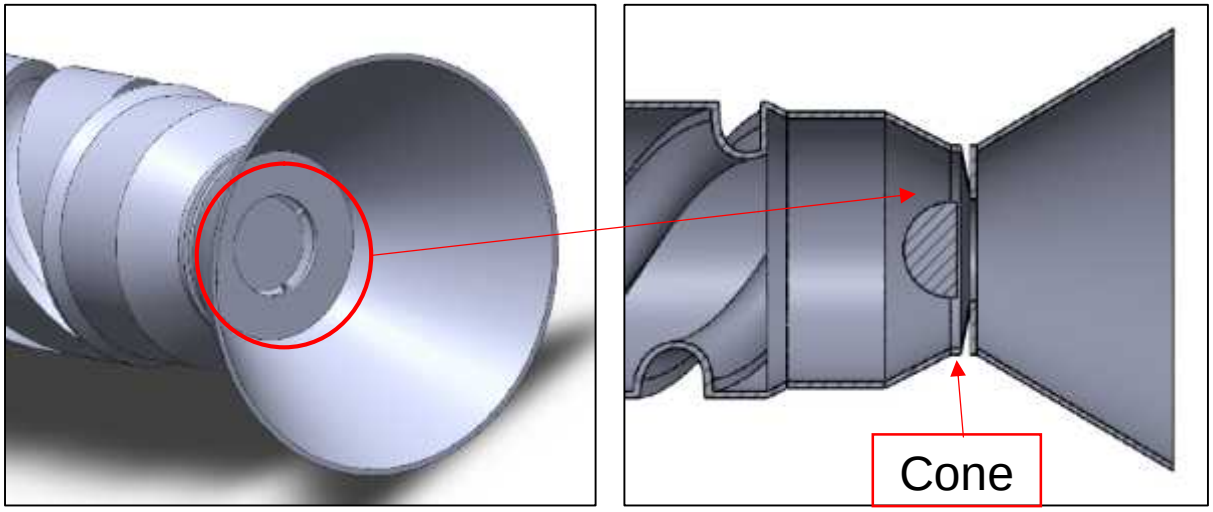

Figure 4: Inhalation Valve Model

The inhalation valve is made of an elastic material, which, when the patient is inhaling rises to allow the passage of the drug particles from the chamber to the mask. When the patient is exhaling, the valve closes, avoiding drug waste.

To simplify the numerical model, the inhalation valve was modeled as just open or closed, and the corresponding opening was set as an interface with a null mass flow condition during the first 0.5 seconds of simulation (when the valve remains closed and the medication is injected), and switched to a fluid-fluid interface where the particles of medication can freely pass through, when the inhalation + expiration cycle begins, at 0.5 s. Figure 4 shows the cone which models the inhalation valve.

2.2 Mathematical Model

The problem was implemented in the commercial software CFX using high resolution schemes for spatial discretization and a second order backward Euler scheme for the time evolution, with a time step of 0.001 s, adequate for capturing the particle motion. The *k-ω SST* turbulence model was chosen for this study because of its successful implementation in previous research works, and because of its ability to compute the flow within the boundary layer, which is crucial for the evaluation of particle interaction with the spacer walls.

2.2.1 Particle Injection

A Lagrangean approach was performed for the model of particle tracking. The continuous phase (air) and the discrete particles (medication droplets) interact in a "Fully Coupled" way: the particles exchange momentum with the continuous phase (air), which allows the continuous flow to affect the particle motion and the particles to affect the continuous flow (double interaction).

The parameters of the medication injection model are detailed in Table 1.

Table 1: Medication injection characteristics

Parameter	Property / value	Units
Fluid	Salbutamol	-
Density (ρ_p)	1230	kg/m^3
pMDI propellant	HFA-134[a]	-
Injection method	Complete Cone	-
Actuation time (t_{iny})	0.1	s
Particle mass flow ($\dot{m}_{...}$	$1*10^{-6}$	kg/s
Actuation dose	100 (1 dose)	µg
Actuation Origin Radius	0.00025	m
Actuation Velocity	60	m/s
Cone Angle	15	°
Particle diameter distribution	Rosin Rammler	-
Mean diameter	16.54	µm
Spread parameter	1.86	-
Particle Coupling	Fully Coupled	-
Drag Force	Schiller-Naumann	-

The injection velocity of 60 m/s and cone angle of 15°, found in Oliveira et al, 2012, were further verified by means of slow motion camera videos taken at the lab.

Salbutamol injection lasts 0.1 s. The first breathing cycle begins 0.4 s later. It means that, during the first 0.5 s the inspiratory flow is null. After 0.5 s the inhalation begins, which has a duration of 1.5 s for adults and 1 s for children.

For liquid sprays, a convenient representation of the droplet size distribution is the Rosin-Rammler expression [17]. The complete range of sizes is divided into an adequate number of discrete intervals, each one represented by a mean diameter, for which trajectory calculations are performed. If the size distribution is of the Rosin-Rammler type, the mass fraction of droplets of diameter greater than *d* is given by

$$Y_d = e^{-(d/\bar{d})^n}$$

where $\bar{d}$ (mean diameter) is the size constant and *n* (spread parameter) is the size distribution parameter.

Moreover, an interaction rule between the drug droplets and the chamber walls was defined, such that when particles touch these surfaces, they remain attached and do not continue moving ("stick to wall" condition).

2.2.2 Boundary Conditions for the continuous phase (air).

The total simulation time was divided into two periods in which the boundary conditions were modified.

- **Injection Period:**

From 0 to 0.5 s where only the particles are injected and there is no inhalation air flow. In this case, the following boundary conditions are defined for the continuous phase, air:

- ***Inlet***: Wall condition
- ***Outlet:*** Wall condition
- ***Valve Interface model:*** null mass flow (Closed Inhalation Valve)

- **Inspiratory Period**

From 0.5 s until the end of the respiratory cycle for each case, inhalation begins, therefore the boundary conditions change:

- ***Inlet:*** condition defined with an ANSYS CFX CEL EXPRESSION of mass air flow (see Figures 5 and 7).
- ***Outlet:*** negative pressure (INSPIRATION) condition defined with an ANYS CFX CEL EXPRESSION (Figures 6 and 8). It must be pointed out that no attempt was made at this stage to simulate the mouth or nose cavities. Since the goal of this work is to study the influence of the grooved geometry on the droplets flow, the domain outlet boundary was modeled as a time-varying average pressure section.
- ***Valve Interface model:*** Fluid-fluid interface (opened inhalation valve)

A mass air flow curve was established at the inlet (flow expression called "inlet") and the corresponding negative pressure (aspiration pressure) at the outlet surface of the mask (called "outletp") in order to simulate a respiratory cycle considering two different tidal volumes for each case: adult and child.

2.2.2.1 Child Case

- Tidal Volume (TV)= 100 ml
- Inhalation Time (T_i)= 1 s
- Exhalation Time ($T_{e)=}$ 2 s

Considering a tidal volume of 100 ml in a respiratory cycle for a child, with a total duration of 3 seconds (inspiration time = 1 s; exhalation time = 2 s, (London University College, 2018) [18], the time evolution shown in Figure 5 and 6 were defined for the air mass flow at the inlet and the negative pressure at the outlet.

In the child case, for both chamber designs, a minimum of three breathing cycles were needed in order to reduce the number of particles suspended in the spacer to under 1% of the amount injected. After three breaths, a few medication particles still remained in the interior of the aerodynamic chamber of the spacer device. The simulation was finished at that moment, not only because of the small percentage (less than 0.5%) of suspended salbutamol particles, but also due to the medical recommendation to leave the mask at least 10 seconds over the child´s face.

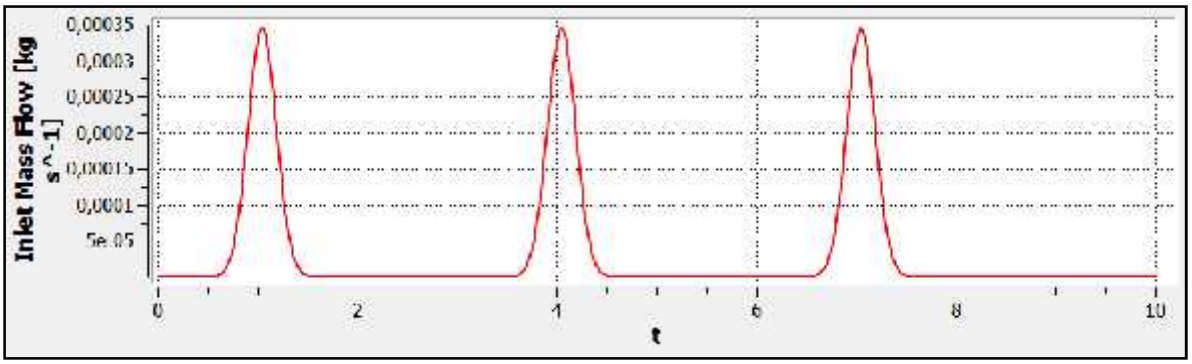

Figure 5: Mass flow inlet. Child Case

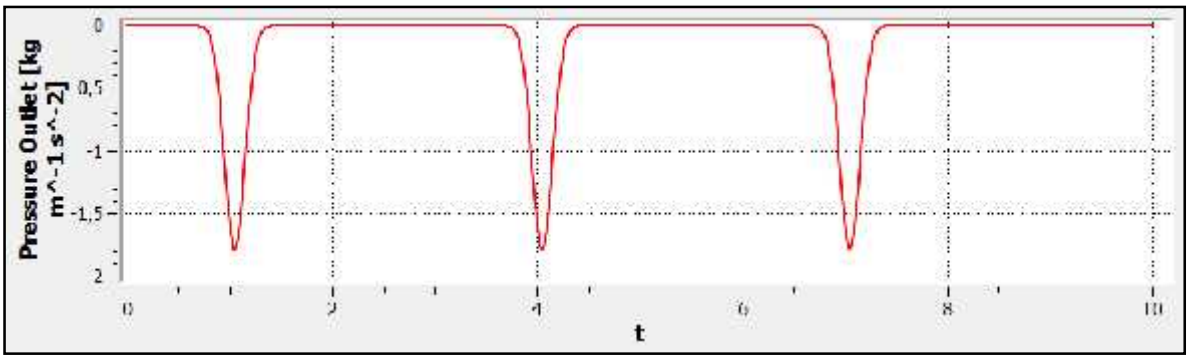

Figure 6: Pressure Outlet. Child Case

2.2.2.2 Adult case

- Tidal Volume (TV)= 500 ml
- Inhalation Time (T_i)= 1.5 s
- Exhalation Time ($T_{e)=}$ 3 s

Considering a tidal volume of inspiration of 500 ml in a respiratory cycle with a total duration of 4.5 seconds (inspiration time = 1.5 s; exhalation time = 3 s, London University College, 2018), the corresponding profiles shown in Figures 7 and 8 were defined for the mass flow of air at the inlet and the negative pressure (suction) at the output:

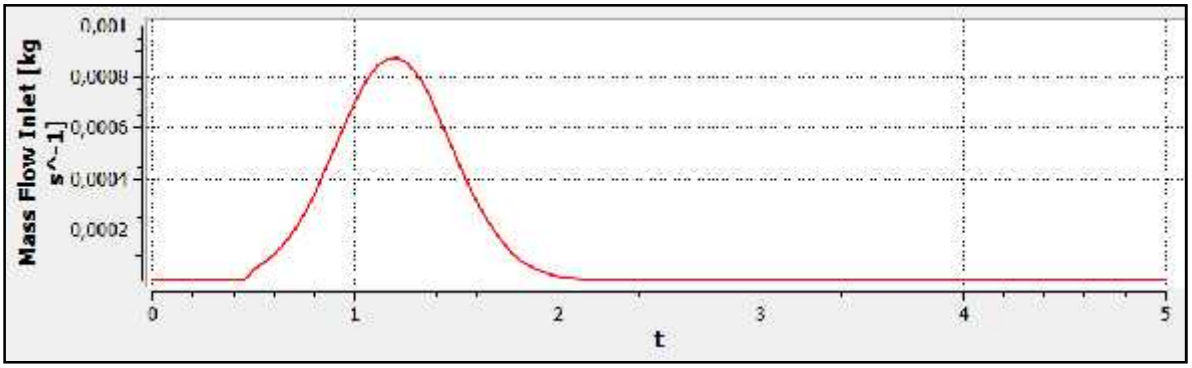

Figure 7: Mass Flow Inlet. Adult Case

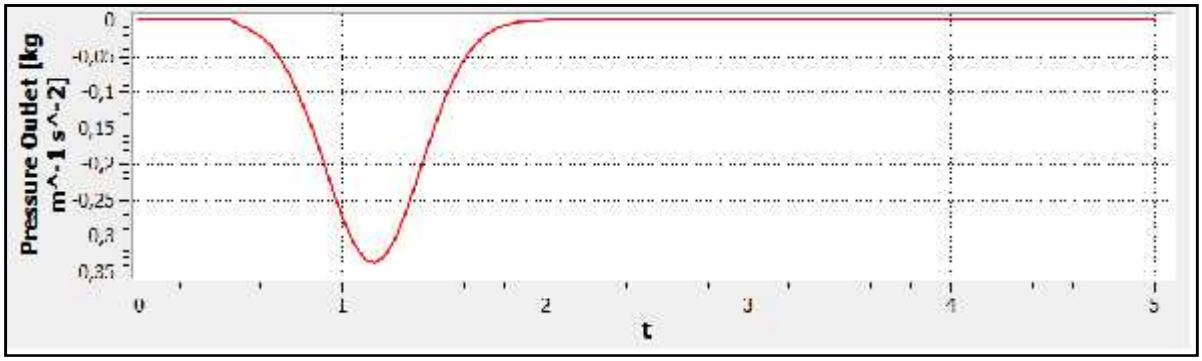

Figure 8: Pressure Outlet. Adult Case

In this case, the simulation for both spacers ended after one breathing cycle, since the number of drug particles suspended in the spacer was negligible, less than 0.4% of those injected.

2.2.3 Mesh

In order to ensure mesh independence, the mesh was successively refined until the amount of medication across the outlet did not change significantly. As an example, Table 2 shows the results for the standard chamber for

three different meshes of 4.4e5, 9.0e5 and 1.2e6 elements respectively, for an adult´s inhalation profile. Due to the small difference in results (1.46 %) obtained with the finest mesh, the "Medium" mesh, of approx. 9e5 elements, was chosen. For the "SwirlChamber" a similar mesh led to 9.7e5 elements. Table 2 shows these results, as well as the average value of y+ for the first element in the boundary layers. Figures 9 and 10 show the employed meshes.

Table 2: Mesh Convergence Analysis

Mesh	**#Elements**	**Av. y+**	**Inhaled Salbutamol [µg]**	**% Difference with Medium mesh**
Coarse	436.460	5	90.21	8.5 %
Medium	895.976	1.7	83.13	-
Fine	1.238.729	1	84.35	1,46 %

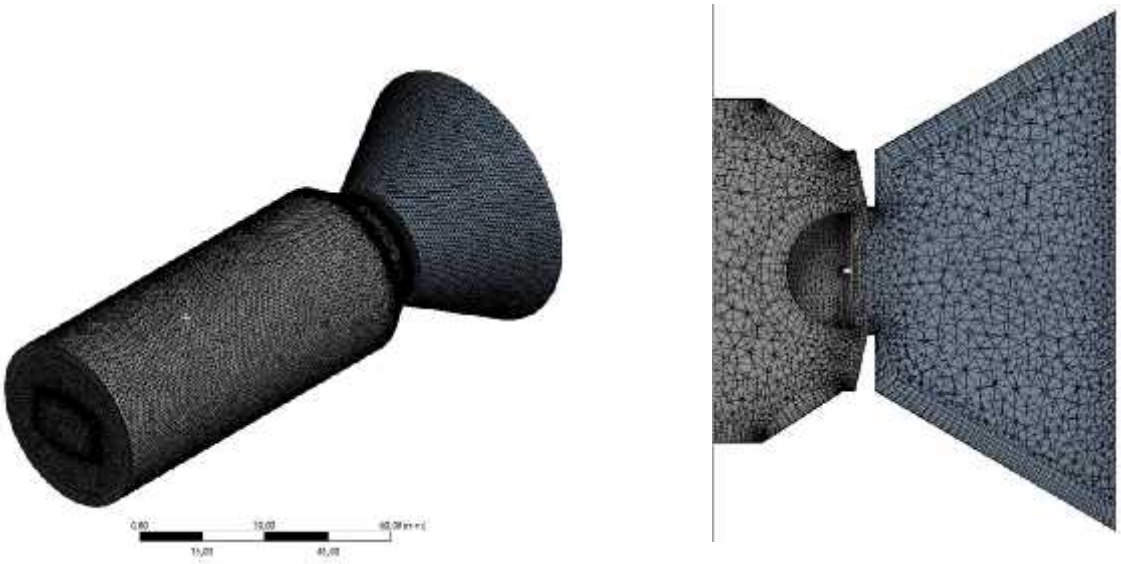

Figure 9: Standard chamber mesh and detail of the inhalation valve zone

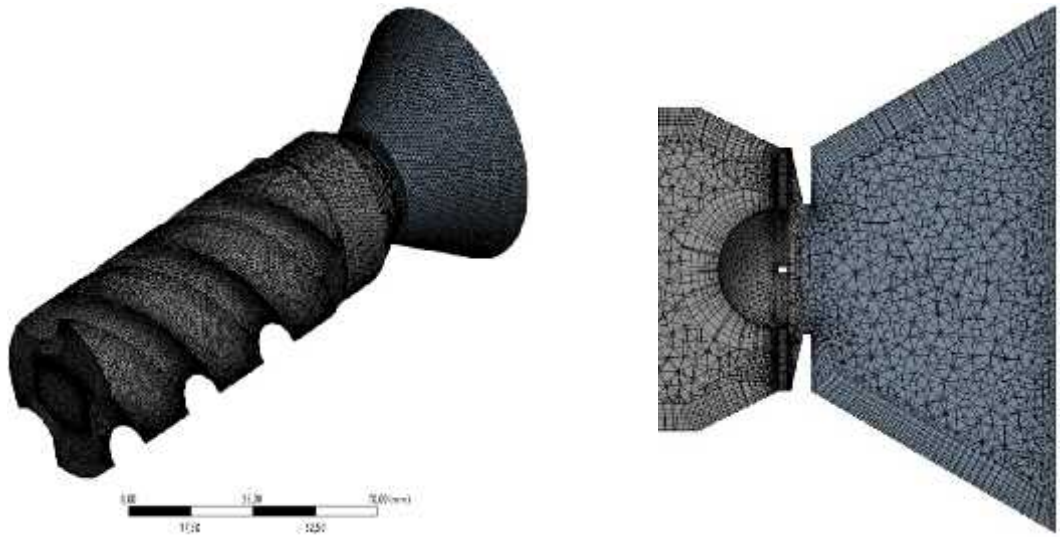

Figure 10: "SwirlChamber" mesh and detail of the inhalation valve zone

3. Results

3.1. Particle Injection

In order to visualize the behavior of the fluid spray, a volume rendering was defined, which colors from blue to red, by intensity, show the concentration of salbutamol inside the chambers (Salbutamol Averaged Volume Fraction). Figures 11 and 12 show this concentration at the end of the injection phase (t = 0.1 s) and just before the beginning of the inhalation phase (t = 0.5 s), respectively. No air flow occurred yet, except the air motion induced by the spray. It can be seen in both chambers that recirculation occurred at the closed valve. This configuration was the same for adults and children.

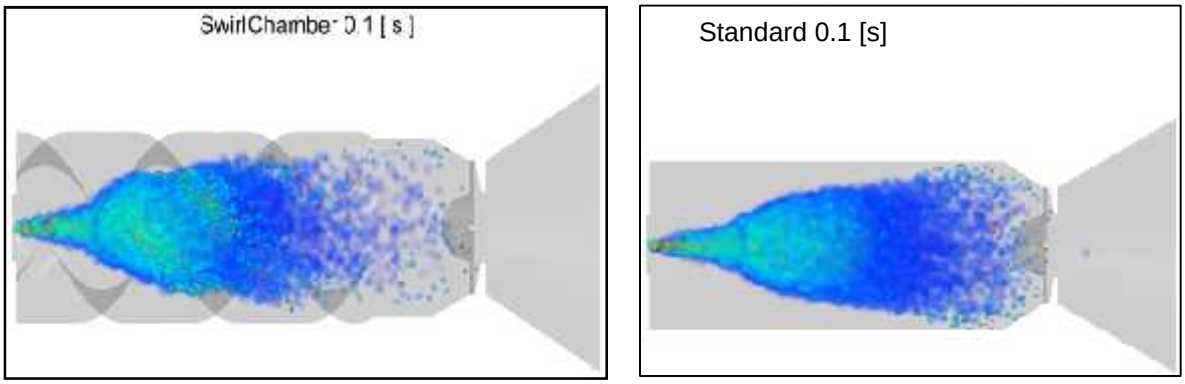

Figure 11: Salbutamol fraction in both spacers at the end of particle injection (0.1 s).

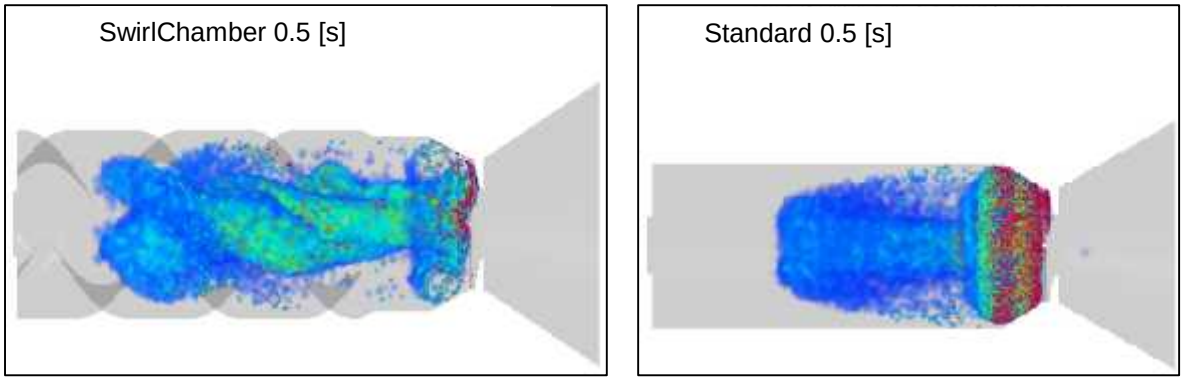

Figure 12: Salbutamol fraction in both spacers just before inhalation (0.5 s).

3.2. Child case

Figure shows the Salbutamol fraction at two stages of a child´s inspiratory sequence: 1 s (first inspiration) and 4 s (second inspiration). It can be seen that a small, but sizable, fraction of medication was still in suspension after the first inhalation, so a second and a third ones contributed to increase the inhaled amount of drug. The analysis of the flow evolution also showed that following the valve opening at the beginning of the inhalation, the particle flow experienced a great acceleration through the valve and then a sudden decrease in its velocity, which produced the sudden widening of the jet after the valve, which can be seen at 1s. Videos of these simulation can be seen at Ana a, 2018 [19].

The concentration of salbutamol that was stuck to the walls of the chambers at the end of the breathing cycles is shown in Figure 14 (Salbutamol Averaged Volume Fraction Wall). This shows that, for the standard chamber, particles tended to stick to the wall at the valve entrance, while for the “SwirlChamber”, they were more widely distributed. Nevertheless, as shown in Table 3, the total number of particles which remained stuck to the wall was about 7.5% smaller for the “SwirlChamber”.

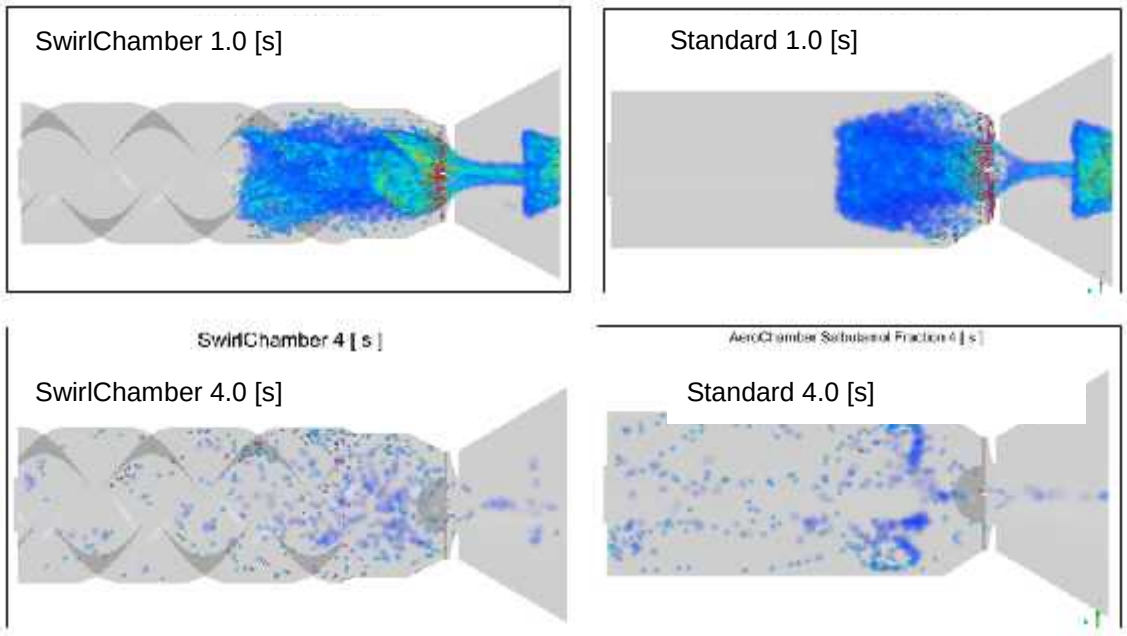

Figure13: Salbutamol fraction in different times of inspiratory period (1 and 4 s). children case.

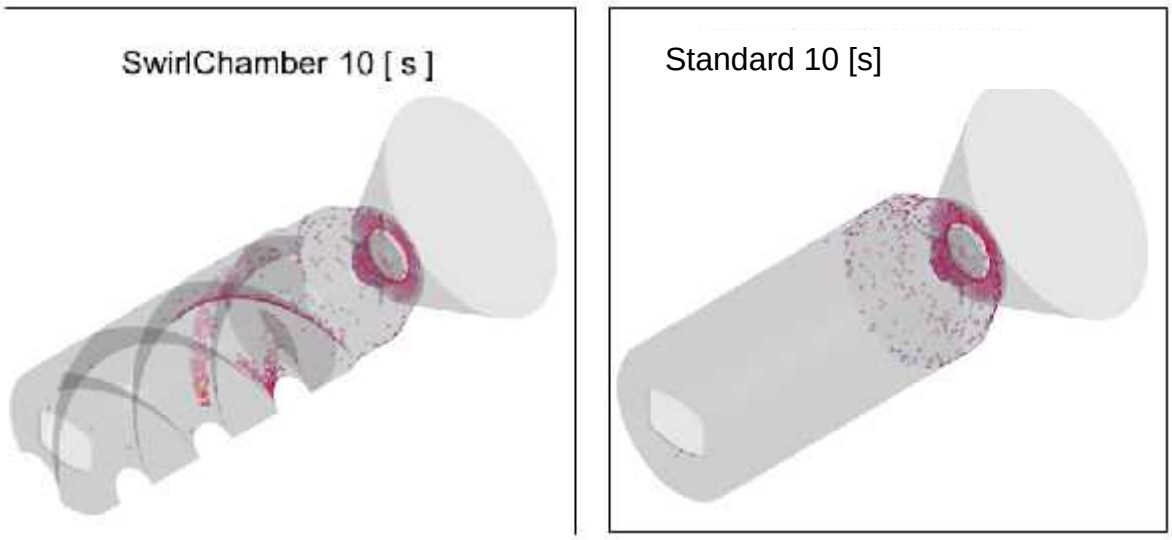

Figure 14: Salbutamol fraction at walls. End of inspiratory period, child case

Table 3: Numerical results. Child case

Children	SwirlChamber	Standard	Difference
Inhaled Salbutamol [μg]	88.45	80.81	7.64
% of injected Inhaled	88.45%	80.81%	7.64%
Salbutamol sticked to wall [μg]	11.21	18.68	-7.46
% of injected Salbutamol in Wall	11.21%	18.68%	-7.46%
Suspended Salbutamol in spacer [μg]	0.33	0.41	-0.08
% of injected Salbutamol suspended in Spacer	0.33%	0.41%	-0.08%

When analyzing the medication flow through the outlet (that is, the medication which leaves the spacer), it was found that the instantaneous mass flow and the cumulative mass vary with time as shown in Figures 15 and 16.

Although the first inhalation took most of the drug out of the domain, a second and a third inhalation contributed to extract some of the medication still suspended in the spacer.

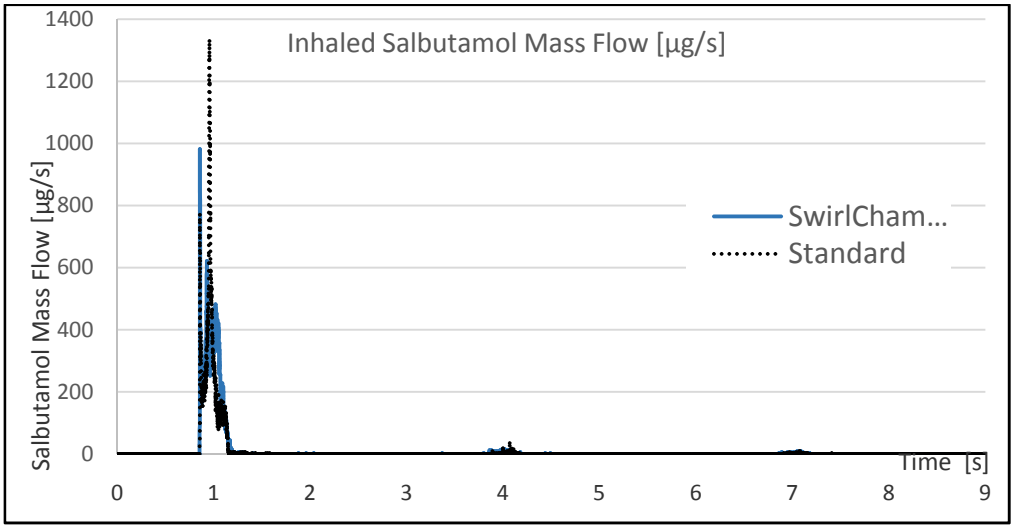

Figure 15: Inhaled Salbutamol mass flow. Child case

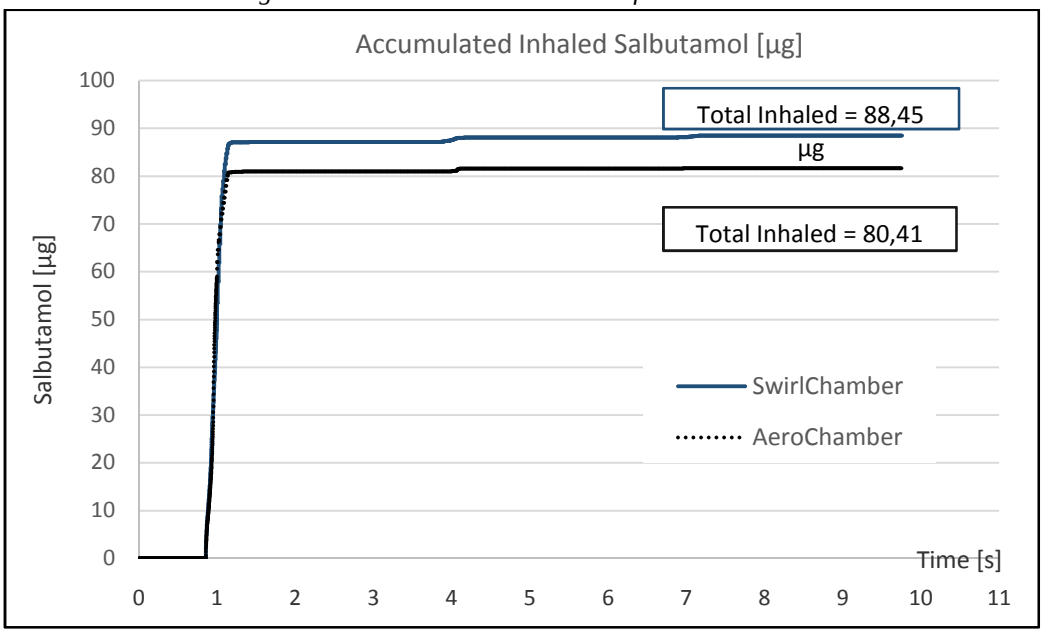

Figure 16: Accumulated Inhaled Salbutamol. Child Case

3.3. Adult case

Analog pictures as the ones shown in Figures 13 and 14 were obtained for the adults" inhalation profiles. For adults, one single inhalation was enough to reduce the number of suspended particles to under 0.4% of those injected, so the simulations did not include further inspirations. Results are summarized in Table 4.

Table 4: Numerical results, adults case

Adults	SwirlChamber	Standard	Difference
Inhaled Salbutamol [µg]	88.82	83.13	5.70
% of injected Inhaled	88.82%	83.13%	5.70%
Salbutamol sticked to wall [µg]	11.21	16.69	-5.48
% of injected Salbutamol in Wall	11.21%	16.69%	-5.48%
Suspended Salbutamol in spacer [µg]	0.33	0.10	0.23
% of injected Salbutamol suspended in Spacer	0.33%	0.10%	0.23%

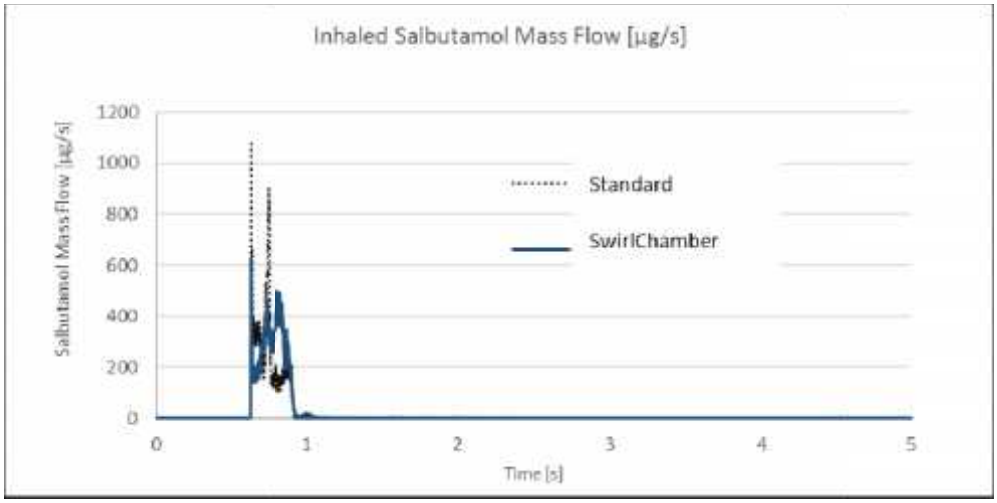

Figure 17: Inhaled Salbutamol Mass Flow in time. Adult Case

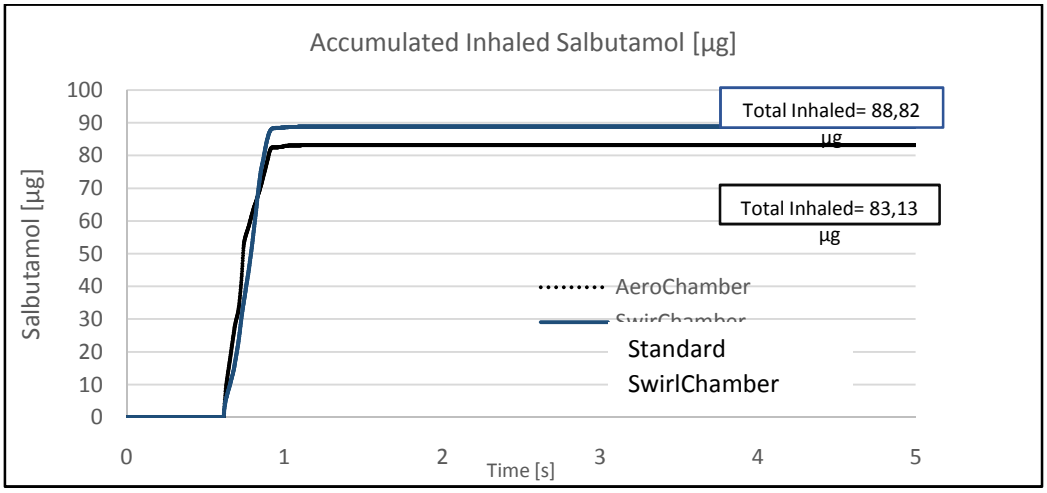

Figure 18: Total Inhaled Salbutamol. Adult Case

Figures 17 and 18 show that the "SwirlChamber" produced a slower but steadier flow of droplets to the nasal and oral cavities, which in the end increased the amount of inhaled medication.

3.4. Air rotation in the "SwirlChamber"

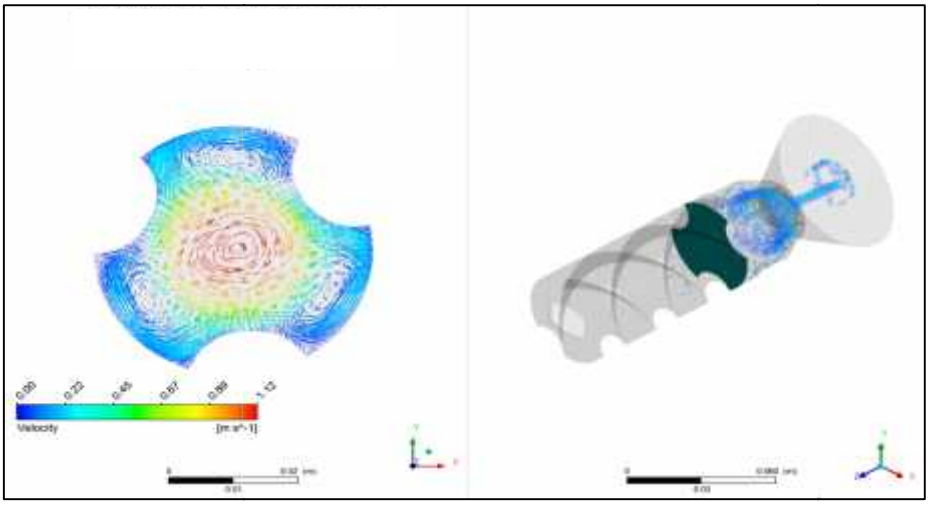

Figure 191: The tangential velocity field proves air rotation in the "SwirlChamber spacer" (adult case).

The tangential vector plot in Figure 19 illustrates the swirling effect in the center of the "SwirlChamber", at a transversal plane located 8 cm from the inlet (shown at the right), during the inhalation phase (0.9 s of simulation time, or 0.4 s from inhalation start). The grooved geometry also induced secondary vortices of slow rotation within the grooves. Both motions contributed to concentrate the droplet flow near the chamber center, reducing the number of particles which stick to the wall. The time evolution of the swirling field can be visualized in Ana b, 2018 [20].

3.5. Summary of results for different injection velocities and angles:

In order to confirm the findings of the previous model runs, further simulations were carried out for different particle injection velocities (60, 100 and 150 m/s) and spreading cone angles (10 and 15 degrees), as typically found in the literature for pMDI [16]. In these simulations, only the child case was taken into account. The inhaled mass of medication was in all cases higher for the "SwirlChamber", as shown in Table 5, which confirms the improvements caused by the induced flow rotation.

Table 5: Inhaled Salbutamol for different parameters of pmdi spray cones

	Injection Cone Angle [°]			
	10		**15**	
	Inhaled Salbutamol [µg]			
Injection Velocity [m/s]	**Standard**	**SwirlChamber**	**Standard**	**SwirlChamber**
60	79.82	91.00	80.81	88.45
100	67.06	79.00	67.29	77.45
150	65.91	71.51	64.05	67.94

4. Conclusions

After the implementation and setup of a multiphase model for the simulation of aerosol injection to a valved holding chamber and its inhalation by an adult or child, we were able to compare the inhalation efficiency of two spacers designs: one standard cylindrical chamber and a modified design with spiral grooves ("SwirlChamber") which induces a swirling motion in the air flow. Numerical results showed an average increase of 8% for a child and 6% for an adult in the inhalation efficiency, defined as the percentage of medication that leaves the devices to be aspired by the patient.

The mass of medication which remained stuck to the chamber wall after the considered inhalation periods (three cycles for a child, one for an adult) was also reduced in the grooved design, in roughly the same percentages as the inhaled medication was increased. The results were consistent in six simulations of different combinations of injection velocities and cone angles.

Furthermore, for the child case the deposition of particles within the "SwirlChamber" spacer was reduced by 7.5%. In the case of an adult, an improvement was also presented. In the "SwirlChamber" 11% of the injected medication was housed on the walls, while in the standard spacer this percentage rose to 17%.

When analyzing different types of PMDIs, an efficiency improvement was noted for the grooved "SwirlChamber" spacer. Additionally, it was concluded that lower injection velocity and smaller injection angle resulted in more inhaled medication.

It must be pointed out that these improvements were achieved only through geometric modifications of the holding chamber, without changes in the spray or in the inhalation valve or mask.

In conclusion, the hypothesis proposed in the present study was verified by observing an improvement in the inhalation efficiency, a reduction in the percentage of particle deposition on the walls, and the presence of the rotation effect on the spacer device with design modifications in the aerodynamic chamber.

Further work involves designing experiments to better validate the numerical results, exploring an optimal design of the spiral grooves, and including the oropharyngeal tract in the simulation to effectively compare the fraction of medication that reaches the lungs. Interdisciplinary work with pneumonologist experts will certainly lead to further questions to be investigated related to the problem of effective transport of inhaled medication microdrops.

Acknowledgements:
The authors acknowledge and are grateful to Mr. Norberto Martire, author of the concept and design of the spiral grooved valved holding chamber, for sharing his inspired idea and for his financial contribution to this study.

References

[1]. WHO World Health Organization [Online]. - http://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death. 2018.
[2]. GINA Global Initiative for Asthma Global Strategy for Asthma Management and Prevention 2016., https://ginasthma.org/wp-content/uploads/2016/04/wms-GINA-2016-main-report-final.pdf.
[3]. Virchow J. C., Crompton G. K., Dal Negro R., Pedersen S., Magnan A., Seidenberg J.,. Importance of inhaler devices in the management of airway. *Respiratory Medicine*, 2008. - Vol. 102. 1, 10-19.
[4]. National Heart Lung and Blood Institute [Online]. Asthma - How Is Asthma Treated and Controlled? - https://www.nhlbi.nih.gov/node/3894 (2018).
[5]. Sellers, W., Asthma pressurised metered dose inhaler performance: propellant effect studies in delivery systems, *Allergy, Asthma and Clinical Immunology* 13:30, 2017.
[6]. Oliveira, R. F.; Ferreira, A.,; Teixeira. C., Senhorinha F.; Teixeira, J.; Cabral-Marques, H. A CFD Study of a pMDI Plume Spray. In *Transactions on Engineering Technologies*, Springer, 2014.
[7]. Ruzycki C. A., Javaheri E. and Finlay W. H: The use of computational fluid dynamics in inhaler design. *Expert Opinion on Drug Delivery* 10 (3). - 2013.
[8]. Dunbar C. A. An Experimental and Theoretical Investigation of the Spray Issued from a Pressurised Metered-dose Inhaler. Ed. University of Manchester, Institute of Science and Technology. Mechanical Engineering. UMIST, 1996.
[9]. Versteeg H.K., Hargrave G. and Harrington L.: The use of computational fluid dynamics (CFD) to predict pMDI air flows and aerosol plume formation. *Respiratory Drug Delivery*, 2000. - Vol. VII, 257-264.
[10]. Smyth, H.; Hickey, A. J.; Brace, G.; Barbour, T.; Gallion, J.; Grove, J.: Spray pattern analysis for metered dose inhalers I: Orifice size, particle size, and droplet motion correlations. *Drug Development and Industrial Pharmacy*, 9 : Vol. 32. 2006.
[11]. Kleinstreuer C., Shi H. and Zhang Z.: Computational Analyses of a Pressurized Metered Dose Inhaler and a New Drug–Aerosol Targeting Methodology, *Journal of Aerosol Medicine*, 20(3) 294-309. 2007.
[12]. Leach C.L. and Colice G.L.: A pilot study to assess lung deposition of HFA-beclomethasone and CFC-beclomethasone from a pressurized metered dose inhaler with and without add-on spacers and using varying breathhold times. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 23(6): 355-361. -2010.
[13]. Cheng, Y. S., Fu, C. S., Yazzie, D. and Zhou Y., Respiratory Deposition Patterns of Salbutamol pMDI with CFC and HFA-134a Formulations in a Human Airway Replica, *Journal of Aerosol Medicine* 14(2): 255-266. -2001
[14]. Oliveira R.F., Teixeira S.F., Silva L.F., Teixeira J. C. and Antunes H.: Development of new spacer device geometry: a CFD study. *Computer Methods in Biomechanical and Biomedical Engineering*, 15(8) 825-33, 2011.
[15]. Grotberg J.B. Respiratory mechanics and gas exchange. Ch. 4 in *Standard Handbook of Biomedical Engineering and Design*. -McGraw-Hill, 2004.
[16]. Oliveira R.F. Teixeira S.F., Teixeira J.C., Silva L.F., and Antunes H.: pMDI Sprays: Theory, experiment and numerical simulation. In *Advances in Modeling of Fluid Dynamics*, 2012. DOI: 10.5772/46099
[17]. Rosin P. and Rammler, E. The Laws Governing the Fineness of Powdered Coal. *Journal of the Institute of Fuel*. - 1933. - Vol. 7. - pp. 29-36.
[18]. London University College, Respiratory Physiology [Online] https://www.ucl.ac.uk/anaesthesia/people/stephens/edit/RespPhysiolLong.pdf

[19]. Ana a, 2018. *Infantes VRSF - Grupo Fluidodinámica Computacional UNLP* [online video] Available at: https://youtu.be/PIkvoPpT3MY.

[20]. Ana b, 2018. *Infantes SC swirl – Grupo Fluidodinámica Computacional UNLP* [online video] Available at: https://youtu.be/f8BDgyth_Ko.