pMDI Spray Plume Analysis: A CFD Study

Ricardo F. Oliveira, Ana C. Ferreira, Senhorinha F. Teixeira, José C. Teixeira and Helena C. Marques

***Abstract*—Asthma is an inflammatory chronic disease characterized by airway obstructions disorders. The treatment is usually done by inhalation therapy, where pressurized metered-dose inhalers (pMDIs) are a preferred device. The objective of this paper is to characterize and simulate a pMDI spray plume by introducing realistic factors through a computational fluid dynamics (CFD) study. Numerical simulations were performed with Fluent® software, by using a three-dimensional "testbox" for room environment representation. An HFA-134a with salbutamol formulation was used for characterization. Its properties were taken as input for the CFD simulations. Spray droplets were considered to be composed by ethanol, salbutamol and HFA-134a. Propellant evaporation was taken into consideration, as well as, drag coefficient correction. Results showed an air temperature drop of 3.3 ºC near the nozzle. Also, an increase in air velocity of 3.27 m/s was noticed.**

***Index Terms*—Computational Fluid Dynamics (CFD), drug particles, pMDI spray, characterization**

I. Introduction

THE inhalation therapy is a cornerstone in treatment of airway diseases. Asthma is a chronic inflammatory disorder associated with airway hyper responsiveness, which can be characterized by episodes of wheezing, breathing difficulties, chest tightness and coughing [1]. More than 300 million worldwide are affected by this disease which is responsible for the death of 220 thousand per year, growing at a rate of 50% per decade [2]. Anti-inflammatory and bronchodilator drugs are used with the objective of reducing the inflammation of the pulmonary tissue, which causes the diameter reduction of the bronchus [3].

Pressurized metered-dose inhalers (pMDIs) are one of the major aerosol-generating devices used for aerosol delivery of bronchodilators in ambulatory patients [4]. 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. The pMDI is a small, cost-effective and very portable device containing between 100 to 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 [4].

The particle size of the aerosol produced by a pMDI depends on the pressure of the propellant mixture, ambient temperature, valve design, drug concentration and actuator orifices. In fact, there is a relationship between the actuator nozzle diameter and the particle size distribution, as well as, the ethanol concentration [5].

Moreover, the effectiveness of pMDIs is deeply associated with how the metering valve delivers, in an accurately and reproducibly manner, a measured volume and how it forms a propellant-tight seal for high pressure. According to Dhand [4], high-vapor-pressure propellants produce finer aerosol sprays, whereas increasing the drug concentration increases aerosol particle size. The actuator nozzle controls the atomization process in order to guarantee the formation of a spray plume. The canister, typically made of aluminum, holds a high internal pressure of 3 to 5 atm [6]–[8].

Computational fluid dynamics (CFD) application 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, heat and mass 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 inhaled air is the continuous phase and the particles or droplets the discrete phase.

Dunbar *et al.* performed a theoretical investigation on pMDI spray by a CFD study consisting on the construction of actuator flow from the metered chamber to the nozzle, which was based on a quasi-steady-state for flow analysis during a single actuation. The objective was to examine droplet formation and its trajectory 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 are in agreement, although such correlation is not further downstream [9].

Kleinstreuer *et al.* [10], experimentally validated a

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computational fluid-particle dynamics model developed to simulate the airflow, droplet spray transport and aerosol deposition in a pMDI considering several conditions, including different nozzle diameters and the use of a spacer. Also, the properties of both chlorofluorocarbon (CFC) and hydrofluoroalkane-134a (HFA) were investigated. The results indicated that the use of HFA, smaller valve orifices and the inclusion of spacers yields the best performance in terms of droplets deposition. Smyth *et al*. [11] also performed a spray pattern analysis for pMDIs, studying the influence of orifice size, particle size, and droplet motion correlations.

Recently, Ruzycki and co-authors [12] presented a comprehensive review in the use of CFD in inhaler design. The authors enlightened that the application of CFD modeling techniques for pMDIs, nebulizers and DPIs improves the aerosol transport and deposition understanding and, therefore, allows for an intuitive optimization of inhaler technologies whereas saving time and resources.

Previous studies in the simulation of the pMDI spray plume were made by the authors [13]–[15]. After an extensive review of the pMDI properties and characteristics, a CFD simulation was made but considering the particles to be solid (i.e. made of active pharmaceutical ingredient) [15].

This work aims to characterize and simulate a pMDI spray by means of a commercial CFD software (i.e. Fluent® v14.0 from ANSYS®). A pMDI salbutamol formulation was used for characterization. CFD simulations were performed in a three-dimensional "testbox". Spray droplets were injected and tracked accounting for propellant evaporation, aerodynamic size distribution, gravity, Brownian motion, drag coefficient corrections, turbulence and energy exchange. The input injection file was created by using a Python language script.

II. Spray Characterization

A. High-speed images

The spray dynamics can be effectively evaluated through images obtained by using a high speed digital video camera. This technique is able to record up to 10,000 frames per second, which is very suitable for understanding and capturing details of transient phenomena despite the difficulties related with the illumination required. Specifically for the delivery of aerosol drugs, the potential of such technique is suitable due to the very nature of the spray resulting from a high pressure canister. Nevertheless, the greatest advantage of this technique is its ability to capture the transient nature of the aerosol formation over the delivery time.

Using a high-speed camera (FASTCAM-APX RS 250KC), a puff event from the pMDI HFA-134a spray was recorded. Images were captured with an interval of 0.02 seconds (see Figure 1). Those were taken at a rate of 6,000 frames per second, allowing to confirm the duration of the spray (0.1 seconds) and to calculate the spray angle (approximately 17 degrees) by visual analysis.

B. Aerodynamic size distribution

Particle size distribution can be characterized either as

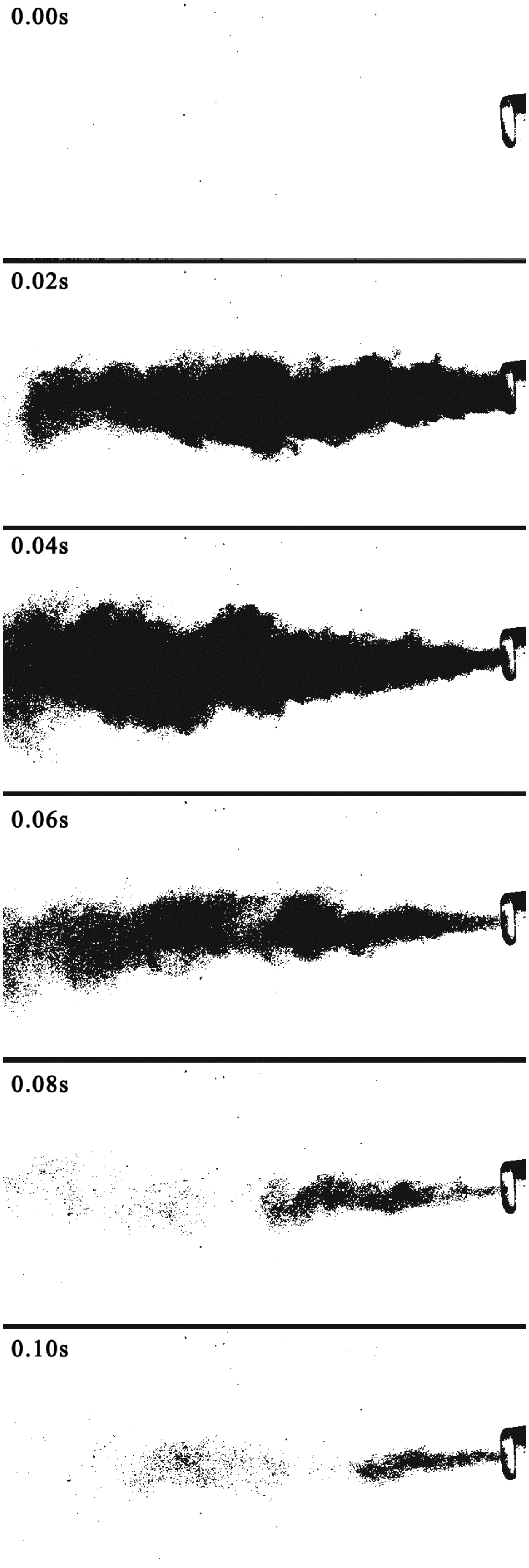

Fig 1. High speed images of a puff taken from a salbutamol HFA-134a pMDI. These images were treated with greyscale and inverted colors after application of a threshold filter for easier visualization of the plume.

Probability Density Function (PDF) or as a Cumulative Distribution Function (CDF). A particle size distribution is usually denoted by an independent variable, *x*, and two additional adaptable parameters [16].

The spray particle/droplets can be described through different mathematical distributions, being the Log-Normal, Rosin-Rammler and Nukiyama-Tanasawa the most cited. Amongst these distributions, it is well accepted that the pharmaceutical aerosols can be reasonable represented by the Log-Normal distribution fitting the measured data to the CDF as shown by Equation (1). The Log-Normal PDF (Equation 2) was derived from the normal distribution [16].

$$F(x;\mu,\sigma)=\frac{1}{2}erfc\left[-\frac{\ln x-\mu}{\sigma\sqrt{2}}\right] \qquad (1)$$

$$f(x;\mu,\sigma)=\frac{1}{x\sigma\sqrt{2\pi}}e^{-(\ln x-\mu)^2/2\sigma^2} \qquad (2)$$

where σ is the geometric standard deviation (which shall be $\neq 0$), μ represents the mean diameter and *erfc* is the complementary error function. Using the laser diffraction analysis technique (Malvern 2600 particle sizer), a pMDI spray plume of HFA-134a formulation of salbutamol was measured. The data were fitted to the Log-Nornal CDF distribution model (1) using the least-squares method. Through the calculation of the Pearson coefficient of determination (i.e. R^2-squared value) and its maximization (R^2 = 0.993), the distribution parameters were obtained: $\mu = 2.55$ and $\sigma = 0.634$. Such values are in agreement with those usually reported in the literature. The experimental results and its Log-Normal CDF curve are shown in Figure 2.

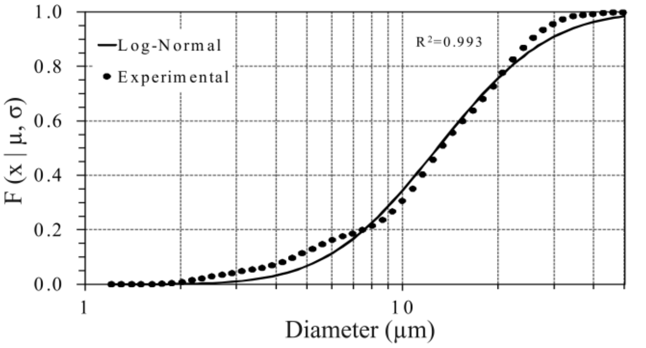

Fig 2. Graphical representation of the pMDI HFA-134a salbutamol experimental data and its fitting for the Log-Normal CDF distribution. Measurements obtained at 100 mm from the laser beam.

C. Axial velocity

The velocity of the droplets decreases along the axial distance from the nozzle, due the momentum exchange with the air. As reported by Dunbar *et al.* [17], using PDPA measurements of a HFA-134a spray plume during an actuation, values were taken at different distances from the nozzle of the actuator (see Figure 3).

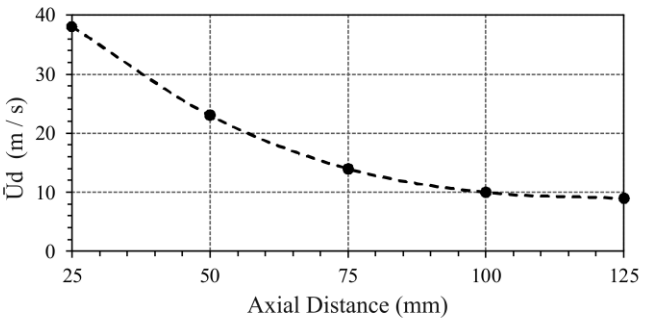

Fig. 3 Droplet mean velocity along the axial distance from the nozzle of a pMDI using a formulation only with HFA-134a. Adapted from [17].

Consistent with their measurements, Dunbar concluded that a HFA propellant formulation produces a spray with higher velocities than a CFC formulation. This outcome is due to the higher vapor pressure used in the HFA formulation. The plume behaves like a spray up to a distance of 75 mm from the nozzle and as an aerosol downstream that distance, where the droplet motion is being influenced by the gas [17].

D. Microscopy images

Using an optical microscope (Leica DM 2500 M) for the visual analysis of the particle shape and size, a set of images were taken. After a single puff being discharged against a glass plate, it was observed under the microscope at two different magnifications (see Figure 4). It is possible to observe that the particles present a very irregular shape, although a limitation of the technique is the reduced depth of field. Also, it can be noticed that some particles present a solid craggy surface (i.e. salbutamol sulfate crystals) and others are encapsulated within a smooth spherical droplet of propellant that did not evaporate.

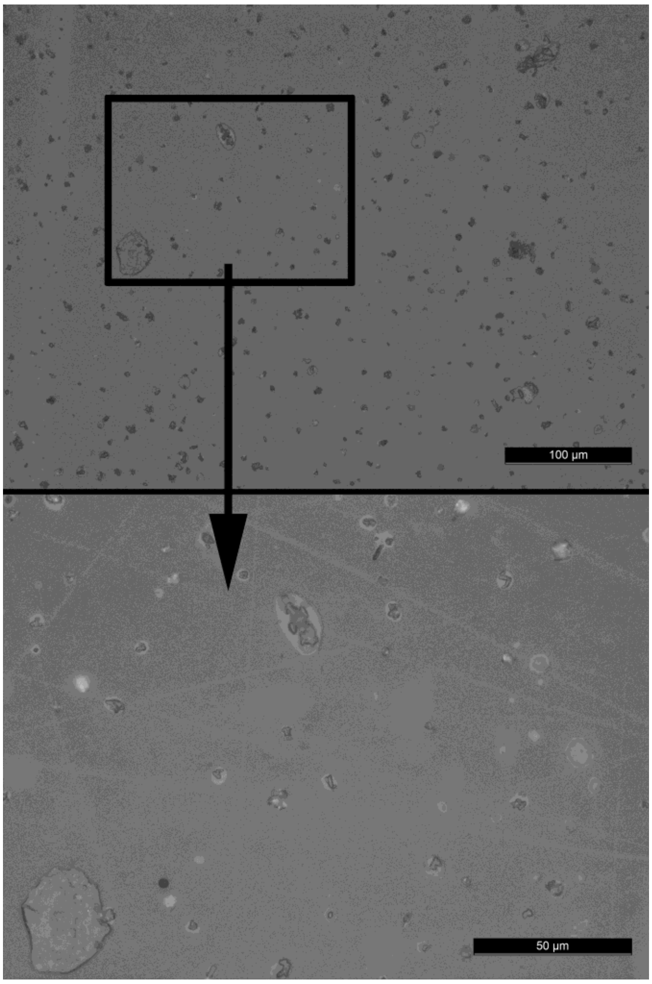

Fig 4. pMDI spray particles and droplets observed through the optical microscope at two different magnifications.

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III. Spray simulation

The pMDI is one of the most common drug delivery devices used in developed countries to treat asthma in children and adults. It mainly consists of salbutamol, which is the most frequently prescribed short-acting β-agonist (SABA) [7], [18], [19].

This CFD study accounts for the temperature, velocity, turbulence, droplet tracking and evaporation of its propellant, as well as, its concentration in the air.

A. Spray injection properties

The most important characteristics of the pMDI spray for the simulation are: spray cone angle (see section II-A); initial velocity (considered 100 m/s [8], [20]); aerodynamic size distribution; components present in the formulation; nozzle diameter (i.e. 0.25 mm [8], [10], [11], [20]); temperature (i.e. 215 K [21]); and mass flow rate. The aerodynamic size distribution parameters, discussed above in section II-B, used to configure the injection input file ranged from 1.22 μm to 49.5 μm, discretized along 80 intervals. From the knowledge of the drug dose delivered per puff labeled by the manufacturer (i.e. 100 μg) and the puff duration discussed in section II-A (i.e. 0.1 s), a spray mass flow rate of 1.0E-6 kg/s was estimated.

For the creation of the input injection file, a Python language script was programmed. Into this file, the injections are placed, by a uniform random distribution, within the nozzle area. Properties such as diameter, temperature, and mass flow rate are attributed to each injection. After that assignment, the corresponding velocity components for each injection are calculated. They are calculated according to their distance to the center of the nozzle, so that their initial velocity vectors form a solid cone. The algorithm also calculates the corresponding mass flow rate value for each injection, as a function of its diameter assuming a Log-Normal distribution. It is ensured that the sum of all mass flow rates in the file equals the total mass flow rate defined initially. The total number of injections on the file was 16,200.

The formulation properties of the pMDI spray droplets were assumed to be composed by partial factions of HFA-134a (91.1 % w/w), ethanol (8.5 % w/w) and salbutamol (0.4 % w/w) [22]. The properties for each component are listed in Table 1.

The spray parameters used to configure the solver were obtained from various references, though some caution is required.

B. Geometry and grid

For the geometric definition of the domain, a “testbox” was defined which consists of a simple parallelepiped form with the dimensions of 0.2×0.2×0.3 (m) representing a fraction of a room environment. The pMDI actuator and canister was included in the middle of it. The spray injection point, the actuator’s nozzle, is located in the origin point, see Figure 5. The geometry was drawn using an external design program and then loaded into the ANSYS® platform.

A numerical grid, by discretization of the domain, was generated, consisting in tetrahedral and wedge elements, with sizes ranging from 0.1 mm to 20.0 mm. That resulted in

TABLE I
THERMO-PHYSICAL PROPERTIES OF THE FORMULATION

Properties	HFA-134a	Ethanol	Salbutamol
Density (kg/m^3)	1,311	790	1,230
Specific Heat (J/kg·K)	982	2,470	-
Latent Heat (J/kg)	182,000	855,237	-
Boiling Point (K)	247	351	-
Binary Diffusivity (m^2/s)	9.709E-6	1.370E-5	-

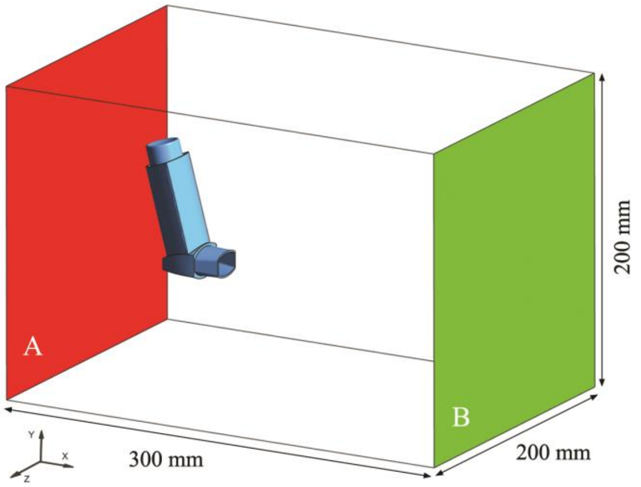

Fig 5. A "testbox" representation constituted, the red plane (A) is the boundary condition ‘Velocity Inlet’ and the green plane (B) is the boundary ‘Outflow’.

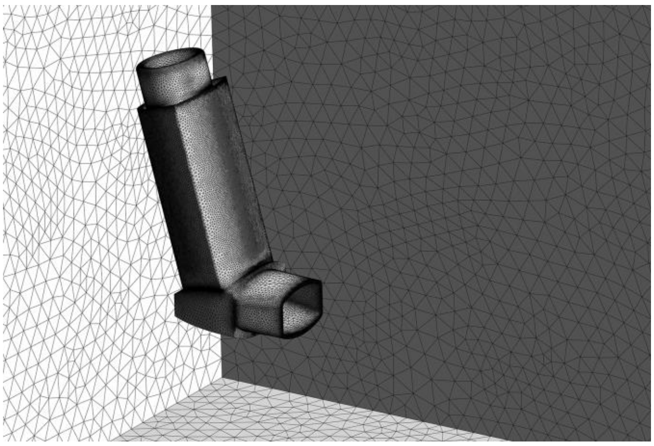

Fig 6. 3D domain grid representation, focusing the pMDI walls refinements for proximity and curvature.

a computational grid of 3060339 elements and 1022403 nodes. Several refinements, near to wall zones of high proximity and curvature, were included (as shown in Figure 6). The grid quality reports showed a good quality according to the Skewness parameter, with an average value of 0.21.

The boundary conditions were defined as: a ‘Velocity Inlet’ (see Figure 5 – “A”), forcing air to move uniformly inside the domain at 0.01 m/s and with a temperature of 293 K; and an ‘Outflow’ (see Figure 5 – “B”), enabling the freely motion of the air, as well as particles. For the remaining four external walls, a ‘Symmetry’ boundary condition was assumed. The pMDI actuator and canister boundaries were considered ‘Wall’, trapping all the particles that collide with them.

C. CFD configuration

To account for the transient effects of a real pMDI spray

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plume, an unsteady simulation was made. A time step of 0.01 s for the flow field and 0.005 s for the particle tracking algorithm was used. The solution of the differential equations for mass and momentum was done in a sequential manner, using the SIMPLE algorithm [23]–[25]. The standard discretization scheme was used for the pressure and the second order upwind scheme for the energy, turbulence, momentum, air species concentration equations.

For the turbulence calculation the SST *k-ω* model was used. This model is adequate for low-Re simulations and it has been used in the literature for this type of flow [10], [26]–[28].

Convergence was reached in the simulation by using a criterion value of 1.0E-5 for the continuity (pressure), velocity components, turbulence, species and a value of 1.0E-10 for the energy.

Droplets were considered as being multi component, as described above, where only the HFA is evaporating to the environment. One is initialized without any HFA gas, as well as, the air entering by the "velocity Inlet" boundary. As the HFA fraction is evaporating, it drastically reduces the diameter of the droplet, and changes its trajectory in the flow. In the other hand, the HFA concentration in the environment increases, making it harder for more particles to evaporate in zones of high concentration. The gravitational acceleration was assumed 9.81 m/s^2 along the *y* axis direction. For the configuration of the Discrete Phase Model (DPM) droplet tracking model was accounted the drag between both phases, Brownian motion for small particles and turbulence exchange. Through a User Defined Function (UDF), a customized drag law was included in the solver. This law was based in the work Clift and his collaborators plus a correction for particles below 1 µm known as the Cunningham correction slip factor [27], [29].

The total number of particle streams injected during the simulation was approximately 323,200.

IV. Results

A. Contour fields

Figures 7, 8 and 9 show the contours for air velocity magnitude, air temperature and spray mass concentration, respectively, taken at a XY plane located at z = 0 and t = 0.1 s. The air velocity field (see Figure 7) ranges from 0.0 to 3.27 m/s, being the lowest value found in almost all domain, because the ambient air was assumed stagnant. The maximum value is found at the nozzle exit, resulting from momentum exchange imposed by the high velocity spray particle injection.

Observing the air temperature (see Figure 8), it can be concluded that it ranges from 289.89 to 293.15 K, where the higher variation can be found at the spray plume formation zone. A sudden drop of 3.3 K occurs at the nozzle exit, due to the injection of droplets with an initial temperature of 215.15 K [21]. This temperature drop arises from the energy exchange needed to evaporate the propellant.

Analyzing the HFA mass fraction present in the air (see Figure 9), it can be perceived that its values are between 0 and 2.9E-3. The higher concentration zone, at the end of the injection period (t = 0.1 s), it is located ahead of the nozzle,

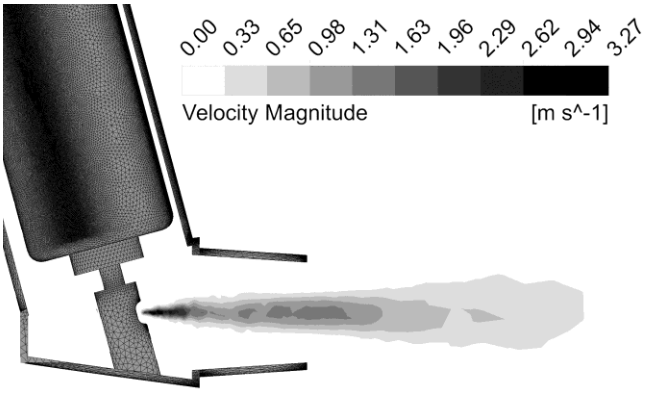

Fig 7. Air velocity magnitude contours took at the XY plane (z = 0 and t = 0.1 s).

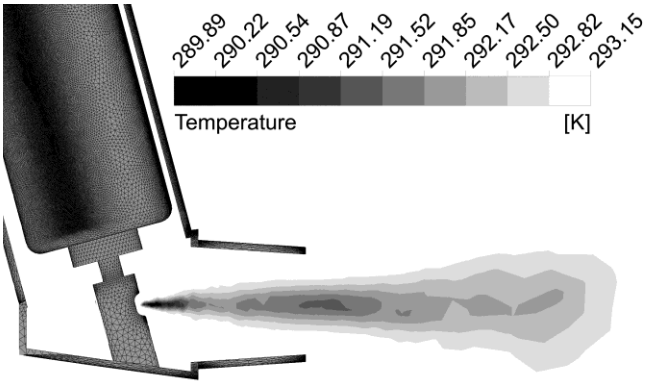

Fig 8. Air temperature contours took at the XY plane (z = 0 and t = 0.1 s).

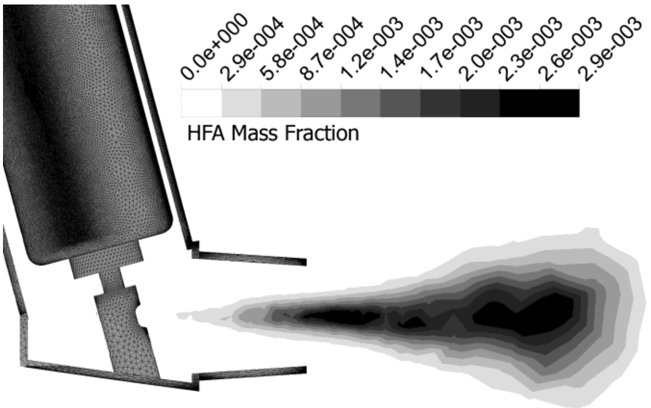

Fig 9. HFA mass fraction contours took at the XY plane (z = 0 and t = 0.1 s).

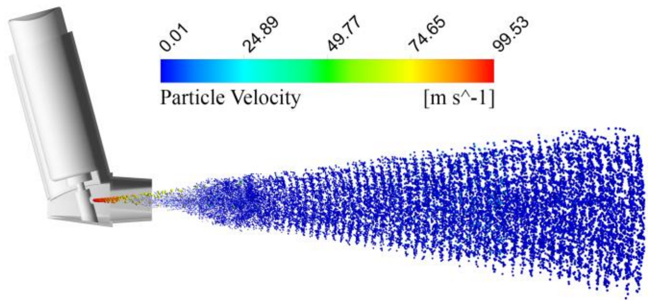

Fig 10. Representation of the particle streams at the end of the injection (t=0.11 s), image shows the particles colored by its velocity magnitude. The particle streams are draw as spheres with proportional size scaled 20 times more than the real diameter.

more specifically at the exit of the pMDI actuator mouthpiece. It has the shape of a spray plume. As expected, the droplets evaporate more in the periphery of the actuator

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zone, where HFA diffusion into the air is more effective.

B. *Particle trajectory*

As shown in Figure 10, the particle velocity magnitude in the spray plume ranges from approximately 100 m/s (as described in section III-A) to 0.01 m/s (the input air velocity as described in section III-B). The particles located downstream the actuator mouthpiece decelerate rapidly until they match the air velocity. Larger particles travel further into the still air than the small ones. The influence of the gravitational acceleration is noticeable for higher particles when the slip velocity equals zero.

V. Conclusion

The study herein reported the characterization of a pMDI spray plume, of salbutamol and HFA-134a as propellant. The spray plume showed to be a transient jet, with effects that are dependent on the canister pressure. There is no constant delivery of the spray plume, but almost all the dose is aerosolized in the first 4/10 of the spray duration.

Microscopy showed that particles do not present a regular shape when in solid/dry state, although if they are involved in propellant they are almost spherical. The existence of a multi-component droplet confirmed the need for that approach in the simulation.

The aerodynamic size distribution of the pMDI sprays are usually accurately fitted by Log-Normal distribution. Whereas it was confirmed showing a good coefficient of determination for the experimental data obtained by laser diffraction analysis.

These characteristics were introduced in the CFD model and the spray droplets trajectory calculated in still air. Results showed that air temperature can drop over 3.3 K and increase its velocity 3.27 m/s, in the proximities of the actuator's nozzle.

Spray characteristics helped a correct configuration of the spray in the CFD software. Although improvements are need to make the numerical results match the experimental observations of Dunbar *et al* [9].

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