Metadata of the chapter that will be visualized in SpringerLink

Book Title	Transactions on Engineering Technologies	
Series Title		
Chapter Title	A CFD Study of a pMDI Plume Spray	
Copyright Year	2014	
Copyright HolderName	Springer Science+Business Media Dordrecht	
Corresponding Author	Family Name	**Oliveira**
	Particle	
	Given Name	**Ricardo F.**
	Prefix	
	Suffix	
	Division	CT2M R&D Center, Department of Mechanical Engineering
	Organization	University of Minho
	Address	4800-058, Guimarães, Portugal
	Email	ricardo.falcao.oliveira@gmail.com
Author	Family Name	**Ferreira**
	Particle	
	Given Name	**Ana C.**
	Prefix	
	Suffix	
	Division	CGIT R&D Center, Department of Production and Systems
	Organization	University of Minho
	Address	4800-058, Guimarães, Portugal
	Email	acferreira@dps.uminho.pt
Author	Family Name	**Teixeira**
	Particle	
	Given Name	**Senhorinha F.**
	Prefix	
	Suffix	
	Division	CGIT R&D Center, Department of Production and Systems
	Organization	University of Minho
	Address	4800-058, Guimarães, Portugal
	Email	st@dps.uminho.pt
Author	Family Name	**Teixeira**
	Particle	
	Given Name	**José C.**
	Prefix	
	Suffix	
	Division	CT2M R&D Center, Department of Mechanical Engineering
	Organization	University of Minho
	Address	4800-058, Guimarães, Portugal

	Email	jt@dem.uminho.pt
Author	Family Name	**Marques**
	Particle	
	Given Name	**Helena C.**
	Prefix	
	Suffix	
	Division	iMed.UL R&D Center, Faculty of Pharmacy
	Organization	University of Lisbon
	Address	1649-003, Lisbon, Portugal
	Email	hcmarques@ff.ul.pt

Abstract	Asthma is an inflammatory chronic disease characterized by airway obstructions disorders. The treatment is usually done by inhalation therapy, in which 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, whose 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 °C near the nozzle. Also, an increase in air velocity of 3.27 m/s was noticed. The CFD results seem to be in good agreement with Dunbar (1997) data on particle average velocity along the axial distance from the nozzle.

Keywords (separated by '-')	Computational fluid dynamics - Discrete phase model - Drug particles - Lagrangian tracking - pMDI - Spray characterization

A CFD Study of a pMDI Plume Spray

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, in which 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, whose 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 °C near the nozzle. Also, an increase in air velocity of 3.27 m/s was noticed. The CFD results seem to be in good agreement with Dunbar (1997) data on particle average velocity along the axial distance from the nozzle.

R. F. Oliveira (✉) · J. C. Teixeira
CT2M R&D Center, Department of Mechanical Engineering, University of Minho,
4800-058 Guimarães, Portugal
e-mail: ricardo.falcao.oliveira@gmail.com

J. C. Teixeira
e-mail: jt@dem.uminho.pt

A. C. Ferreira · S. F. Teixeira
CGIT R&D Center, Department of Production and Systems, University of Minho,
4800-058 Guimarães, Portugal
e-mail: acferreira@dps.uminho.pt

S. F. Teixeira
e-mail: st@dps.uminho.pt

H. C. Marques
iMed.UL R&D Center, Faculty of Pharmacy, University of Lisbon,
1649-003 Lisbon, Portugal
e-mail: hcmarques@ff.ul.pt

G.-C. Yang et al. (eds.), *Transactions on Engineering Technologies*,
DOI: 10.1007/978-94-017-8832-8_13,

Keywords Computational fluid dynamics · Discrete phase model · Drug particles · Lagrangian tracking · pMDI · Spray characterization

1 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 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 [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 3–5 atm [6–8].

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, 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. [9], performed a theoretical investigation of a 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 does not hold further downstream [9].

Kleinstreuer et al. [10], experimentally validated a 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 et al. [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 [13–16]. 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 using a Python language script.

2 Spray Characterization

2.1 Spray Dynamics

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

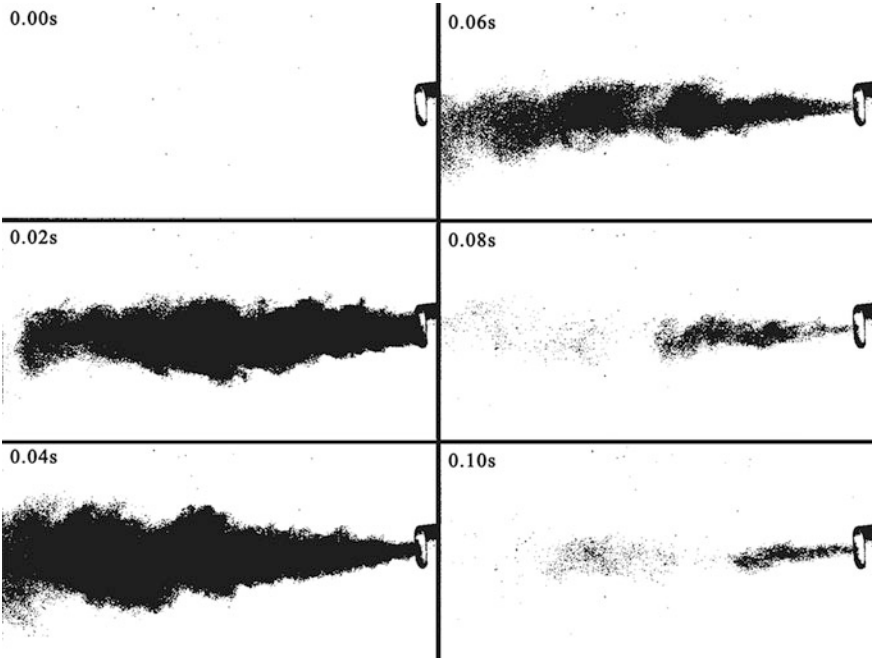

Fig. 1 High speed images of a puff taken from a salbutamol HFA-134a pMDI. These images were treated with greyscale and inverted colors after application of a threshold filter for easier visualization of the plume

suitable due to the very nature of the spray exiting 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 s (see Fig. 1). Those were taken at a rate of 6,000 frames per second, allowing to confirm the duration of the spray (0.1 s) and to calculate the spray angle (approximately 17°) by visual analysis.

2.2 Aerodynamic Size Distribution

Particle size distribution can be characterized either as 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 [17].

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

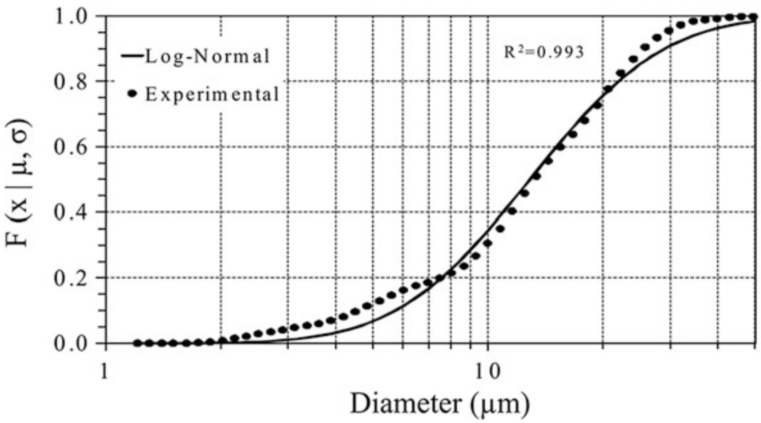

Fig. 2 Graphical representation of the pMDI HFA-134a salbutamol experimental data and its fitting for the log-normal CDF distribution. Measurements obtained at 100 mm from the laser beam

aerosols can be reasonable represented by the Log-Normal distribution fitting the measured data to the CDF as shown by Eq. (1). The Log-Normal PDF (Eq. 2) was derived from the normal distribution [17].

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

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

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 2,600 particle sizer), a pMDI spray plume of HFA-134a formulation of salbutamol was measured. 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 Fig. 2. AQ1

2.3 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 [18], using PDPA measurements of a HFA-134a spray plume during an actuation, values were taken

Layout: T1 Standard SC | Book ID: 321866_1_En | Book ISBN: 978-94-017-8831-1
Chapter No.: 13 | Date: 6-3-2014 | Page: 6/14

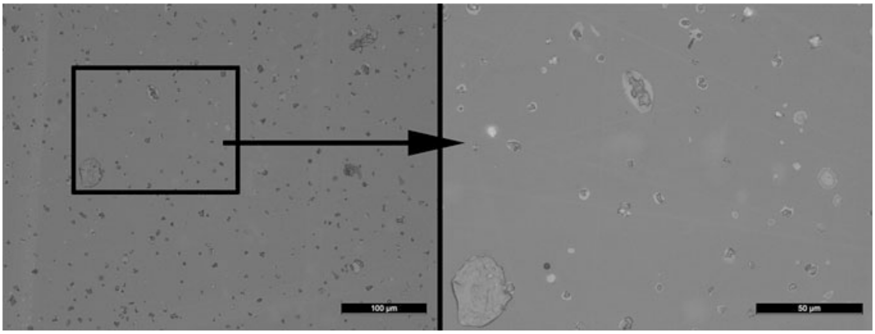

Fig. 3 Graphical representation of the pMDI HFA-134a salbutamol experimental data and its fitting for the log-normal CDF distribution. Measurements obtained at 100 mm from the laser beam

at different distances from the nozzle of the actuator. Consistent with their measurements, Dunbar concluded that a HFA propellant formulation produces a spray with higher velocities than a CFC formulation. This feature 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 [18].

2.4 Particle Shape and Size

Using an optical microscope (Leica DM 2,500 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 Fig. 3). 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.

3 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, 19, 20].

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

Table 1 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	–

3.1 Spray Injection Properties

The most important characteristics of the pMDI spray for the simulation are: spray cone angle (see Sect. 2.1); initial velocity (considered 100 m/s [8, 21]); aerodynamic size distribution; components present in the formulation; nozzle diameter (i.e. 0.25 mm [8, 10, 11, 21]); temperature (i.e. 215 K [22]); and mass flow rate. The aerodynamic size distribution parameters, discussed above in Sect. 2.2, used to configure the injection input file ranged from 1.22 to 49.5 µm, distributed 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 Sect. 2.1 (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) [23]. 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.

3.2 Geometry and Grid

The domain geometry was taken as a "testbox" consisting 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

Layout: T1 Standard SC | Book ID: 321866_1_En | Book ISBN: 978-94-017-8831-1
Chapter No.: 13 | Date: 6-3-2014 | Page: 8/14

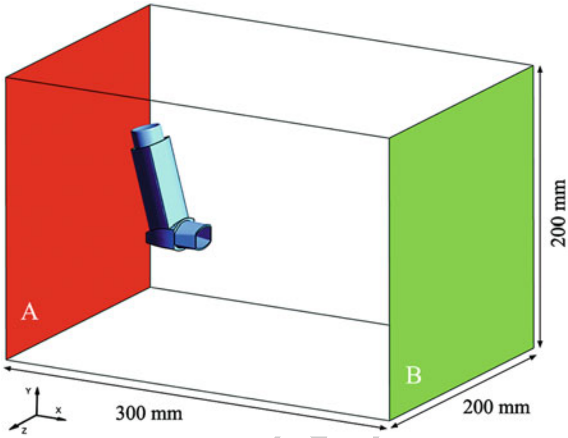

Fig. 4 A "testbox" representation where, the *red* plane (*A*) is the boundary condition 'velocity inlet' and the *green* plane (*B*) is the boundary 'outflow'

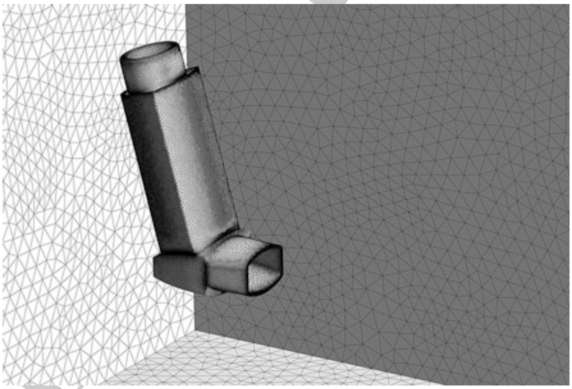

Fig. 5 3D domain grid representation, focusing the pMDI walls refinements for proximity and curvature

it. The spray injection point, the actuator's nozzle, is located in the origin point, see Fig. 4. The geometry was drawn using an external design program and then loaded into the ANSYS® platform.

The numerical grid, by discretization of the domain, was generated, consisting in tetrahedral and wedge elements, with sizes ranging from 0.1 to 20.0 mm. That resulted in a computational grid of 3,060,339 elements and 1,022,403 nodes. Several refinements, close to the wall zones of high proximity and curvature, were included (as shown in Fig. 5). 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 Fig. 4 "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 Fig. 4 "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.

3.3 CFD Configuration

To account for the transient effects of a real pMDI spray plume, an unsteady simulation was made using a time step of 0.01 s for the flow field and 0.005 s for the particle tracking. The solution of the differential equations for mass and momentum was done in a sequential manner, using the SIMPLE algorithm [24–26]. The standard discretization scheme was used for the pressure and the second order upwind scheme for the energy, turbulence, momentum and 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, 27–29].

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 into the environment. This is initially simulated 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. On the other hand, the HFA concentration in the environment increases, making it harder for more particles to evaporate in areas 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, the drag between both phases, Brownian motion for small particles and turbulence exchange were accounted. Through a User Defined Function (UDF), a customized drag law was included in the solver. This law was based in the work of Clift and his collaborators plus a correction for particles below 1 µm known as the Cunningham correction slip factor [28, 30].

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

4 Results

4.1 Contour Fields

Figures 6, 7 and 8 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 Fig. 6) 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.

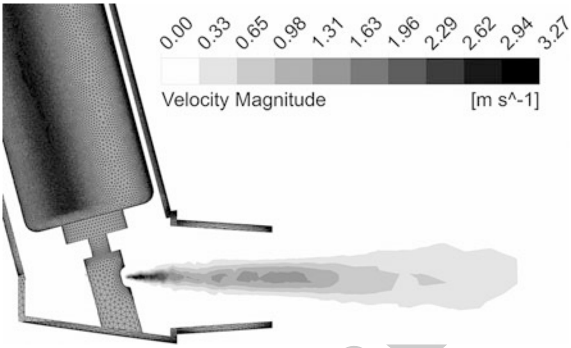

Fig. 6 Air velocity magnitude contours took at the XY plane (z = 0 and t = 0.1 s)

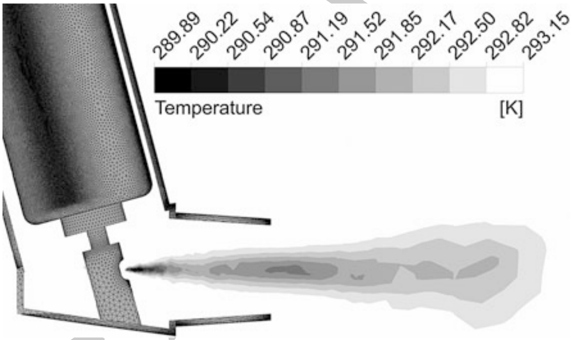

Fig. 7 Air temperature contours took at the XY plane (z = 0 and t = 0.1 s)

Observing the air temperature (see Fig. 7), 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 [22]. This temperature drop results from the energy exchange needed to evaporate the propellant.

Analyzing the HFA mass fraction present in the air (see Fig. 8), it can be perceived that its value is between 0 and 2.9E−3. The higher concentration zone, at the end of the injection period (t = 0.1 s), is located ahead of the nozzle, 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 zone, where HFA diffusion into the air is more effective.

4.2 Particle Trajectory

As shown in Fig. 9, the particle velocity magnitude in the spray plume ranges from approximately 100 m/s (as described in Sect. 3.1) to 0.01 m/s (the input air velocity as described in Sect. 3.2). The particles located downstream the actuator mouthpiece decelerate rapidly until they match the air velocity. Larger particles

Layout: T1 Standard SC | Book ID: 321866_1_En | Book ISBN: 978-94-017-8831-1
Chapter No.: 13 | Date: 6-3-2014 | Page: 11/14

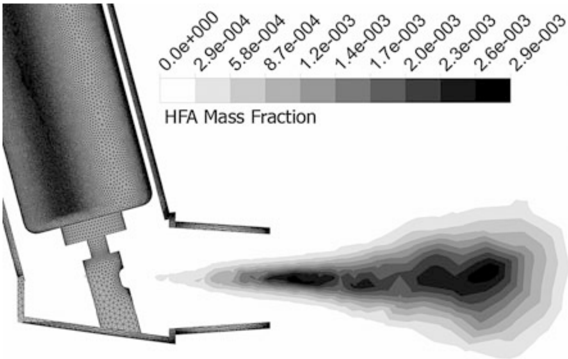

Fig. 8 HFA mass fraction contours took at the XY plane (z = 0 and t = 0.1 s)

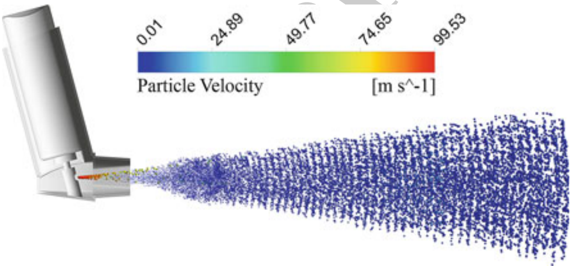

Fig. 9 Representation of the particle streams at the end of the injection (t = 0.11 s), with particles colored by its velocity magnitude. The particle streams are draw as spheres with proportional size scaled 20 times more than the real diameter

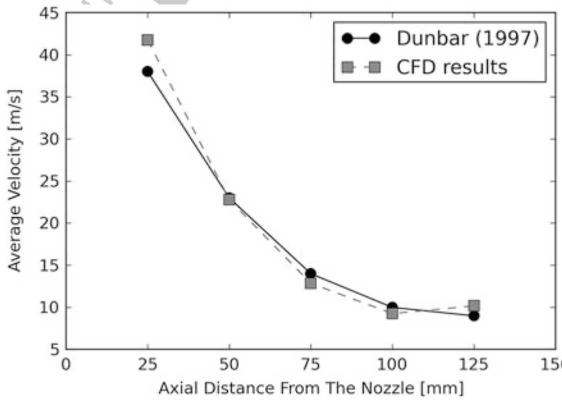

Fig. 10 Comparison of Dunbar [18] data with our CFD results, in terms of particle averaged velocity along the axial distance from the nozzle of a pMDI using a formulation only with HFA-134a

travel further into the still air than smaller ones. The influence of the gravitational acceleration is noticeable for higher particles when the slip velocity equals zero.

After other post-processing of the CFD results, took at different nozzle distances, results were obtained (see Figs. 10, 11).

In Fig. 10, the average velocity of the drug particles/droplets, took at the spray plume centerline for different distances from the nozzle, is reported. The results are then compared against data reported by Dunbar [18] for a formulation

Layout: T1 Standard SC | Book ID: 321866_1_En | Book ISBN: 978-94-017-8831-1
Chapter No.: 13 | Date: 6-3-2014 | Page: 12/14

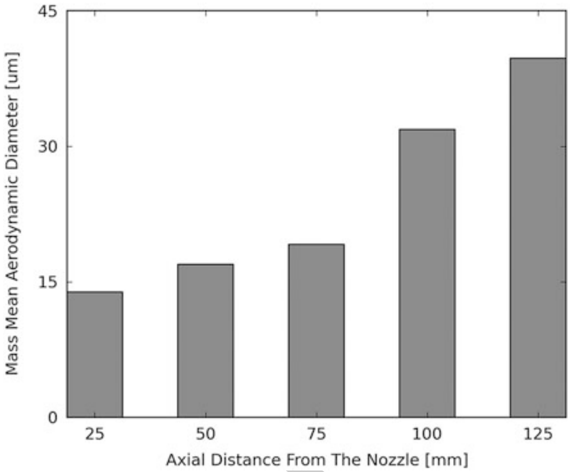

Fig. 11 Representation of the mass mean aerodynamic diameter along the axial distance from the nozzle

containing only HFA 134a. A good agreement between the CFD and the experimental results was found.

Figure 11 reports the Mass Mean Aerodynamic Diameter (MMAD), which is a common pharmaceutical measure to evaluate the size distribution of particles. This was calculated by considering the mass in the cumulative form and plotted against its corresponding diameter. Then, the diameter for which the mass fraction reached 50 % of the total was calculated. The results show that the value of MMAD increases with the distance from the nozzle, which can be indicative that particles of higher diameter travel further than the smaller ones.

5 Conclusions and Future Work

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. This was confirmed showing a good coefficient of determination for the experimental data obtained by laser diffraction analysis.

The spray 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.

A good agreement between the CFD and the experimental data from Dunbar [18] was found, regarding the average velocity along the axial distance. Also, it was found that the MMAD value increases with the axial distance.

Spray characteristics used contributed to a correct configuration of the spray in the CFD software.

Acknowledgments The first author would like to express his acknowledgments for the support given by the Portuguese Foundation for Science and Technology (FCT) through the PhD Grant SFRH/BD/76458/2011. This work was financed by National Funds-Portuguese Foundation for Science and Technology, under Strategic Project PEst-C/EME/UI4077/2011 and PEst-OE/EME/UI0252/2011.

References

1. Global Initiative for Asthma: Global strategy for asthma management and prevention. GINA (2012)
2. M. Masoli, D. Fabian, S. Holt, R. Beasley, The global burden of asthma: executive summary of the GINA dissemination committee report. Allergy **59**, 469–478 (2004)
3. M.B. Dolovich, In my opinion—interview with the expert. Pediatr. Asthma Allergy Immunol. **17**, 292–300 (2004)
4. R. Dhand, Inhalation therapy with metered-dose inhalers and dry powder inhalers in mechanically ventilated patients. Respir. Care. **50**, 1331–1345 (2005)
5. S.W. Stein, Estimating the number of droplets and drug particles emitted from MDIs. AAPS PharmSciTech. **9**, 112–115 (2008)
6. S.P. Newman, in *Aerosols*, eds. by G.J. Laurent, S.D. Shapiro. Encyclopedia of Respiratory Medicine (Elsevier, Amsterdam, 2006), pp. 58–64
7. G. Crompton, A brief history of inhaled asthma therapy over the last fifty years. Prim. Care Respir. J. **15**, 326–331 (2006)
8. S.P. Newman, Principles of metered-dose inhaler design. Respir. Care. **50**, 1177–1190 (2005)
9. C.A. Dunbar, A.P. Watkins, J.F. Miller, An experimental investigation of the spray issued from a pMDI using laser diagnostic techniques. J. Aerosol Med. **10**, 351–368 (1997)
10. C. Kleinstreuer, H. Shi, Z. Zhang, Computational analyses of a pressurized metered dose inhaler and a new drug-aerosol targeting methodology. J. Aerosol Med. **20**, 294–309 (2007)
11. H. Smyth, A.J. Hickey, G. Brace, T. Barbour, J. Gallion, J. Grove, Spray pattern analysis for metered dose inhalers I: orifice size, particle size, and droplet motion correlations. Drug Dev. Ind. Pharm. **32**, 1033–1041 (2006)
12. C.A. Ruzycki, E. Javaheri, W.H. Finlay, The use of computational fluid dynamics in inhaler design. Expert Opin. Drug Deliv. **10**, 307–323 (2013)
13. R.F. Oliveira, S.F.C.F. Teixeira, L.F. Silva, J.C. Teixeira, H. Antunes, in *Study of a Pressurized Metered-dose Inhaler Spray Parameters in Fluent™*. WCE 2010—World Congress on Engineering 2010, London, UK (2010), pp. 1083–1087
14. R.F. Oliveira, S.F.C.F. Teixeira, L.F. Silva, J.C. Teixeira, H. Antunes, in *CFD Study of the Volumatic Spacer: A Realistic Approach*, eds. by J.C.F. Pereira, A. Sequeira, J.M.C. Pereira. V European Conference on Computational Fluid Dynamics ECCOMAS CFD 2010. ECCOMAS, Lisbon, Portugal (2010)

15. R.F. Oliveira, S.F.C.F. Teixeira, J.C. Teixeira, L.F. Silva, H. Antunes, in *pMDI Sprays: Theory, Experiment and Numerical Simulation*, ed. by C. Liu. Advances in Modeling of Fluid Dynamics (Intech, Rijeka, Croatia, 2012), p. 300
16. R.F. Oliveira, A.C.M. Ferreira, S.F.C.F. Teixeira, J.C. Teixeira, H.M.C. Marques, in *pMDI Spray Plume Analysis: A CFD Study*, eds. by S.I. Ao, L. Gelman, D.W.L. Hukins, A. Hunter, A.M. Korsunsk. Lecture Notes in Engineering and Computer Science: Proceedings of the World Congress on Engineering 2013, WCE 2013 (Newswood Limited, London, UK, 2013), pp. 1883–1888
17. C.A. Dunbar, A.J. Hickey, Evaluation of probability density functions to approximate particle size distributions of representative pharmaceutical aerosols. J. Aerosol Sci. **31**, 813–831 (2000)
18. C.A. Dunbar, Atomization mechanisms of the pressurized metered dose inhaler. Part. Sci. Technol. **15**, 253–271 (1997)
19. G. Jepson, T. Butler, D. Gregory, K. Jones, Prescribing patterns for asthma by general practitioners in six European countries. Respir. Med. **94**, 578–583 (2000)
20. M.G. Zuidgeest, H.A. Smit, M. Bracke, A.H. Wijga, B. Brunekreef, M.O. Hoekstra, J. Gerritsen, M. Kerkhof, J.C. Jongste, H.G. Leufkens, Persistence of asthma medication use in preschool children. Respir. Med. **102**, 1446–1451 (2008)
21. A.R. Clark, MDIs: physics of aerosol formation. J. aerosol Med. **9**(Suppl. 1), S19–S26 (1996)
22. S.W. Stein, P.B. Myrdal, The relative influence of atomization and evaporation on metered dose inhaler drug delivery efficiency. Aerosol Sci. Technol. **40**, 335–347 (2006)
23. S.W. Stein, P. Sheth, P.B. Myrdal, A model for predicting size distributions delivered from pMDIs with suspended drug. Int. J. Pharm. **422**, 101–115 (2012)
24. J.H. Ferziger, M. Peric, *Computational Methods for Fluid Dynamics* (Springer, Berlin, 2003)
25. H.K. Versteeg, W. Malalasekera, *An Introduction to Computational Fluid Dynamics: The Finite Method* (Longman, Harlow, England, 1995)
26. ANSYS: *ANSYS Fluent Theory Guide* (ANSYS Inc, Canonsburg, PA, USA 2011)
27. P.W. Longest, G. Tian, R.L. Walenga, M. Hindle, Comparing MDI and DPI aerosol deposition using in vitro experiments and a new stochastic individual path (SIP) model of the conducting airways. Pharm. Res. **29**, 1670–1688 (2012)
28. P.W. Longest, J. Xi, Effectiveness of direct lagrangian tracking models for simulating nanoparticle deposition in the upper airways. Aerosol Sci. Technol. **41**, 380–397 (2007)
29. G. Tian, P.W. Longest, G. Su, R.L. Walenga, M. Hindle, Development of a stochastic individual path (SIP) model for predicting the tracheobronchial deposition of pharmaceutical aerosols: effects of transient inhalation and sampling the airways. J. Aerosol Sci. **42**, 781–799 (2011)
30. R. Clift, J.R. Grace, M.E. Weber, *Bubbles, Drops, and Particles* (Dover Publications, New York, 2005)

Author Query Form

Book ID :	**321866_1_En**
Chapter No.:	**13**

Springer
the language of science

Please ensure you fill out your response to the queries raised below and return this form along with your corrections

Dear Author
During the process of typesetting your chapter, the following queries have arisen. Please check your typeset proof carefully against the queries listed below and mark the necessary changes either directly on the proof/online grid or in the 'Author's response' area provided below

Query Refs.	Details Required	Author's Response
AQ1	Kindly note that figure caption for Figs. 2 and 3 are same. Please check and confirm.	

MARKED PROOF

Please correct and return this set

Please use the proof correction marks shown below for all alterations and corrections. If you wish to return your proof by fax you should ensure that all amendments are written clearly in dark ink and are made well within the page margins.

Instruction to printer	*Textual mark*	*Marginal mark*
Leave unchanged	• • • under matter to remain	
Insert in text the matter indicated in the margin		New matter followed by or
Delete	/ through single character, rule or underline or through all characters to be deleted	or
Substitute character or substitute part of one or more word(s)	/ through letter or through characters	new character / or new characters /
Change to italics	under matter to be changed	
Change to capitals	under matter to be changed	
Change to small capitals	under matter to be changed	
Change to bold type	under matter to be changed	
Change to bold italic	under matter to be changed	
Change to lower case	Encircle matter to be changed	
Change italic to upright type	(As above)	
Change bold to non-bold type	(As above)	
Insert ‘superior’ character	/ through character or where required	or under character e.g. or
Insert ‘inferior’ character	(As above)	over character e.g.
Insert full stop	(As above)	⊙
Insert comma	(As above)	,
Insert single quotation marks	(As above)	or and/or or
Insert double quotation marks	(As above)	or and/or or
Insert hyphen	(As above)	
Start new paragraph		
No new paragraph		
Transpose		
Close up	linking characters	
Insert or substitute space between characters or words	/ through character or where required	
Reduce space between characters or words	between characters or words affected	