Flow Simulations in TwinCaps Dry Powder Inhaler using OpenFOAM

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April 2016
This thesis is dedicated to my parents
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Abstract

To date inhalation has been the preferred route for the treatment of lung-associated conditions, for instance asthma, cystic fibrosis or chronic obstructive pulmonary disease (COPD). Dry powder inhalers (DPIs) are a commonly used vehicle for pulmonary drug delivery, with the majority of the marketed devices being of the passive type. Passive dry powder inhalers (DPIs) rely exclusively on the patient’s inspiratory effort to fluidize, deaggregate and disperse the resulting active pharmaceutical ingredient (API) particles into the airflow which then carries them to the lungs.

Setting a mathematical model able to predict particle behavior within the TwinCaps® DPI as the end goal, this thesis work has focused on formulating a model capable of simulating the device’s internal airflow when suction is applied at its exit.

Because real particle distribution inside TwinCaps® is hardly ever symmetric, the presented simulations were run taking the whole domain into consideration despite of it being symmetric about two planes. Symmetric solutions to this problem would require the meshes, discretization schemes and discretization errors to be symmetric, which is impossible to guarantee. Considering this, iterative convergence had to be thoroughly controlled in all the simulations. To this end, explicit under-relaxation was added to OpenFOAM®. Combining both types of under-relaxation, the model was able to capture the experimental $Q$ vs. $\Delta p$ curve behavior and to predict the device’s outlet flow rate with an associated modeling error in the range $[4.1\%; 9.3\%]$.

Keywords: Pulmonary drug delivery, Dry powder inhaler, TwinCaps®, CFD, OpenFOAM®
Resumo

Até à data a inalação tem sido a via de administração predilecta para o tratamento de doenças da pneumologia, nomeadamente a asma, fibrose cística e doença pulmonar obstrutiva crónica (DPOC). Os inaladores de pó seco são um tipo de veículo comum para a administração do fármaco ao pulmão, com a maioria dos dispositivos no mercado sendo passivos. Inaladores passivos dependem exclusivamente do esforço inspiratório do paciente para fluidizar, desagregar e dispersar as partículas finas do princípio activo no escoamento de ar que as transporta até aos pulmões.

Tendo como objectivo final o desenvolvimento de um modelo matemático capaz de prever o comportamento das partículas e seus agregados dentro do inalador TwinCaps®, o trabalho desta tese incidiu na formulação de um modelo para simular o escoamento dentro do inalador. A solução numérica é obtida usando o código open-source de CFD, OpenFOAM®.

Dado que a distribuição real de partículas dentro do TwinCaps® dificilmente será simétrica, as simulações representadas foram efectuadas considerando o domínio completo apesar deste ser simétrico em relação a dois planos. Soluções simétricas para este problema requereriam malhas, esquemas de discretização e erros de discretização simétricos, o que é impossível de garantir. Desta forma, a convergência iterativa teve de ser cuidadosamente controlada em todas as simulações efectuadas. Para o efeito, adicionou-se ao OpenFOAM® a possibilidade de utilizar sub-relaxação explícita. Combinando os dois tipos de sub-relaxação, o modelo proposto foi capaz de capturar o compartamento da curva $Q \text{ vs. } \Delta p$ experimental e de prever o caudal volumétrico de saída com um erro de modelação associado no intervalo $[4\%, 9\%, 3\%]$.

Palavras-chave: Administração de fármacos pulmonares, Inalador de pó seco, TwinCaps®, CFD, OpenFOAM®
# Contents

Acknowledgements .......................................................... v
List of Tables .............................................................. xv
List of Figures ................................................................ xvii
Nomenclature .................................................................. xxi
Acronyms .......................................................................... xxiii

## 1 Introduction

1.1 Pulmonary drug delivery .................................................. 2
1.2 Inhaler devices ............................................................... 3
  1.2.1 Nebulizers ................................................................. 3
  1.2.2 Pressurized metered-dose inhalers ............................... 4
  1.2.3 Dry powder inhalers .................................................. 5
  1.2.4 Soft mist inhalers ...................................................... 6
1.3 Fundamentals of inhaled Aerosol mechanics .................... 6
  1.3.1 Aerosol properties ...................................................... 6
  1.3.2 Deposition mechanisms in the lung ............................ 7
1.4 Dry powder inhaler development ..................................... 10
  1.4.1 Principles used in aerosol generation ......................... 11
  1.4.2 DPI design requirements .......................................... 13
  1.4.3 Types of DPIs ........................................................ 13
1.5 Thesis motivation ........................................................... 14
1.6 Thesis objectives ........................................................... 16
1.7 Thesis outline ............................................................... 18

## 2 Numerical solution method

2.1 TwinCaps DPI ............................................................... 21
2.2 Mathematical model ..................................................... 22
  2.2.1 RANS equations ...................................................... 23
  2.2.2 Turbulence modeling ................................................ 24
2.3 Boundary conditions .................................................. 24
  2.3.1 Inlet boundary conditions ...................................... 25
  2.3.2 Outlet boundary conditions ..................................... 26
  2.3.3 Wall boundary conditions ...................................... 26
2.4 Initial conditions .................................................. 28
2.5 Space discretization ................................................. 29
  2.5.1 Discretization schemes properties ............................. 29
  2.5.2 Upwind scheme ................................................... 30
  2.5.3 Hybrid upwind scheme .......................................... 31
  2.5.4 Discretized set of equations ................................... 31
2.6 Computational domain .............................................. 32
2.7 Meshing in OpenFOAM .............................................. 34
  2.7.1 OpenFOAM ......................................................... 34
  2.7.2 Solvers ........................................................... 34
  2.7.3 Meshing .......................................................... 35
3 Results & discussion .................................................. 39
  3.1 Steady flow ........................................................ 39
    3.1.1 Iterative convergence ......................................... 40
    3.1.2 Solution relaxation ............................................ 44
    3.1.3 Numerical error ................................................ 45
    3.1.4 Experimental methodology ................................... 48
    3.1.5 Inhaler resistance .............................................. 48
    3.1.6 Validation ....................................................... 49
    3.1.7 Flow characterization ......................................... 52
    3.1.8 Powder compartment flow .................................... 53
    3.1.9 Mouthpiece flow ............................................... 56
    3.1.10 Flow rate influence ........................................... 61
  3.2 Transient flow .................................................... 65
    3.2.1 Time discretization ............................................ 65
    3.2.2 Time dependent boundary condition .......................... 67
    3.2.3 Transient case configuration .................................. 68
    3.2.4 Powder compartment flow .................................... 69
    3.2.5 Mouthpiece flow ............................................... 72
    3.2.6 Particle visualization ......................................... 76

4 Conclusions and suggestions for future work ....................... 79

References .......................................................... 81

Appendices .......................................................... 85
## List of Tables

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1</td>
<td>Comparative analysis of drug administration routes</td>
<td>3</td>
</tr>
<tr>
<td>1.2</td>
<td>Ideal dry powder inhaler characteristics</td>
<td>13</td>
</tr>
<tr>
<td>1.3</td>
<td>Dry powder inhaler technology</td>
<td>15</td>
</tr>
<tr>
<td>1.4</td>
<td>Literature review</td>
<td>17</td>
</tr>
<tr>
<td>2.1</td>
<td>Governing equations</td>
<td>22</td>
</tr>
<tr>
<td>2.2</td>
<td>Differencing schemes comparison</td>
<td>31</td>
</tr>
<tr>
<td>2.3</td>
<td>Overall TwinCaps® dimensions</td>
<td>33</td>
</tr>
<tr>
<td>2.4</td>
<td>Quality parameters of the generated meshes</td>
<td>37</td>
</tr>
<tr>
<td>3.1</td>
<td>Steady-state cases matrix</td>
<td>39</td>
</tr>
<tr>
<td>3.2</td>
<td>The new and former relaxation factors configuration</td>
<td>45</td>
</tr>
<tr>
<td>3.3</td>
<td>The number of volumes in each grid and their matrix index</td>
<td>46</td>
</tr>
<tr>
<td>3.4</td>
<td>Numerical uncertainties for the 4.1, 4.2 and 4.3 test cases ran with the upwind scheme</td>
<td>47</td>
</tr>
<tr>
<td>3.5</td>
<td>Numerical uncertainties for the 4.1, 4.2 and 4.3 test cases ran with the linear upwind scheme</td>
<td>48</td>
</tr>
<tr>
<td>3.6</td>
<td>Volumetric flow rate measurements of N TwinCaps® devices</td>
<td>49</td>
</tr>
<tr>
<td>3.7</td>
<td>Calculation of the comparison error between simulation results and experiment</td>
<td>50</td>
</tr>
<tr>
<td>3.8</td>
<td>Inlet/Outlet flow rate ratio</td>
<td>63</td>
</tr>
<tr>
<td>3.9</td>
<td>Maximum flow velocity $U_x$ for the cases 3.2, 4.2 and 5.2</td>
<td>64</td>
</tr>
<tr>
<td>3.10</td>
<td>Time discretization schemes</td>
<td>66</td>
</tr>
</tbody>
</table>
List of Figures

1.1 Pressurized metered-dose inhaler (pMDI) technique ................................. 2
1.2 Jet nebulizer working principle ................................................................. 4
1.3 Pressurized metered-dose inhaler ............................................................... 5
1.4 Dry powder inhaler schematics ................................................................. 5
1.5 Soft mist inhaler schematics ................................................................. 6
1.6 Deposition mechanisms in the lung .......................................................... 10
1.7 Next generation impactor (NGI) .............................................................. 11
1.8 Aerosol generation ...................................................................................... 12
1.9 Powder bed fluidization ............................................................................. 12
1.10 Dry powder inhaler device types ............................................................. 14
2.1 TwinCaps® dry powder inhaler ................................................................. 20
2.2 TwinCaps® schematics ............................................................................... 21
2.3 TwinCaps® inhalation procedure ............................................................... 22
2.4 Turbulent boundary layer ........................................................................... 26
2.5 Wall treatment approaches ......................................................................... 27
2.6 Boundary conditions of pressure, velocity and turbulent quantities .......... 28
2.7 The transportiveness property of a discretization method ......................... 30
2.8 TwinCaps® internal surfaces ....................................................................... 32
2.9 Computational domain symmetry about planes X and Z ......................... 33
2.10 Computational domain simplifications: Top ............................................... 33
2.11 Computational domain simplifications: Middle ................................ .......... 33
2.12 Computational domain simplifications: Bottom ......................................... 34
2.13 TwinCaps® computational domain ............................................................. 35
2.14 OpenFOAM meshing procedure .................................................................. 36
2.15 Near-wall mesh topology .......................................................................... 36
2.16 Mesh quality parameters ......................................................................... 38
3.1 Equation residuals ...................................................................................... 40
3.2 Control surfaces for flow rate probing ....................................................... 41
3.3 Volumetric flow rates probed on the defined surfaces at the device's outlet and inlets ... 42
3.4 Equation residuals of the final solution ........................................ 43
3.5 Body side inlet flow velocity profile .............................................. 43
3.6 Asymmetry of the predicted flow field ........................................... 43
3.7 Body side inlets jets mixing site flow field .................................. 45
3.8 Convergence of the outflow numerical prediction with increasing mesh refinement using
    the upwind scheme ............................................................. 46
3.9 Convergence of the outflow numerical prediction with increasing mesh refinement using
    the linear upwind scheme ..................................................... 47
3.10 Experimental tests equipment set-up ............................................. 48
3.11 Relationship between pressure drop and flow rate across DPI devices .......... 49
3.12 Comparison of numerical and experimental data ................................ 51
3.13 Comparison between fitted linear curves of experimental and computational data .... 52
3.14 The aerodynamic channel cross sectional Y planes ........................... 52
3.15 Flow streamlines at the powder compartment inlet ............................ 53
3.16 Flow field velocity profiles across the length of the powder compartment ........ 54
3.17 Flow field turbulent kinetic energy profiles across the length of the powder compartment .... 54
3.18 Streamlines projected in three X-plane cross sections of the powder compartment ..... 55
3.19 Velocity profile at one of the body side inlets .................................. 56
3.20 Frontal collision between opposite body side inlet jets ........................ 57
3.21 Flow field velocity profiles across the length of the mouthpiece: 0L, 0.05L and 0.15L ... 57
3.22 Flow field turbulent kinetic energy profiles across the length of the mouthpiece: 0L, 0.05L
    and 0.15L ............................................................................. 57
3.23 Flow field velocity profiles across the length of the powder compartment: 0, 25L, 0.5L and
    0.75L ................................................................................. 59
3.24 Flow field velocity profiles across the length of the powder compartment 0, 25L, 0.5L and
    0.75L ................................................................................. 59
3.25 Flow field velocity profiles across the length of the powder compartment: L ........ 60
3.26 Flow field velocity profiles across the length of the powder compartment: ½L .......... 60
3.27 Effect of increasing flow rate on the solution flow field ....................... 62
3.28 Mean uy value on various powder compartment cross-sections .................. 62
3.29 Mean K value on various mouthpiece cross-sections ............................ 63
3.30 Flow regimes according to the Mach number .................................... 65
3.31 Patient inspiratory effort ............................................................... 67
3.32 Time-dependent pressure boundary condition .................................... 68
3.33 Evolution of the Courant number and time step values with iteration number .... 69
3.34 Powder compartment flow streamlines projected in the Z plane across inhalation time ... 69
3.35 Powder compartment flow streamlines projected in the X plane across inhalation time ... 70
3.36 Mean uy value on various aerodynamic channel cross-sections across time t .......... 71
3.37 Mean uy and K value on various powder compartment cross-sections across time t ...... 71
3.43 Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.001s$ .......................... 72
3.44 Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.002s$ .......................... 73
3.45 Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.003s$ .......................... 73
3.46 Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.004s$ .......................... 73
3.47 Symmetric configuration of the "stagnation points" system .......................... 73
3.48 Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.006s$ and $t = 0.008s$ .......................... 74
3.49 Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time steps $t = 0.006s$ and $t = 0.008s$ .......................... 74
3.50 Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time steps $t = 0.006s$ and $t = 0.008s$ .......................... 74
3.51 Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.05s$ .......................... 74
3.52 Final configuration of the "stagnation points" system .......................... 74
3.53 Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.16s$ .......................... 75
3.54 $t = 0.001s$ .......................... 75
3.55 Mean $\overline{U_y}$ and $\overline{K}$ value on various mouthpiece cross-sections across time $t$ .......................... 75
3.56 Mean $\overline{K}$ value on various mouthpiece cross-sections across time $t$ .......................... 76
3.57 Powder bed fluidization in the real and simulated flow .......................... 77

A.0 High speed filming frames of the TwinCaps® powder compartment .......................... 86
A.0 Fluidization of a massless particle bed in a transient simulation .......................... 87
B.1 Powder compartment flow streamlines at the first four time steps .......................... 89
B.2 Powder compartment flow streamlines at several time steps .......................... 90
# Nomenclature

## Roman Symbols

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{\text{out}}$</td>
<td>Outlet area</td>
<td>m²</td>
</tr>
<tr>
<td>$C_c$</td>
<td>Cunningham slip factor</td>
<td>-</td>
</tr>
<tr>
<td>$C_D$</td>
<td>Drag force coefficient</td>
<td>-</td>
</tr>
<tr>
<td>$d$</td>
<td>Particle diameter</td>
<td>m</td>
</tr>
<tr>
<td>$D_d$</td>
<td>Particle diffusion coefficient</td>
<td>m² s⁻¹</td>
</tr>
<tr>
<td>$d_{ae}$</td>
<td>Particle equivalent aerodynamic diameter</td>
<td>m</td>
</tr>
<tr>
<td>$F_d$</td>
<td>Drag Force</td>
<td>N</td>
</tr>
<tr>
<td>$F_g$</td>
<td>Gravity force</td>
<td>N</td>
</tr>
<tr>
<td>$g$</td>
<td>Constant gravitational acceleration</td>
<td>m s⁻²</td>
</tr>
<tr>
<td>$I$</td>
<td>Turbulence intensity</td>
<td>-</td>
</tr>
<tr>
<td>$k$</td>
<td>Boltzmann’s constant</td>
<td>J K⁻¹</td>
</tr>
<tr>
<td>$k$</td>
<td>Turbulent kinetic energy</td>
<td>m² s⁻²</td>
</tr>
<tr>
<td>$k_\infty$</td>
<td>Freestream turbulent kinetic energy</td>
<td>m s⁻²</td>
</tr>
<tr>
<td>$p_0$</td>
<td>Total pressure</td>
<td>kPa</td>
</tr>
<tr>
<td>$p_s$</td>
<td>Static pressure</td>
<td>kPa</td>
</tr>
<tr>
<td>$p_{\text{atm}}$</td>
<td>Atmospheric pressure</td>
<td>kPa</td>
</tr>
<tr>
<td>$Q_{\text{out}}$</td>
<td>Outlet flow rate</td>
<td>L min⁻¹</td>
</tr>
<tr>
<td>$T$</td>
<td>Particle temperature</td>
<td>K</td>
</tr>
<tr>
<td>$u_\tau$</td>
<td>Friction velocity</td>
<td>-</td>
</tr>
<tr>
<td>$v_{\text{rel}}$</td>
<td>Particle relative velocity to the fluid</td>
<td>m s⁻¹</td>
</tr>
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</table>
$v_{settling}$ Particle terminal settling velocity $\text{m s}^{-1}$

$x_d$ Distance covered by particle when diffusing in a fluid m

$y$ Distance to the wall m

$y^+$ Dimensionless distance to the wall -

**Greek Symbols**

$\epsilon$ Turbulence dissipation rate $\text{m}^2 \text{s}^{-3}$

$\kappa$ von Kármán constant -

$\mu$ Fluid dynamic viscosity $\text{Pa} \cdot \text{s}$

$\omega$ Turbulence specific dissipation rate $\text{s}^{-1}$

$\omega_\infty$ Freestream turbulence specific dissipation rate $\text{s}^{-1}$

$\rho_p$ Particle density $\text{kg m}^{-3}$

$\rho_w$ Water density $\text{kg m}^{-3}$

$\rho_f$ Fluid density $\text{kg m}^{-3}$

$\tau$ Particle relaxation time s

$\tau_w$ shear stress at the wall surface -

**Dimensionless Numbers**

$C$ Courant number $\frac{u \Delta t}{\Delta x}$

$M$ Mach number $\frac{v}{a}$

$Pe$ Peclet number $\frac{\rho u}{\Gamma / \delta x}$

$Re$ Reynolds number $\frac{\rho_p v_{rel} d}{\mu}$

$Stk$ Stokes number $\frac{\tau U_0}{D}$
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACI</td>
<td>andersen cascade impactor</td>
</tr>
<tr>
<td>API</td>
<td>active pharmaceutical ingredient</td>
</tr>
<tr>
<td>ASME</td>
<td>american society of mechanical engineers</td>
</tr>
<tr>
<td>CAD</td>
<td>computer-aided design</td>
</tr>
<tr>
<td>CDS</td>
<td>central differencing scheme</td>
</tr>
<tr>
<td>CFC</td>
<td>clorofluorocarbonate</td>
</tr>
<tr>
<td>CFD</td>
<td>computational fluid dynamics</td>
</tr>
<tr>
<td>CFL</td>
<td>Courant-Friedrichs-Lewy</td>
</tr>
<tr>
<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CV</td>
<td>control volume</td>
</tr>
<tr>
<td>DEM</td>
<td>discrete element method</td>
</tr>
<tr>
<td>DNS</td>
<td>direct numerical simulation</td>
</tr>
<tr>
<td>DPI</td>
<td>dry powder inhaler</td>
</tr>
<tr>
<td>DUSA</td>
<td>dosage unit sampling apparatus</td>
</tr>
<tr>
<td>ED</td>
<td>emitted dose</td>
</tr>
<tr>
<td>FD</td>
<td>finite difference</td>
</tr>
<tr>
<td>FE</td>
<td>finite element</td>
</tr>
<tr>
<td>FPF</td>
<td>fine particle fraction</td>
</tr>
<tr>
<td>FV</td>
<td>finite volume</td>
</tr>
<tr>
<td>GPL</td>
<td>general public licence</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>HFA</td>
<td>hydrofluoroalkane</td>
</tr>
<tr>
<td>LES</td>
<td>large eddy simulation</td>
</tr>
<tr>
<td>LHS</td>
<td>left-hand side</td>
</tr>
<tr>
<td>MMAD</td>
<td>mass median aerodynamic diameter</td>
</tr>
<tr>
<td>NGI</td>
<td>next generation impactor</td>
</tr>
<tr>
<td>PDE</td>
<td>partial differential equations</td>
</tr>
<tr>
<td>PIF</td>
<td>peak inspiratory flow</td>
</tr>
<tr>
<td>PISO</td>
<td>pressure implicit with splitting of operator</td>
</tr>
<tr>
<td>pMDI</td>
<td>pressurized metered dose inhaler</td>
</tr>
<tr>
<td>PSD</td>
<td>particle size distribution</td>
</tr>
<tr>
<td>RANS</td>
<td>Reynolds averaged Navier-Stokes</td>
</tr>
<tr>
<td>RHS</td>
<td>right-hand side</td>
</tr>
</tbody>
</table>
| SIMPLE       | semi-implicit method for pressure linked equa-
|              | tions                                            |
| SMI          | soft mist inhaler                                 |
| SST          | shear stress transport                            |
| STL          | stereolithography                                 |
| TIL          | turbulence intensity level                        |
| TLC          | total lung capacity                               |
| UDS          | upwind differencing scheme                        |
| WLD          | whole-lung deposition                             |
Chapter 1

Introduction

Inhalation of black henbane vapor is probably the first recorded use of inhalation as therapy in ancient Egyptian Ebers papyrus (1,554 BC). Physicians threw the weed onto hot bricks, vaporizing its contents so that the breathless patient could inhale (Sanders, 2007). Other civilizations also endorsed inhalation therapy: in India, by inhaling fumes of hemp; and in Ancient Greece by inhalation of vinegar and oil boiled vapors of herbs and resins which were later administered to the lungs through a tube (Sanders, 2007).

The first administration of anesthesia via inhalation occurred in the year of 1846 (Sanders, 2007). This specific application required special inhalation apparatus and was the driving force behind numerous new nebulizer designs. Eighteen years later, Newton (1864) developed an apparatus for dry powder delivery to the lungs. He inferred through experimentation that the powder formulation needed to be finely pulverized and that it should be kept dry: principles that are still valid for dry powder inhalers (DPIs) nowadays (Sanders, 2007).

In 1956, the first pressurized metered dose inhaler (pMDI) was cleared for clinical use, followed by the SpinHaler™DPI in 1971 (Rau, 2005). Although data on the drug delivery efficiency of inhaler devices (pMDI, DPI, and nebulizer) showed lung deposition of approximately 10 to 15% of label dose, evidence accumulated suggested advantages of the inhalation route over other drug administration routes (Rau, 2005). For asthma and other respiratory conditions, inhaled drugs represent on-target delivery, which significantly lowers label dose when compared with systemic delivery (oral or injection), thus diminishing otherwise severe adverse effects.

For decades the aforementioned respiratory diseases (e.g. asthma) propelled drug delivery device technology development. The same inhalation route traits, discussed in section 1.1, that once spurred this development now spike interest for possible systemic delivery via this route.

In sections 1.2 and 1.3 the four most common drug delivery device families: nebulizers; pMDIs; DPIs; and soft mist inhalers (SMIs) are described and the fundamental mechanics of aerosol formation and pharmaceutical powder formulation are discussed, respectively. The implications of device design parameters, together with patient compliance, on inhaled drug delivery performance are examined in section 1.4. The motivation and objectives for the present work are outlined in sections 1.5 and 1.6.
respectively. Finally, the contents of each chapter are summarized in section 1.7.

1.1 Pulmonary drug delivery

To date inhalation has been the most commonly endorsed route for the treatment of lung-associated conditions, for instance asthma, cystic fibrosis or COPD. When experiencing symptoms (e.g. COPD or asthma exacerbation), the patient equipped with the prescribed pulmonary drug delivery device, inhales a pharmaceutical aerosol which after traveling the respiratory tract settles on the bronchi-alveolar region, providing on-target therapeutic effect (Table 1.1). Moreover, by being absorbed directly into the bloodstream at the alveolar region, the drug bypasses the first-pass metabolism in the liver and intestines, thus requiring smaller doses of pharmaceutical active ingredient to provide the desired therapeutic effect (e.g. bronchodilation) and consequently diminishing unwanted side effects. However, the large variety of inhaler devices and corresponding inhalation techniques make the task of teaching by the clinician and of learning by the patient rather daunting and prone to error.

Figure 1.1 illustrates the numerous steps in the use of a generic pMDI. First the patient removes the mouthpiece cap which prevents foreign particles or dust from entering the device while in storage. Then, because the drug is usually suspended in the propellant gas, the user needs to shake the device to stir the mixture. The third step is to exhale right before actuating the device in step four and inhaling slowly until total lung capacity (TLC) is depleted (Beaucage and Nesbitt, 2002). In his study Crompton (1982) observed that the lack of coordination between actuation and inhalation (step four and five respectively) represented in 51% of the cases the source of problem in administration of the labeled dose.

![Figure 1.1: Pressurized metered-dose inhaler: illustration of the technique, adapted from Beaucage and Nesbitt, 2002](image)

Given the problems with patient compliance and the consequently low percentage of device label dose that reaches the lungs, clinicians and patients alike could certainly advocate other administration routes besides inhalation. It is indeed faster and more convenient to take a pill than to use an pMDI, a nebulizer, or a DPI (Rau, 2005). Moreover, the oral route is generally the least expensive and the most patient-friendly of the three most common drug administration routes: oral; parental and inhalation. However, absorption of the drug via digestive system is not as direct as injecting it into the bloodstream.
or even as inhaling it. The drug's absorption time is not only variable across patients, due to the natural duration of the digestive process, but may also be naturally inactivated (e.g. by the food ingested). Table 1.1 presents a summary of the most relevant benefits and shortcomings of each route.

Table 1.1: Comparative analysis of drug administration routes

<table>
<thead>
<tr>
<th>Route</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Convenient</td>
<td>Highly variable absorption time</td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td>Systemic side affects (e.g. First pass metabolism)</td>
</tr>
<tr>
<td></td>
<td>Portable</td>
<td>Drug may be inactivated (e.g. Food ingested)</td>
</tr>
<tr>
<td>Injection</td>
<td>Bioavailability (100%)</td>
<td>Special equipment and trained personnel required</td>
</tr>
<tr>
<td></td>
<td>Fastest onset of action</td>
<td>Expensive (Transportation and storage costs)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasive, can cause injuries and disease transmission (e.g. Embolism, Phlebitis)</td>
</tr>
<tr>
<td>Inhalation</td>
<td>On-target delivery</td>
<td>Irritation of the respiratory tract may take place</td>
</tr>
<tr>
<td></td>
<td>(Lung related diseases)</td>
<td>Variable dosing (e.g. Faulty inhalation technique)</td>
</tr>
<tr>
<td></td>
<td>Rapid onset of action</td>
<td>Special apparatus is required</td>
</tr>
<tr>
<td></td>
<td>Low drug dosage</td>
<td></td>
</tr>
</tbody>
</table>

It is well established that the treatment of respiratory diseases is more effective via inhalation administration (Rau, 2005). Besides featuring lower onset of action, i.e. the time the drug takes to take effect, and lower susceptibility to systemic side effects this route also has an immense end target, the lungs. The contact area at the alveolar region, between air and the blood vessels, where blood is oxygenated is roughly equivalent to that of a tennis court. These traits that once spawned the first respiratory condition treatments, now spike both academic and industrial interest in novel applications. In recent years, treatment of systemic diseases such as diabetes via inhalation has been the focus of inhaled drug delivery research, making the development of new cost-effective inhaler devices of improved efficacy a crucial topic.

1.2 Inhaler devices

Modern pulmonary drug inhaler devices date back to Sales-Girons’s pressurized inhaler in 1858 (Sanders, 2007), and have been object of ongoing research ever since. Four technologies of devices currently coexist at a commercial stage: Nebulizers; pMDI; DPI; and SMI. Each of them has its particular set of characteristics that make them more suitable to a given application than the other.

1.2.1 Nebulizers

Nebulizers are the most mature drug delivery device technology marketed today and are widely used in clinical and home care. This type of device uses water-soluble drug formulations and a means of dispersing it, to generate inhalable aerosols. Jet nebulizers (Figure 1.2) employ the venturi principle as
a dispersion mechanism, whereas ultrasonic nebulizers use the converse piezoelectric effect to fluidize the drug particles (Rau, 2002).

The wasted percentage of drug during patient exhalation, the long treatment times (typically 20 to 30 minutes) and low device portability are the main drawbacks of this technology (Chan et al., 2014). However, progresses have been made to optimize aerosol release by coupling a jet or mesh nebulizer with an electronic control unit (eg. AKITA®) to precisely time it to the desirable periods of the respiratory cycle, thus shortening both treatment time and reducing drug waste. These devices are particularly useful for diseases that require large amounts of emitted dose (ED), i.e. the percentage of label drug that exits the inhaler mouthpiece. Clinicians typically prescribe nebulizers to the elderly and younger children, due to their inability of both producing high peak inspiratory flow (PIF) and coordinating any ‘press and breathe’ techniques required with other inhalers.

Figure 1.2: Working principle behind a jet nebulizer, adapted from Medscape®

1.2.2 Pressurized metered-dose inhalers

pMDIs are still the most used device to date due to their compact size, portability, cost-effectiveness, power source independence, and capacity for delivering repeated consistent drug doses. Originally pMDIs used a chlorofluorocarbonate (CFC) mixture propellant as a means to produce a high-velocity plume to lift particles into the airflow (Figure 1.3a). But in 1988, generalized concerns about greenhouse gas emissions led to a phase-out of CFCs and consequently to the 10 year long search of an alternative, the hydrofluoroalkane (HFA).

Despite their undisputed popularity, pMDIs have one major drawback: the need of coordination between device actuation and patient inhalation. Failing to inhale at the right time might result in severely reduced doses of drug reaching the lungs, especially for patients of reduced dexterity like the elderly or the children.

The use of a spacer like the one depicted in Figure 1.3b for instance, mitigates some of these disadvantages. A spacer is a cylindrical chamber attached by one end to the inhaler’s outlet and equipped with a mouthpiece at the other. This accessory device acts much like an expansion chamber in which the propellant-drug flow exiting the device’s outlet is suddenly slowed down by the abrupt change in cross sectional area of the channel it travels in. This aerodynamic phenomenon sharply reduces the risk of
upper-airway drug deposition, by reducing particle velocity consequently preventing them from directly impacting the mouth cavity or on the back of the throat. However any potential advantages subsequent of its use, come at the price of additional device complexity and overall cost.

### 1.2.3 Dry powder inhalers

DPIs serve as an alternative to pMDIs and are the preferred device technology for treating a number of increasingly diverse diseases (Islam and Cleary, 2012). Unlike their counterparts, DPIs contain a dry powder formulation (hence their name) stored in the form of capsules (e.g. Handihaler®), blisters (e.g. Diskhaler®) or reservoirs (e.g. Turbuhaler®, see Figure 1.4). Upon patient actuation a label dose of dry powder is entrained and dispersed in the inspiratory airflow by a variety of fluidization and dispersion mechanisms specific to each device.

![Dry powder inhaler: configuration of the Turbuhaler® device, adapted from Beaucage and Nesbitt, 2002](image)

The DPI family is subdivided into active and passive devices, the difference between them being that the latter relies solely on the patients inspiratory flow, whilst the first also relies on an additional source of power (e.g. mechanical). In part, using passive DPI devices has diminished the coordination problems experienced by patients using traditional pMDI. However, correct use of one DPI does not guarantee the same outcome with a different one because each device has specific characteristics and handling requirements. In addition, DPI performance strongly depends on drug formulation, device design (e.g. outlet diameter size) and patient compliance, making the development of this drug delivery
technology a multidisciplinary challenge.

1.2.4 Soft mist inhalers

Soft Mist Inhalers (SMI) are the most recent inhaler technology, being Respimat® Soft Mist™ by Boehringer Ingelheim the first of its kind. In Respimat® (Figure 1.5), upon actuation, the metered dose of water-based drug solution is forced through a nozzle, producing two fine jets of liquid that converge at a predefined angle to create a soft mist. The mist contains a high fine particle fraction, a key inhaler performance indicator, of approximately 65 to 80% (Dalby et al., 2004). A value much higher than those of either pMDIs and DPIs inhalers. These numbers adding to the slow moving mist preventing high upper airway deposition make SMI a though competitor for the more conventional devices.

Figure 1.5: Soft mist inhaler: configuration of the Respimat® device

1.3 Fundamentals of inhaled Aerosol mechanics

The term Aerosol refers to a colloid of liquid droplets or solid particles in a gas. Aerosols can be either of natural or artificial origin. A well known natural aerosol is fog, a colloidal suspension of water particles in air that forms when ambient temperature drops below dew point on days of high relative humidity. Examples of artificial aerosols are smoke, pollutants and dust.

Aerosols for medicinal purposes date back at least 4,000 years (Anderson, 2005) where, as today, fumigation herbal preparations therapies took advantage of the vast lung area to deliver the desired therapeutic effect. Since then, both aerosol characterization and delivery techniques have largely developed.

1.3.1 Aerosol properties

Particle size is the single most important attribute characterizing both properties and behavior of aerosols. Most aerosols are poly-dispersed, i.e. consist in particles of variable size, making characterizing its properties much harder than for mono-dispersed ones. Moreover, the average pharmaceutical powder particle exhibits an irregular shape, rendering the task of exactly predicting the forces exerted on
it and its trajectory quite challenging. To tackle this issue, Aerosol scientific studies have been conducted under two major assumptions: (a) the particle is assumed to be spherical; and (b) its density is much higher than that of the surrounding gas (Warren H. Finlay, 2013).

In inhalable aerosols, the first assumption is accurate for small liquid droplets and also applicable for dry powder particles since they are usually compact and the drag force exerted on them is close to that of a sphere. To theoretically implement this assumption, a correction factor or equivalent diameter approach is frequently applied (Ruzer and H. Harley, 2004). In this context, the equivalent diameter is the size of a spherical particle that exhibits similar properties or characteristics as its non spherical counterpart. From a mechanical standpoint, since it influences various deposition mechanisms in the respiratory tract, the most widely employed equivalent diameter is the aerodynamic one.

Equation 1.1 defines the particle Reynolds number, a dimensionless number, that in this context represents the ratio between the particle inertial force and the viscous force (drag) exerted on it by the fluid. Where \( d \) is the particle diameter, \( v_{rel} \) its velocity relative to the fluid and \( \mu \) is the fluid’s dynamic viscosity.

\[
Re = \frac{\rho_p v_{rel} d}{\mu} = \frac{\text{inertial forces}}{\text{viscous forces}}
\]  

(1.1)

In the simplified case of a particle with Reynolds number \( Re \ll 1 \), actuated only by gravity and fluid drag, the equivalent aerodynamic diameter is defined as in Equation 1.2 (Warren H. Finlay, 2013). Where \( \rho_p \), \( \rho_w \) are the particle and water densities respectively and \( d \) is the particle’s diameter.

\[
d_{ae} = \sqrt{\frac{\rho_p d}{\rho_w}}
\]  

(1.2)

The second assumption is also valid for inhalable aerosols, since the density of pharmaceutical drug particles is similar to that of water (1000 kg m\(^{-3}\)) which is three orders of magnitude greater that of the surrounding fluid, which is typically air (1.2 kg m\(^{-3}\)) (Warren H. Finlay, 2013).

1.3.2 Deposition mechanisms in the lung

The most important kind of aerosol particle motion is steady, straight-line motion resulting from a constant external force exerted on the particle in still fluid. Under these conditions, the particle reaches constant terminal velocity that is proportional to the magnitude of the external force. If the external force is gravity, the resulting motion is called settling and the particle is said to deposit by sedimentation (Warren H. Finlay, 2013).

This motion is governed by Newton’s Second Law (Equation 1.3), where \( m \) and \( v \) are the particle’s mass and velocity respectively. The external force is partitioned in gravity \( F_g \) and drag \( F_d \) forces.

\[
m \frac{dv(t)}{dt} = F_g + F_d
\]  

(1.3)

\[
F_g = \rho_p g \frac{\pi d^3}{6}
\]  

(1.4)
\[ F_d = -\frac{1}{2} \rho_f v_{rel}^2 C_D \frac{\pi d^2}{4} \] (1.5)

Where \( C_D(Re) \) is the particle’s drag force coefficient, which is exclusively a function of the Reynolds number. Many empirical correlations based on experimental data exist in literature for the drag coefficient of spherical bodies. Schiller and Naumann (1935) developed for laminar flow the following correlation,

\[
C_D(Re) = \begin{cases} 
24(1 + 0.15Re^{0.687})/Re & Re \leq 1000 \\
0.44 & Re > 1000 
\end{cases} \] (1.6)

Since most aerosol particles have small diameters and travel at low relative velocities in the lungs, the assumption that \( Re \ll 1 \) holds and \( C_D \sim 24/Re \). Substituting \( C_D \) in Equation 1.5, yields the Stokes law for spherical particles

\[ F_d = -3\pi d \mu v_{rel} \] (1.7)

When terminal settling velocity is reached, the particle’s acceleration \( \frac{dv}{dt} \) is zero and thus gravity is balanced by the drag force. Equating both forces,

\[ F_g = F_d \equiv \rho_p g \frac{\pi d^3}{6} = 3\pi d \mu v_{settling} \] (1.8)

\[ v_{settling} = \frac{gd^2}{18\mu \rho_p} \] (1.9)

The expression for the particle’s settling velocity is reached (1.9), which can be rewritten in terms of aerodynamic diameter by using Equation 1.2

\[ v_{settling} = \frac{gd^2_{ae}}{18\mu \rho_\omega} \] (1.10)

It is clear that \( v_{settling} \) is directly proportional to the square \( d_{ae} \), this means that a particle traveling on a flow inside an idealized tube will settle faster as its diameter increases.

Another deposition mechanism is Brownian motion, which arises from particle energy exchange with the surrounding gas molecules. Warren H. Finlay (2013) describes it as a nondeterministic random walk motion of aerosol particles and diffusion as the net transport of aerosol particles in a concentration gradient. Owing to the nondeterministic nature of this motion, predicting the particles trajectory is only possible over much longer periods of time than those of collision with the gas molecules. Einstein (1905) found the mean displacement value of particles in a given direction \( x_d \) to be described by

\[ x_d = (2D_d t)^{1/2} \] (1.11)

Where \( D_d \) is the particle diffusion coefficient
Here, \( k = 1.38 \times 10^{-23} \text{JK}^{-1} \) is Boltzmann’s constant, \( T \) is the absolute temperature, and \( C_c \) is Cunningham’s slip factor.

The relative importance of Brownian diffusion over sedimentation can be understood by comparing the distance \( x_s = v_{settling}t \) that a particle will settle in time \( t \) to the distance \( x_d \) (Equation 1.11) that the particle will diffuse in the same time span.

\[
\frac{x_d}{x_s} = \frac{18\mu\sqrt{2D_d t}}{\rho_p g d^2 C_c t} \tag{1.13}
\]

Introducing the definition of both \( D_d \) (Equation 1.12) and \( d_{ae} \) (Equation 1.2) with the ratio is now given by

\[
\frac{x_d}{x_s} = \frac{1}{\rho_p g} \left( \frac{\rho_w}{\rho_p} \right)^5 \sqrt{\frac{216\mu kT}{\pi t d_{ae}^5 C_c}} \tag{1.14}
\]

If \( x_d/x_s < 0.1 \) diffusion can be neglected (Warren H. Finlay, 2013). Substituting this value in Equation 1.14 allows to estimate, for a given particle residence time in the airways, the \( d_{ae} \) for which diffusion is negligible when compared with sedimentation. For an inhalation flow rate of 60 L min\(^{-1}\) (typical of DPIs and pMDI) residence time is typically \( t < 0.01 \text{ s} \) suggesting that particles of the size \( d_{ae} > 3.5 \mu\text{m} \) are unlikely to deposit by diffusion. According to Warren H. Finlay (2013), adding a ten second breath hold after inhalation lowers this threshold to \( d_{ae} > 0.9 \mu\text{m} \).

The third most important deposition mechanism is inertial impactation. Traveling through the naturally irregular lung airways, particles eventually reach a bend (e.g. bifurcation of trachea into the main bronchi). Whether they follow the flow making the bend, or they impact on the airway wall depends on their own inertia.

Rewriting Equation 1.3 by replacing the drag and gravity forces by their own expressions and then dividing by particle mass yields

\[
\frac{dv}{dt} = g - \frac{1}{\tau} v_{rel} \tag{1.15}
\]

Where \( \tau \) is the particle relaxation time, a constant in the exponential decay of the particle velocity due to drag,

\[
\tau = \rho_p d^2 C_c / 18\mu \tag{1.16}
\]

Now nondimensionlizing Equation 1.3 by introducing \( U_0 \) as reference velocity of the fluid flow an \( D \) as the typical dimension of the airways containing the flow, yields

\[
Stk\frac{dv'}{dt'} = \hat{g} - \frac{1}{\tau'} v'_{rel} \tag{1.17}
\]
Where $Stk$ is the Stokes number and $v', t'$ and $\hat{g}$ are, respectively, each variable’s dimensionless form. The Stokes number is defined as follows

$$Stk = \tau U_0 / D = U_0 \rho p d^2 C_c / 18 \mu D$$  \hspace{1cm} (1.18)

Smaller particles $Stk \ll 1$ more easily follow the flow’s streamlines whereas the larger $Stk \sim 1$ ones tend to pursue their original path and potentially stick to the wall (Warren H. Finlay, 2013). From this discussion it follows that the value of the Stokes number determines whether a particle will undergo inertial impaction.

Equations 1.10, 1.14 and 1.18 that are representative of the main three depositions mechanisms: sedimentation, Brownian motion and inertial impaction (Figure 1.6) respectively, all depend on the particles aerodynamic diameter $d_{ae}$. For the purpose of quantitatively predicting particle deposition, it is therefore not necessary to know the true size, shape, or density of a particle if the mass median aerodynamic diameter (MMAD) is known. Instruments that rely on gravimetric aerodynamic separation, such as cascades impactors known as the andersen cascade impactor (ACI) or the next generation impactor (NGI) (Figure 1.7), are used to measure this parameter.

1.4 Dry powder inhaler development

The Montreal Protocol, issued in 1987, that dictated the end of virtually any CFC based product on the market to date, spurred severe repercussions to the inhaler field, more specifically to pMDIs. These inhalers depended on a CFC mixture propellant to generate a plume that would carry the inhalable aerosol to the patients lungs. The aforementioned protocol not only rendered the existing technology inappropriate, but also triggered extra research on alternatives, which paved the way for the growth of DPIs market share.

The performance of a DPI system is governed by a combination of factors including: the properties of
the pharmaceutical powder formulation, the design of the devices dose metering systems, and the physical mechanisms (e.g. turbulence, shear and/or impactions) used to fluidize, deagglomerate, disperse and deposit drug powders in the farther distal regions of the lungs (Islam and Cleary, 2012).

Better performance is usually associated with a higher fine particle fraction (FPF) as smaller particles are more likely to reach the lungs upon inhalation. FPF is the mass fraction of individual or agglomerated particles measuring less than approximately 5µm in the dispersed powder exiting the inhaler. The FPF is known to be strongly affected by factors such as the powder formulation size distribution, cohesiveness and other material properties in addition to external factors such as ambient humidity (Chan and Chew, 2002).

1.4.1 Principles used in aerosol generation

The paramount of a pharmaceutical powder formulation is the API. It consists in micronized inhalable particles, typically in the size range of 0.5 to 5µm, that deliver the desired therapeutic effect upon administration. Given their reduced size and by virtue of interparticulate forces (e.g. electrostatic) these particles are extremely cohesive in nature and tend to form agglomerates with poor flowability that may hinder the aerosol generation process and lead to unreliable dosing.

Spheronization is one of the techniques applied to control the aggregation of micronized particles into larger soft spherical agglomerates with requisite flow properties (Pilcer and Amighi, 2010). Deaggregation then occurs inside the inhaler (e.g. Turbohaler®) by a designed dispersion mechanism, which should be able to overcome the interparticulate bonds and scatter the API particles in the inhalation flow.

This type of formulation is particularly interesting for high dose applications such as the treatment of systemic diseases, where the requisite ED is often above the microgram scale.

Another common drug formulation is the adhesive mixture, where the API is blended in a loose aggregate with larger (50–100 µm) carrier particles. Carrier consist of coarse, inert particles on to which drug particles latch to enhance their flowability.

Upon inhalation, the drug and carrier are released from the capsule or blister pack and subjected to
the inhaler’s dispersion mechanism separating small particles from the carrier (Figure 1.8). Incomplete deaggregation results in part of the ED depositing in the upper airways, more likely in the mouth cavity.

![Image of fluidization and dry powder dispersion mechanisms](image_url)

**Figure 1.8:** Fluidization and dry powder dispersion mechanisms, image adapted from Pilcer et al., 2012

As most of the currently marketed DPIs were generally designed for the specific use of adhesive mixtures, drug-to-carrier adhesion properties play a crucial part in DPI development (Pilcer et al., 2012).

The physics governing dry powder fluidization within a DPI inhaler is complex and attempts at characterizing it are still fairly new to the inhalation literature. It does however share a number of common traits with the fluidized bed technology area (Tuley, 2007) and therefore some understanding could be extrapolated to pharmaceutical powder fluidization. In a fluidized bed, air is blasted upwards through a packed powder bed. The flow impinges upward momentum to each particle, thus lifting and entraining them in the air stream i.e. “fluidizing” them (Tuley, 2007).

Fluidized bed technology has been object of extensive research (Tuley, 2007). So far some distinct behaviors of particle flow have been classified into different regimes. The powder’s properties are the key factor which set the regimes apart (Geldart, 1973). The challenge lies in properly characterizing a powder and using its material properties (the key factor) to accurately predict its behavior. Relevant powder properties for particle/fluid interaction include: particle size distribution (PSD); MMAD, particle and fluid density, shape and surface characteristics.

![Image of powder bed fluidization](image_url)

**Figure 1.9:** The process of powder bed fluidization, image adapted from Telko and Hickey, 2005

12
On the other hand, literature about the characterization of the fluidization process inside a DPI is still scarce, instead the existing studies either focus on powder formulation or performance of specific commercial devices. In some studies, the behavior of a powder blend inside a DPI was visualized using in-vivo radionuclide imaging methods (Newman and Busse, 2002). In others, experiments with special apparatus like the Cascade-Impactor (Figure 1.8) were used to measure the fine particle fraction (FPF) at DPI outlet.

1.4.2 DPI design requirements

A well devised dry powder inhaler embodies a number of primary and secondary functional parts. The primary parts consist of a suitable pharmaceutical powder formulation, a pre-filled single dose compartment or multi-dose container with a powder measuring mechanism, a powder dispersion principle and a housing for all parts (Hoppentocht et al., 2014). Secondary features can include ways to feedback the patient regarding correct dose administration and number of doses left. They may also consist on measures to prevent moisture uptake by the formulation (Hoppentocht et al., 2014), for example the Diskus (GSK) inhaler encloses an aluminum foil strip with individual dose blisters that protect the drug from ambient air.

Table 1.2: Some of the ideal DPI characteristics, adapted from Newman and Busse, 2002

<table>
<thead>
<tr>
<th>Effective dosing</th>
<th>Uniform dose throughout the DPI life</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Targeted, accurate, consistent and reproducible delivery</td>
</tr>
<tr>
<td></td>
<td>Generates full dose at low inspiratory flow rates</td>
</tr>
<tr>
<td>Efficient device</td>
<td>Design optimized by device and powder formulation innovation</td>
</tr>
<tr>
<td></td>
<td>Compact, portable</td>
</tr>
<tr>
<td></td>
<td>Cost-effective</td>
</tr>
<tr>
<td></td>
<td>Good moisture protection</td>
</tr>
<tr>
<td>Ease of use</td>
<td>Easy technique for clinician to teach and for patient to learn</td>
</tr>
<tr>
<td></td>
<td>Dose counter to prevent device over usage</td>
</tr>
<tr>
<td></td>
<td>Mechanism to prevent multiple dosing</td>
</tr>
<tr>
<td></td>
<td>Ergonomic</td>
</tr>
</tbody>
</table>

1.4.3 Types of DPIs

Unlike their counterparts, DPIs are breath-actuated devices that rely either solely on the patients respiratory effort (passive) or also on another power source (active).

Active devices are more complex by nature, as they need the extra parts (e.g springs) to provide the additional form of deaggregating power. A notable example is MicroDose® (Figure 1.10b), patient
inhalation triggers a piezoelectric element that induces vibrations which help to deaggregate the formulation powder (Newman and Peart, 2009).

On the other hand, passive devices like Hovione’s TwinCaps® inhaler (Figure 1.10a) are made from a small number of parts and are therefore much easier and cheaper (Chan et al., 2014) to produce. They also eliminate the need for any hand to breath coordination as the patient’s inhalation is the only vehicle the powder needs to reach the target location.

![Figure 1.10: (a) Hovione’s TwinCaps® Inhaler; (b) MicroDose® DPI](image)

Besides the classification based on dispersion mechanisms, the DPI technology family can also be split into three branches based on how they store their powder doses (Prime, 1997):

- **Single dose devices** store only one pre-metered dose at a time, usually in the form of a gelatin capsule that has to be loaded in before each use. They can either be discarded after usage as is the case of TwinCaps® or refilled an re-used (e.g. Handihaler®).

- **Multiple unit dose devices** store multiple pre-metered doses so can be used multiple times before either refilling or disposing. In the case of the Advair Diskus®, the inhaler contains a coiled sealed foil strip bearing 60 doses in separate blisters. Upon each actuation a blister is ruptured, exposing a single dose.

- **Reservoir devices** are also of the multiple dose type, but instead they store the entire amount of pharmaceutical drug in a single container or cannister. Upon actuation a metered amount of powder is harvested from the bulk and exposed to the airflow (e.g. Turbohaler®).

Passive devices currently dominate the DPI market, with Nektar’s Pulmonary Inhaler™ (marketed with the first inhalable insulin medication) being arguably the best known active device (Newman and Peart, 2009). A summary of the DPI categories is presented in Table 1.3. To the author’s knowledge, so far, no active reservoir device type has been marketed or submitted for clinical trials.

### 1.5 Thesis motivation

Past dry powder inhaler (DPI) research has focused either solely on specific device design or on powder formulation. For example, active DPIs have been designed specifically for patients, or for clinical situations in which patients cannot generate sufficient inspiratory effort. Variability in drug delivery due to insufficient inspiratory flow is often not a major problem for localized conditions (lung related diseases)
but it would probably be unsatisfactory for novel drugs such as inhaled proteins and macromolecules used in the treatment of systemic diseases (Islam and Gladki, 2008).

In most DPI in vitro experimental studies, the FPF measured at the device outlet, is regarded as an indicator of device performance. Because the deaggregation and dispersion mechanisms of the device occur upstream of the FPF measuring site, they remain unexplained. It is commonly accepted that DPIs design significantly tampers with FPF, mainly because it affects the flow’s turbulent structures and particle-particle and particle-device collisions (Tuley, 2007). For instance, Fernandes et al. (2015) demonstrated that for a constant flow rate, increasing the aerodynamic channel geometric blockage $\sigma = A_{\text{obstructed}}/A_{\text{channel}}$ could significantly improve FPFs. In other words, changing the channel’s design by increasing the obstruction to airflow, $\sigma \to 1$, promoted further particle agglomerate collisions with the channel’s walls resulting in a higher number of fine particles release, ultimately improving the device’s performance.

The fundamental operating principle of a dry powder inhaler involves the entrainment and subsequent dispersion of micro-sized powder particles for inhalation and delivery to the lungs. Successful drug dose delivery relies on complex processes including: the fluidization of the powder, deagglomeration of particle agglomerates; aerosol dispersion; aerosol deposition within the device and convection through the inhaler (Ruzycki et al., 2013). Moreover, the irregular shapes, rough-surface and reduced size of pharmaceutical powder particles hinder the task of exactly predicting adhesive (between particles) and aerodynamic forces (exerted by the fluid), leaving the understanding of aerosol generation and delivery at a qualitative level. Aerosol dispersion mechanisms are also complex, involving airflow-induced forces, particle-wall impactions within the device and particle-particle collisions. In addition, the relative importance of these mechanisms remains unclear (Warren H. Finlay, 2013) and may vary with inhaler design, inhaler operating conditions (e.g. flow rate) and powder formulation properties.

In several studies (Table 1.4), computational fluid dynamics (CFD) has granted wider insight on how inhaler design and dispersion mechanisms impact powder deagglomeration, dispersion and deposition. In his work, Coates et al. (2004) investigated the effect of changing both mouthpiece and inhaler grid morphology in Aerolizer®’s performance, concluding that small modifications on device design can significantly tamper device performance. Modeling of particle deagglomeration was not included in these studies (Coates et al., 2004; Coates et al., 2005; Coates et al., 2007), i.e. dispersion performance of the

<table>
<thead>
<tr>
<th>Single Dose</th>
<th>Multiple Unit Dose</th>
<th>Reservoir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirair® (Vectura)</td>
<td>&quot;Tape based&quot; (3M Pharmaceuticals)</td>
<td>Turbohaler® (Astra Zeneca)</td>
</tr>
<tr>
<td>Nektar Pulmonary (Nektar)</td>
<td>Oriel™inhaler (Oriel Therapeutics)</td>
<td>Novolizer® (ASTA Medica)</td>
</tr>
<tr>
<td>PuffHaler™ (Activ-Dry)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Passive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TwinCaps® (Hovione)</td>
<td>FlowCaps® (Hovione)</td>
<td></td>
</tr>
<tr>
<td>SpinHaler® (Aventis)</td>
<td>Diskus® (GSK)</td>
<td></td>
</tr>
<tr>
<td>HandiHaler®</td>
<td>Aerohaler®</td>
<td></td>
</tr>
<tr>
<td>(Boehringer-Ingelheim)</td>
<td>(Boehringer-Ingelheim)</td>
<td>(ASTA Medica)</td>
</tr>
</tbody>
</table>
Aerolizer® device could not be explicitly evaluated by CFD alone. Instead, performance was deducted from measured FPFs and deposited mass distributions. Nevertheless, these studies brought to the literature valuable understanding of the influence of multiple device design features on airflow behavior. Milenkovic et al. (2013) managed, using an Euler-fluid/Lagrangian-particle approach, to track particle deposition and relate it with powder properties, namely particle size. They suggested the description of initial powder deaggregation by discrete element method (DEM) and formulation properties such as PSD (e.g. by population balance models) as a way of deepening our understanding on particle tracking and behavior through the fluidization and dispersion processes. Tong et al. (2013) analyzed particle agglomerates dispersion in various CFD-DEM studies, trying to assess its fundamental mechanisms in dry powder inhalers. Unfortunately for either CFD-DEM or CFD Eulerian-fluid/Lagrangian-particle approaches, current computational power cannot yet cope with the effort of calculating the full number of particles and collisions in pharmaceutical aerosols.

Most studies discussed in Table 1.4 were successful in using CFD codes, validated through experimental data, to assess the air flow field, particle agglomerates break-up and performance of various devices for inhaled pharmaceutical delivery. For this purpose, the majority of authors chose to solve the Reynolds averaged Navier-Stokes (RANS) using commercial CFD codes such as ANSYS CFX or ANSYS Fluent, with two-equation turbulence models being amongst the most utilized for this specific type of application. Indeed, researchers have used either $k$-$\omega$ or $k$-$\omega$ shear stress transport (SST) models, which perform well in fluid flow problems that include adverse pressure gradients (which may lead to flow separation). This is especially important in complex device geometries where flow separation can significantly change flow properties and consequently tamper with device performance.

The current work aims to complement the existing literature on the use of CFD for understanding the main flow features inside commercial DPIs responsible for particle dispersion and deaggregation performance. The currently marketed TwinCaps® dry powder inhaler (Hovione, Portugal) was the first single dose disposable DPI to reach the market in Japan and is currently treating millions of patients every year on influenza. However, no study to this date has been reported on the flow characteristics of this DPI. This thesis thus aims to address this research gap through a retrospective CFD study of the TwinCaps DPI flow characteristics. Ultimately, the work developed throughout this project will serve as a prelude to future more complex studies of particle fluidization and dispersion within the inhaler device.

1.6 Thesis objectives

For the purpose of building a mathematical model capable of predicting particle behavior inside the TwinCaps® DPI, this work encompasses the steady-state flow characterization of the internal airflow of device, which comprises the following steps:

- Finding the set of under-relaxation factors that minimize the discretized partial differential equations (PDE) residuals
- Estimation of the discretization and iterative errors
Table 1.4: Literature review

<table>
<thead>
<tr>
<th>Scope</th>
<th>References</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analysis of commercial DPIs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tibbatts et al. (2010)</td>
<td>Transient Eulerian-Granular multiphase CFD simulations and experimental measurements (ACI) were used to correlate inspiratory effort, powder dispersion and <em>in vitro</em> performance of three DPIs</td>
</tr>
<tr>
<td></td>
<td>Shur et al. (2012)</td>
<td>Steady-state Eulerian-fluid/Lagrangian-particle CFD simulations and experimental measurements were used to evaluate flow field, pressure drop and particle tracking to achieve <em>in vitro</em> comparability of a device to Handihaler®</td>
</tr>
<tr>
<td><strong>Analysis of DPI design features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coates et al. (2004)</td>
<td>Steady-state and transient CFD simulations with Lagrangian particle tracing as a post-processing operation validated with experimental measurements (Laser Doppler Velocimetry) were used to investigate the effect of inhaler design changes such as the grid and mouthpiece length</td>
</tr>
<tr>
<td></td>
<td>Coates et al. (2005)</td>
<td>Steady-state CFD simulations with Lagrangian particle tracing as a post-processing operation validated with experimental measurements (Laser Doppler Velocimetry) were carried out at different flow rates to evaluate air flow influence on device performance</td>
</tr>
<tr>
<td></td>
<td>Coates et al. (2007)</td>
<td>Steady-state CFD simulations with Lagrangian particle tracking as a post-processing operation validated with experimental measurements (Laser Doppler Velocimetry) on four modified versions of Aerolizer were carried out to assess the influence of mouthpiece geometry on inhaler performance</td>
</tr>
<tr>
<td><strong>Analysis of dispersion mechanisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wong et al. (2011)</td>
<td>Combination of CFD and standardized entrainment tubes to investigate the flow field turbulence on powder agglomerate break-up</td>
</tr>
<tr>
<td></td>
<td>Tong et al. (2013)</td>
<td>Two-way CFD-DEM coupling was used to identify the dominant mechanisms of carrier-free powder agglomerates break-up in the Aerolizer®</td>
</tr>
<tr>
<td></td>
<td>Milenkovic et al. (2013)</td>
<td>Steady-state Eulerian-fluid/Lagrangian-particle CFD simulations at different pressure drops and formulation particle sizes were use to compute volumetric flow rate and main particle deposition sites within the Turbohaler®</td>
</tr>
</tbody>
</table>
• Comparison of the numerical predictions with experimental data of the device outflow under operating conditions

• Estimation of the modeling error

• Identifying the main flow patterns responsible for powder entrainment, deaggregation and dispersion

With the knowledge and tools gained from this first stage, an unsteady flow simulation, representative of patient utilization, is carried out. The results are examined with the following post-processing operations:

• Characterizing the previously identified main flow patterns throughout inhalation time

• Qualitatively comparing simulation flow field with high speed filming video frames

1.7 Thesis outline

This thesis comprises four chapters:

• **Chapter 1** provides fundamental background information on the inhalation administration route, the current state of technology behind it and points out how the present work aims to add value to this field. The pulmonary drug delivery devices technology tree is depicted and specifically DPIs inhalers are reviewed in greater detail. Dry powder aerosol characteristics and how they influence particle behavior and depositions mechanisms in the lung are also analyzed. Current knowledge on the impact of powder formulation and device design on DPI performance is revised and finally the main objectives for this work are described.

• **Chapter 2** addresses the formulation of the TwinCaps® internal flow field problem. A mathematical model to tackle this problem is proposed, including the equations governing fluid flow an the turbulence model selected to close the system of equations. The geometry of the inhaler is analyzed and, with the aid of a computer-aided design (CAD) software, the computational domain is devised. Finally, to enable integration of the equations over the computational domain, boundary conditions are prescribed at the domain’s boundaries, and initial conditions are set for each variable field.

• **Chapter 3** presents the numerical solution obtained with the proposed model. The results for several steady-state case studies are analyzed, with special focus on numerical error estimation, comparison of the solution with experimental data and main flow patterns characterization. Finally, the results for a transient case are qualitatively compared to high-speed video frames in an attempt to correlate both behaviors.

• **Chapter 4** summarizes the work carried out during this project and the conclusions that could be drawn from it. Some suggestions of future work are also made.
Chapter 2

Numerical solution method

The main goal of this thesis is to lay the first stone of the multiphase mathematical model building which is able to predict particle trajectory, behavior (e.g. particle-particle and particle-wall collisions) and deposition within the TwinCaps® device. In laboratory experiments, the standard analyzed *in vitro* indicators of device performance are the FPF, ED and MMAD. These powder formulation characteristics have been compared against whole-lung deposition (WLD) data acquired through gamma scintigraphy studies (Newman and Chan, 2008). For instance, drug deposition according to the FPF correlated with WLD across a range of different devices (Newman and Chan, 2008). However, these quantities of interest are measured downstream of the actual flow, and consequently do not provide sufficient information on how the device design-induced main flow field patterns and selected operating conditions relate to the final inhaler performance. To that end, the present work pretends to examine the airflow field generated inside the TwinCaps® inhaler under operating conditions.

TwinCaps® is a single-dose disposable dry powder inhaler marketed by Hovione (Loures, Portugal) as prefilled low-cost device for acute treatments (Myrdal et al., 2015; Fernandes et al., 2015). While most single-dose devices make use of capsules (Spinhaler®, Rotohaler®), which require patient dexterity, and include a cutting or piercing opening mechanism (Handihaler®, FlowCaps®), TwinCaps®'s technology avoids both measures effectively lowering its production cost (Villax et al., 2012). It’s production cost being low enough so that it can be used and disposed of after, make TwinCaps® highly useful in situations where an infectious agent is being treated and there is a need to eliminate the possibility of inhaler contamination (Villax et al., 2012). Since October 2010, it has been marketed in Japan under the name Inavir® (Daiichi Sankyo, Tokyo), an alternative form of *influenza* treatment by delivering the long-acting neuraminidase inhibitor, laninamivir, directly to the lungs. To prepare for that year’s seasonal flu, Daiichi Sankyo planned to supply six million units (Figure 2.1) by the end of March 2011.

Despite its renown success and effectiveness, to date few studies have addressed the internal flow of the device and it is yet to be fully comprehended. Tibbatts et al. (2010) tested *in vitro* performance of three DPIs at a 4kPa pressure drop measuring flow rates of 35, 39, 58Lmin⁻¹ and FPFs of 34%, 23%, 21% for the TwinCaps®, HandiHaler® and Diskus® respectively. This experiment also aimed to correlate high speed filming of powder behavior inside the powder compartment with its CFD simulation.
However this study did not focus on the flow patterns on other important device parts such as the mouthpiece. For instance, the direction of flow streamlines and the uniformity of the outlet velocity profile in the mouthpiece heavily influence particle distribution and later deposition in the oral cavity and upper airways and therefore ought to be studied.

As for most industrial engineering problems, the non-linearity and complexity of the governing equations inhibit an analytical approach to the problem. Instead computational fluid dynamics (CFD), a numerical approach, is going to be applied. CFD is the analysis of fluid flow, heat transfer and other phenomena supported by computation of the PDEs that govern the system in study. The inception of this technique took place in the aeronautics and aerospace industry in the 1960s (Versteeg and Malalasekera, 2005). Ever since, its range of applicability has grown and come to integrate fields such as turbomachinery, biomedical engineering and even meteorology.

Recently, several pulmonary drug delivery related studies, that apply this technique, have been submitted to the literature (Milenkovic et al., 2013; Wong et al., 2012) to gain better understanding of the flow behavior in common commercial devices. Similarly to these studies, this work aims to solve the TwinCaps® internal flow problem by executing a numerical solution method that is structured in the following manner:

- **Mathematical model** is at the core of every numerical method, comprising the set of PDE that govern the system and the boundary conditions of the domain.

- **Discretization method** approximates the PDE by a system of algebraic equations (matrix) for the variables at numerous discrete locations in space and time (in transient problems). The three most common approaches are the: finite difference (FD), finite volume (FV) and finite element (FE) methods.

- **Computational domain** is a closed volume derived from the problem's geometry using appropriate simplifications (for complex geometries).

- **Numerical grid** is a discrete representation of the computational domain comprising various sub-domains (e.g. control volumes in the case of FV) on whose centers the system of algebraic equations is going to be solved. There are three different types of meshes are: structured, multi-block structured and unstructured.
In section 2.1, the TwinCaps®'s usage, geometry and operating conditions are reviewed. Section 2.2, introduces fundamental background information on the system governing equations, associated turbulence model. Next, the boundary conditions and initial values for each variable field, which are necessary to integrate the equations that govern the flow, are defined in sections 2.3 and 2.4 respectively. Before computing the solution, the set of PDE need to be discretized in space and in time (for transient problems). Section 2.5 addresses the two space differencing schemes explored during this work. Their properties are reviewed in a discussion to determine their applicability to the problem at hand. The computational domain, on which these equations are going to be solved, is described and depicted in section 2.6. Lastly, in section 2.7 the mesh generation process and the quality of the resulting grids are analyzed.

### 2.1 TwinCaps DPI

The TwinCaps® dry powder inhaler consists of two plastic parts: the inhaler body; and the powder cartridge, hereby referred to as shuttle (Figure 2.2). The shuttle has two inlets to allow atmospheric air to travel into one of two equal powder compartments, disperse the powder, entrain it into the mouthpiece and ultimately out into the patient’s mouth (Villax et al., 2012). Each compartment has a rear inlet in the form of a slit, small enough to ensure that from the moment the powder is loaded in the compartment until patient actuation, no powder flows out of the device under the force of gravity. Moreover, when in storage position (illustrated in 2.3a)), the compartment's inlet and outlet are sealed, preventing powder from leaking out protecting it from environmental influences (Villax et al., 2012; Myrdal et al., 2015).

The body side inlets (Figure 2.2) bring additional air flux to the small amount of air volume that is able to enter the powder compartment through the narrow slit inlet, penetrate and entrain the powder bed and exit at the mouthpiece inlet. These body side inlets guarantee a comfortable inhalation and enrich the powder-air mix with air, thus maximizing the entrainment capacity of the flow (Villax et al., 2012). Furthermore, Villax et al. (2012) state that with the body side inlets, the user patient can easily generate a 4kPa pressure drop, which the pharmacopoeias recognize as suitable from a patient perspective.

![Figure 2.2: TwinCaps® Schematics: To the left is an isometric view of the inhaler in drug delivery position; To the right another isometric view of the front plane sectional cut that reveals the internal aerodynamic channel and powder storage cavity](image)
To deliver the pharmaceutical powder to his/her lungs, the patient is required to, while holding the inhaler's body still, slide the shuttle to the side (Figure 2.3a). In doing so, one of the dose compartments (inside the shuttle) aligns with the internal body channel, forming a complete aerodynamic channel from top to bottom of the inhaler (Figure 2.3b). Upon patient inhalation, a turbulent airflow in the compartment is created, entraining and deagglomerating the powder (Figure 2.3c) (Myrdal et al., 2015). After inhaling the first dose, the patient needs only to repeat the first three steps in the same order now moving the shuttle backwards (Figure 2.3d,e).

Figure 2.3: The TwinCaps® inhalation procedure steps

2.2 Mathematical model

Internal fluid flow in dry powder inhalers, particularly the case of the TwinCaps® inhaler is assumed to be incompressible, viscous and turbulent in nature. The set of equations governing such flow comprises the continuity (Equation 2.1), Navier-Stokes (Equation 2.2 - 2.4) and energy (Equation 2.5) equations which are shown in Table 2.1.

Table 2.1: The continuity, Navier-Stokes and energy equations in their conservative form, adapted from Versteeg and Malalasekera, 2005

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuity</td>
<td>$\frac{\partial \rho}{\partial t} + \text{div}(\rho \mathbf{u}) = 0$</td>
</tr>
<tr>
<td>x-momentum</td>
<td>$\frac{\partial (\rho u)}{\partial t} + \text{div}(\rho u \mathbf{u}) = -\frac{\partial p}{\partial x} + \text{div}(\mu \text{ grad } u) + S_M$</td>
</tr>
<tr>
<td>y-momentum</td>
<td>$\frac{\partial (\rho v)}{\partial t} + \text{div}(\rho v \mathbf{u}) = -\frac{\partial p}{\partial y} + \text{div}(\mu \text{ grad } v) + S_M$</td>
</tr>
<tr>
<td>z-momentum</td>
<td>$\frac{\partial (\rho w)}{\partial t} + \text{div}(\rho w \mathbf{u}) = -\frac{\partial p}{\partial z} + \text{div}(\mu \text{ grad } w) + S_M$</td>
</tr>
<tr>
<td>Energy</td>
<td>$\frac{\partial (\rho i)}{\partial t} + \text{div}(\rho i \mathbf{u}) = -p \text{ div } \mathbf{u} + \text{div}(k \text{ grad } T) + \Phi + S$</td>
</tr>
</tbody>
</table>

The set of equations were originally derived from the mass conservation principle (continuity), Newton’s second law of motion which implies momentum conservation (Navier-Stokes) and finally the first law of thermodynamics (energy equation). The deduction of this set of equations, collectively designated as Navier-Stokes equations, is covered in most fluid dynamics or CFD (Versteeg and Malalasekera, 2005;
Ferziger and Peric, 2002) text books and will not be addressed in this text.

It can be seen in Table 2.1 that equations share a variety of common traits, effectively exhibiting a similar form. Introducing a general fluid property \( \phi \) and incorporating the terms not shared between equations to their respective source terms yields the transport equation,

\[
\int_{CV} \frac{\partial}{\partial t} (\rho \phi) \, dV + \int_A \mathbf{n} \cdot (\rho \phi \mathbf{u}) \, dA = \int_A \mathbf{n} \cdot (\Gamma \text{grad} \phi) \, dA + \int_{CV} S_\phi \, dV \quad (2.6)
\]

Where \( \phi \) is equal to \( 1, u, v, w \) and \( \phi \) for the mass and momentum conservation and energy equations respectively. The first member on the left-hand side (LHS), which accounts for the rate of change of \( \phi \) over time, is zero for steady-state problems. Moreover, this equation represents the flux balance of a generic property \( \phi \) in a control volume. Its LHS portrays the convective net flux across all surfaces while the right-hand side (RHS) incorporates the net diffusive flux and the volumetric generation or destruction of the property (Versteeg and Malalasekera, 2005). Equation 2.6 is the fundamental base of computational procedures within the finite volume method theory (Ferziger and Peric, 2002).

### 2.2.1 RANS equations

To directly tackle turbulent flows, specifically internal complex flows, with the aforementioned set of equations requires solving of all the turbulent length and time scales. In the industrial setting it is often unnecessary to do so, as generally, engineers are most interested in quantitative properties of the flow such as the average aerodynamic forces on a given body or the flow rate in a pipe flow (Ferziger and Peric, 2002). For these purposes the Reynolds averaged Navier-Stokes (RANS) equations suffice.

The RANS equations, are the time averaged (or Reynolds averaged) Navier-Stokes equations for which only the solution of the mean fields is obtained. New RHS members of the momentum equations such as the Reynolds stresses arise as a side product of the time-averaging process. Because these stresses are unknown they also need transport equations for their calculation. Unfortunately these transport equations inherently spur higher order unknown terms, leaving the system of equations unclosed, i.e it contains more unknown variables than equations. Here turbulence modeling plays a key role in RANS, contributing with approximate closure equations established on simplifications made to the turbulence field. Several approaches, from the algebraic (zero equation models i.e. based on empirical correlations) to the Reynolds stress models (six equation models) are available for turbulence modeling (Nichols, 2001). Each has its own strengths, drawbacks, level of accuracy and degree of applicability when applied to different flow classes.
2.2.2 Turbulence modeling

Since direct numerical simulation (DNS)\(^1\) and large eddy simulation (LES)\(^2\) are available only at the cost of large amounts of computing time for simple low Reynolds number flows, this work focuses on solutions of the RANS equations closed by a classical two-equation turbulence model.

Two-equation turbulence models have been widely used in CFD for the better part of this century. These models solve two extra transport equations: one for turbulent kinetic energy, \(k\), the energy associated to velocity field fluctuations (Equation 2.7), and a second one that allows for a single turbulent length scale to be defined (Nichols, 2001). The most frequent forms of the second transport equation solve for turbulent dissipation rate, \(\epsilon\) (\(k - \epsilon\) models), or turbulent specific dissipation rate, \(\omega\) (\(k - \omega\) models), both representing the rate at which turbulent kinetic energy is converted to internal energy (Equation 2.8). A few of these models are only valid on the outer region of the boundary layer (high Reynolds models) while others remain valid down to the wall (low Reynolds models).

\[
k = \frac{1}{2} u_i' u_i' 
\]

\[
\omega = \frac{\epsilon}{C_\mu k} 
\]

The \(k - \epsilon\) models are generally more accurate in shear type flows and are well behaved in the far field. On the other hand, the \(k - \omega\) models are more accurate in flows where separation occurs and are relatively more numerically stable in the near wall region than the latter. Menter and Rumsey (1994) perceived this, and also recognizing the similar form of both equations, suggested a blended model that would behave as a \(k - \omega\) model near the wall and transition to a \(k - \epsilon\) model in the far field. Such model is known as Menter’s \(k - \omega\) SST model, and has been widely used in the DPI development field, mainly due to its accuracy at capturing flow separation (provided that the mesh is properly refined at the wall). This is especially important in complex device geometries where flow separation can lead to otherwise unpredictable flow behavior and consequently unexpected device performance. Considering this, and having identified the present work’s problem as a complex in geometry wall bounded flow, the \(k-\omega\) SST turbulence model was deemed the most suitable.

2.3 Boundary conditions

At the cell faces centers bounding the domain, there is insufficient information for the integration of the PDE, thus special treatment is required. This treatment consists in the prescription of boundary conditions. These boundary conditions numerically represent real engineering problem physics and must be carefully chosen by the modeler if the numerical solution is to bear physical meaning.

For fluid flow problems, physical boundary conditions can be walls, inlet and outlet conditions. Each

\(^1\)Direct numerical simulations in which the Navier-Stokes equations are computed directly, solving all the turbulent time and space scales

\(^2\)A low-pass filter is applied to the Navier-Stokes equations such that only the larger turbulence scales are resolved leaving the smallest ones to be modeled
of these conditions is represented by a set of numerical boundary conditions for each of the variables that are being computed. There are two fundamental types of boundary conditions, the Dirichlet and Von Neumann conditions. The Dirichlet or fixed value boundary condition prescribes the variable value at the boundary, whereas the Von Neumann boundary condition prescribes the gradient (i.e. rate of change) of a variable in the direction normal to the domain boundary.

The computational domain, discussed in Section 2.3, is bounded by: the device’s internal walls; at the bottom by the powder cavity inlet; at the sides by the body side inlets; and finally at the top by the mouthpiece outlet.

### 2.3.1 Inlet boundary conditions

At the inlets, total pressure $p_0$, is set to the fixed value of atmospheric pressure $p_{atm} = 101,325$ kPa. Assuming first-hand that the TwinCaps® DPI internal flow is incompressible, the inlet total pressure $p_0$, and the static pressure $p_s$, are linked to the inlet velocity $U$ via Bernoulli’s Equation 2.9 and the latter can be readily derived.

$$ p_0 = p_s + \frac{1}{2} \rho U^2 \quad (2.9) $$

The inlet turbulent properties should be defined from experimental data of the case or of available similar cases. In the absence of such data, uniform initial values for the turbulent kinetic energy $k$ and turbulent viscosity $\nu_t$ can be calculated via sensible engineering assumptions (Equations 2.10 and 2.11 respectively).

In this case the value $k$ is specified through a turbulence intensity level (TIL), which is defined as the ratio between the root mean square, $rms$, of the velocity fluctuation $u'$ and the mean velocity $U$:

$$ k_\infty = \frac{3}{2} (U_{ref} I)^2 \quad (2.10) $$

Where $U_{ref} = Q_{out}/A_{out}$ is the reference velocity of the flow, deducted from the the experimental outflow, $Q_{out}$, and outlet cross sectional area $A_{outlet}$. And $I$ is the TIL entering the domain that is assumed to be equal to 1%, a value typical of medium-turbulence cases. The turbulent viscosity can be obtained from the following assumption:

$$ \frac{1}{Re} \times \frac{\nu_t}{\nu_\infty} = 10^{-9} \quad (2.11) $$

And the value for the turbulent specific dissipation $\omega$ is directly deducted from its definition:

$$ \omega_\infty = \frac{k_\infty}{\nu_\infty} \quad (2.12) $$
2.3.2 Outlet boundary conditions

At the mouthpiece outlet a constant pressure drop $\Delta p = 4 \text{kPa}$, representative of the TwinCaps® optimal operating point, needs to be applied in order to simulate the device operating flow at this point. For this purpose the outlet static pressure is fixed to a value $4 \text{kPa}$ under the atmospheric pressure. A Von Neumann condition is applied to the velocity and turbulence quantities $k$ and $\omega$ fields, hence assuming that their profiles do not change across the boundary ($\delta/\delta y = 0$).

2.3.3 Wall boundary conditions

As a fluid flows past a wall, neighboring fluid particles tend to stick to the surface slowing down the surrounding fluid. This way a slim layer of fluid, generally referred to as boundary layer, is formed close to the surface, inside which velocity varies from zero ($U = 0$) at the wall ($y = 0$) to the free stream value ($U = 0.99 U_\infty$) at its upper limit ($y = \delta$). Additionally, turbulent boundary layers exhibit two distinct regions, one inner region, where the flow’s behavior is governed by the wall and one outer region, where its behavior is determined by free stream properties. Moreover, the inner region can also be split into three sub-layers of distinct behaviors (Figure 2.4):

(i) Linear sub-layer ($0 < y^+ < 5$)

(ii) Buffer layer ($5 < y^+ < 30$)

(iii) Log layer ($30 < y^+ < 1000$)

Where $u_\tau = \sqrt{\tau_w/\rho}$ is the friction velocity and $y^+ = u_\tau y/\nu$ is the dimensionless distance to the wall surface.

![Figure 2.4: The different sub-layers within the turbulent boundary layer, adapted from Nichols (2001)](image)

In the linear sub-layer, viscous stresses prevail and the behavior of dimensionless parameters is linear: $U^+ = \frac{U}{u_\tau} = y^+$. Whereas in the log-law zone turbulent stresses are dominant and the velocity profile is well fitted to a logarithmic function:

$$U^+ = \frac{1}{\kappa} \ln(y^+) + B \quad (2.13)$$
Where $\kappa = 0.41$ is the von Kármán constant and $B \approx 5.0$.

To model the large gradients of velocity and quantities characterising turbulence in the turbulent boundary layer, one of three near-wall treatments is adopted:

- **Wall Functions** The log-law function (Equation 2.13) is used to find the shear stress value at the wall surface $\tau_w$. This is the preferred approach for simple flows in plain geometries. It allows for a coarse mesh near the wall, since the first node needs only to be at $y^+ > 30$ (Figure 2.5b). The wall function boundary conditions facilitate iterative convergence, but they do so at the cost of model accuracy (Eça et al., 2015).

- **No Wall Functions** In this approach the flow governing equations are resolved down to the viscous sub-layer and the shear stress at the wall is calculated by $\tau_w = \mu \frac{\Delta U}{\Delta y}$. The fundamental advantages of this approach are its capability of capturing flow separation and its accuracy. They come however at the cost of a necessarily finer mesh (which may relatively increase computational cost), in which typically the first mesh node needs to be located so that $y^+ < 1$ (Figure 2.5a).

- **Automatic Wall Treatment** The idea behind it is that the model shifts gradually between a viscous sublayer formulation (the no wall function approach) and wall functions, based on the grid density (Menter and Esch, 2001). This is accomplished by using a blending function of $U^+$, as it provides analytical solutions for the viscous sublayer and the logarithmic region, depending on $y^+$.

![Figure 2.5: Wall treatment approaches, adapted from Nebenführ (2010)](image)

In low Reynolds number industrial applications where fluid viscous forces play an important role (see Equation 1.1) the wall function approach may not be adequate.

Wall functions do not determine the influence of the viscous sublayer and this fact can have a significant impact on the final solution. In internal flows, it is often desirable to have a robust and accurate viscous sublayer formulation (Menter and Esch, 2001) for solving the governing equations all the way to the bounding wall surface.

With this in mind, and considering that the present work involves internal flow, the no wall function approach was chosen as the near-wall treatment. At the internal walls of the device, by virtue of the no-slip and impermeability conditions, the two tangential components and the normal component of the mean velocity respectively (Eça et al., 2015), are equal to the wall velocity which is zero. For high Reynolds number flows, the standard prescribed mean pressure condition is zero derivative in the direction normal to the wall (Eça et al., 2015). From the no-slip condition for flow mean velocity follows.
that the value of the turbulent kinetic energy \( k \) at the wall is zero. Moreover, the definition of \( \omega \) (Equation 2.8) states that its value tends asymptotically to infinity. To model this infinitely large value, Menter (1993) suggested that the value of \( \omega \) at the wall should be ten times larger than the value at the first cell off the wall \( \omega_{\text{1st cell}} \),

\[
\omega_{\text{wall}} = 10 \times \omega_{\text{1st cell}} = \frac{60\nu}{C'_{\mu} (\Delta y)^2} \tag{2.14}
\]

Figure 2.6 summarizes the boundary conditions of the momentum and turbulent quantities equations, prescribed to the volume bounding surfaces.

2.4 Initial conditions

In non-linear problems, where system variables are co-dependent (e.g. flow velocity and pressure), the adopted numerical solution methods are often iterative. These methods begin by estimating initial values for each variable field and continue performing successive iterative updates to them until a converged solution is obtained. The initial guess may influence convergence rate and, in problems with multiple possible solutions, the converged solution itself. Therefore, it is necessary to set initially a valid solution of the flow equations. The initial values of the variables should try to mimic operating conditions of the TwinCaps® and be as close to the final solution values as possible (potentially reducing the number of iterations needed). Since there is no available data on the set of initial values for each domain point, an uniform distribution is prescribed to each field. The pressure field is initially assumed to be uniform and at an atmospheric pressure level. Because the domain geometry is complex, the flow velocity direction is unpredictable, thus setting an uniform velocity field of reference magnitude and direction (at the outlet) could lead to a non-physical solution or even divergence. To avoid this issue, every initial velocity component value was set to zero. Finally the turbulent properties were initialized with a value equal to their inlet boundary conditions (see section 2.5).
2.5 Space discretization

The next step in numerically obtaining an approximate solution to the problem is to use a discretization method which approximates the PDE by a system of algebraic equations that the computer is able to solve. In this process, the domain is partitioned into several contiguous control volumes (CVs) (each one corresponding to a cell) by a numerical grid, with the set of conservation equations being applied at the center of each CV. Conversion from a PDE to a algebraic equation requires approximations to the integrals, which in turn require the values of variables at locations other than the CV centers (Ferziger and Peric, 2002). A differencing scheme is then needed to compute fluid property values at the control volume faces. A comprehensive list of these schemes can be found in most CFD text books (Versteeg and Malalasekera, 2005; Patankar, 1980), however in this text only the upwind differencing scheme (UDS) and the hybrid scheme will be addressed.

2.5.1 Discretization schemes properties

The accuracy of the numerical approximate solution depends on the chosen differencing scheme. The properties that fundamentally describe each differencing scheme and determine their suitability are:

- **Conservativeness** A differencing method is conservative if conservation of a generic fluid property \( \phi \) for the entire solution domain is guaranteed. In other words, the flux of \( \phi \) leaving a cell’s face must be equal to the one entering the adjacent control volume through the corresponding face. If the strong conservation form of equations and a finite volume method are used, this is guaranteed for each individual control volume and for the solution domain as a whole. Dizer que como estamos a utilizar o FV que à partida a conservativeness

- **Boundedness** If a bounded differencing method is used on a steady state conduction problem with no heat sources and featuring temperatures of 298K and 373K at the boundaries, all interior values of \( T \) must range from 298K to 373K (Versteeg and Malalasekera, 2005). Also, numerical solutions should lie within proper bounds. Physically non-negative quantities (like density, kinetic energy of turbulence) must always be positive; other quantities, such as concentration, must lie between 0% and 100% (Ferziger and Peric, 2002). All higher-order schemes can produce unbounded solutions. Should the boundedness requirement be unmet, it is possible for the solution to not converge at all, or, if it does, to lack physical meaning.

- **Transportiveness** of a fluid flow can be illustrated (in Figure 2.7a) by considering how point P’s properties are influenced by two constant sources of a generic fluid property \( \phi \) at nearby points W and E. In the case of a stationary fluid, which is a pure diffusion problem \( (Pe = 0) \), the iso-surfaces of constant \( \phi \) are concentric circles centered in W and E since the diffusion spreads \( \phi \) equally in every direction (Versteeg and Malalasekera, 2005). \( Pe \) is a non-dimensional number that is measure of the relative strengths of convection and diffusion (Versteeg and Malalasekera, 2005):
\[ Pe = \frac{\rho u}{\Gamma / \delta x} = \frac{\text{convection}}{\text{diffusion}} \]  
\[ (2.15) \]

Where \( \delta x \) is the cell’s characteristic length. As flow speed increases (\( |Pe| \neq 0 \)), so does influencing of point P’s properties by its upstream counterpart W (Figure 2.7b). In the extreme case where \( Pe \rightarrow \infty \) point P’s properties are exclusively influenced by W’s.

![Figure 2.7](image)

**Figure 2.7:** (a) Pure Diffusion (\( Pe \rightarrow 0 \)): Point P’s properties are equally influenced by its neighboring counterparts (W and E) (b) Convection-Diffusion (\( |Pe| \neq 0 \)): Point P’s properties are more heavily influenced by W (upstream) than E (downstream). Adapted from Versteeg and Malalasekera (2005)

### 2.5.2 Upwind scheme

The major drawback of central differencing scheme (CDS), a method mainly used in diffusion-only problems, is its inability to identify flow direction (Versteeg and Malalasekera, 2005). CDS linearly interpolates fluid properties at the cell faces equally in every direction. In a convection dominated flow however, fluid properties of a point downstream should be increasingly influenced by its upstream neighbor as flow speed increases (Figure 2.7). Owing to this limitation, CDS is often not fitting for general-purpose flow calculations (Versteeg and Malalasekera, 2005).

Unlike CDS, the upwind differencing scheme (UDS) accounts for flow direction when determining the value at a cell face. Additionally, it is formulated so that the coefficients of the discretized PDE are always positive, making the upwind scheme unconditionally bounded.

However, these advantages over CDS (Table 2.2) take a toll on the method’s accuracy. Because it is based on the backward differencing formula (Equation 2.16), the method is only first-order accurate on the basis of the Taylor series truncation error (Versteeg and Malalasekera, 2005).

\[ \phi_w = \begin{cases} 
\phi_W & \text{if } (v.n_e) > 0 \\
\phi_P & \text{if } (v.n_e) < 0 
\end{cases} \]  
\[ (2.16) \]

Due to the leading term of the truncation error resembling a diffusive flux, the resulting numerical error is often designated as numerical diffusion. UDS produces numerical diffusion both in the streamwise direction and the direction normal to it, with its effect being amplified when the flow is oblique to the grid (Ferziger and Peric, 2002).

Numerical diffusion blurs the distributions of transported properties (e.g. dampens concentration gradients), with peaks or rapid variations in the variables being smeared out. Additionally, because the rate of error reduction is proportional to \( \Delta x \), very fine grids are needed to obtain accurate solutions (Ferziger and Peric, 2002).
Table 2.2: Properties of the Upwind and Central differences schemes

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Conservativeness</th>
<th>Boundedness</th>
<th>Transportiveness</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDS</td>
<td>✓</td>
<td>✓</td>
<td>✗</td>
<td>2nd Order</td>
</tr>
<tr>
<td>UDS</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>1st Order</td>
</tr>
</tbody>
</table>

Despite these drawbacks, the upwind differencing scheme has been widely applied in early CFD calculations. Its simplicity, stability and boundedness, make it a particularly useful scheme to start a simulation, specially for non-orthogonal unstructured meshes. Nonetheless, the scheme is only first-order accurate and it induces numerical diffusion, it is therefore unsuitable for computing final results. For this purpose, a higher order differencing scheme is needed to finish the simulation with greater level of accuracy.

2.5.3 Hybrid upwind scheme

Recognizing strengths and weaknesses of both the CDS and UDS schemes, Spalding (1972) conceived the hybrid differencing scheme, based on a combination of the two schemes. The second-order accurate CDS, is employed at smaller Peclet numbers whereas the upwind scheme, which is first-order accurate, is employed for larger Peclet numbers (Versteeg and Malalasekera, 2005).

The scheme is fully conservative like both the original schemes, and unconditionally bounded. It also inherits the transportiveness property of upwind formulation for values of the cell Peclet number which verify the condition \( Pe > 2 \). On the other hand, it is only formerly first-order accurate and for multidimensional flows it still exhibits the numerical diffusion. However the effect of numerical diffusion is not as severe as in the original upwind scheme. This is due to the deferred correction method used,

\[
A_l \phi^n = b + (A_l \phi^{n-1} - A_h \phi^{n-1})
\]

where \( A_l \) and \( A_h \) are the systems of algebraic equations resulting from the low-order (in this case UDS) and high-order (in this case CDS) schemes respectively and \( A_l \phi = b \) is the system to be solved at the \( n^{th} \) iteration.

2.5.4 Discretized set of equations

Regardless of the discretization method used, the final result of the discretization process is a set of algebraic equations with the following form,

\[
A_P \phi^n_P + \sum_i A_i \phi^n_i = Q_P
\]

where \( Q^3 \) incorporates all terms that are \( \phi^n \) independent, while \( A_P \) is the coefficient matrix at a generic point \( P \) (which is discretization method dependent) and \( A_i \) refers to a neighboring coefficient matrix that captures the effect of the neighboring points on the variables at point \( P \). Depending on the

\(^{3}\text{Here the upper case roman letter refers to a matrix}\)
chosen discretization method, the matrix comprising the set of equations (represented in Equation 2.18) may be diagonally dominant which is, as already discussed, a crucial requisite for solution stability and boundedness.

### 2.6 Computational domain

The next step in modeling process is to devise the computational domain from the device’s geometry. The earliest draft of the domain was obtained from a CAD model made available by Hovione 4, by extracting the internal wall surfaces (Figure 2.8) of the device using the CAD software SolidWorks v2015. Next, to achieve a manifold surface 5 enclosing the domain, open surfaces such as: the mouthpiece outlet; bottom inlet and side channels inlets were closed to achieve a closed volume.

This volume, illustrated in Figure 2.13, has values of maximum size $\Delta x_i$ in each Cartesian coordinate direction $x$, $y$ and $z$ represented in Table 2.3. Here the $y$ axis is aligned with the device’s aerodynamic channel centerline, whereas the $x$ plane is perpendicular to the inhaler’s body side inlets and $z$ is perpendicular to both. By not extending the volume outwards (i.e. including air volume not enclosed by the device), at the inlets and at the outlet, it is inherently being assumed that the prescribed conditions not only apply to the respective surfaces but also continue to hold in their vicinity.

Figure 2.9 shows a top view ($Y$ plane) of the volume, where its symmetry about both the $X$ and $Z$ planes is evident. Recognizing this, it is possible to compute the solution in only one quarter of the domain thus reducing the computational cost. The final complete solution would then be obtained by first replicating the flow field about one plane of symmetry and later about the other.

---

4 corresponding to the component geometry in current production
5 surface which encloses a single volume
Table 2.3: Overall TwinCaps® dimensions

<table>
<thead>
<tr>
<th>Δx</th>
<th>Δy</th>
<th>Δz</th>
</tr>
</thead>
<tbody>
<tr>
<td>(m)</td>
<td>(m)</td>
<td>(m)</td>
</tr>
<tr>
<td>3,2 × 10⁻²</td>
<td>5,9 × 10⁻²</td>
<td>7,5 × 10⁻³</td>
</tr>
</tbody>
</table>

However, being this work's ultimate goal computing an unsteady simulation of the flow, the whole domain is going to be computed in order to capture any possible non-symmetric flow patterns of interest.

![Figure 2.9: The computational domain is symmetric about plane Z (horizontal axis) and plane X (vertical axis). The highlighted top left quarter of the domain represents another possible configuration of the domain in which to compute the solution. Should this configuration be used, the complete final solution would be obtained by copying the solution about the two planes of symmetry.](image)

Lastly, some surface geometry simplifications were made to ease the task of generating a grid over specific locations. The oval shaped edge of the original mouthpiece outlet is booled and was made sharp to avoid distorted elements in this region (Figure 2.10). The protruding rim at the top of powder compartment, depicted in Figure 2.11, was trimmed also to avoid distorted elements in this region. Finally, the two bottom protruding surfaces in Figure 2.12 were cut to shuttle inlet height and all the remaining open surfaces (with edges highlighted in blue) were closed. The resulting computational domain is depicted in Figure 2.13, where the surfaces to which the boundary conditions are prescribed: the mouthpiece outlet, the body side inlets and the shuttle (or bottom) inlet as well as the two sub-volumes: powder compartment and mouthpiece channel are identified.

![Figure 2.10: Simplification of the Mouthpiece outlet: (a) before; (b) after](image)

![Figure 2.11: Simplification of the upper powder compartment surface: (a) before; (b) after](image)
2.7 Meshing in OpenFOAM

This section presents the software packages used to pursue this thesis goals set in section 1.6. First, geometry preprocessing was carried out with the SolidWorks v2015 CAD program. Secondly, all CFD simulations were run using OpenFOAM v2.4.0 distributed under the general public licence (GPL) by the OpenFOAM Foundation. And finally, post-processing tasks were mainly undertaken with Paraview, seldom assisted by MATLAB® and Tecplot.

2.7.1 OpenFOAM

OpenFOAM® is an open-source software package for CFD where FOAM stands for Field Operation And Manipulation. It is a software developed by CFD Direct on behalf of its owner the OpenFOAM Foundation. Jasak (2013) describes OpenFOAM® as an object-oriented library for computational continuum mechanics designed with researchers in mind, allowing them to explore new physical models, to validate these models through experimentation and assess their predictive power of real industrial problems in a seamless cost-effective manner. The FV implemented physical models are based on the idea of mimicking the PDE analytical form in software (Jasak, 2013). Auxiliary tools, from pre-processing, mesh generation (e.g. SnappyHexMesh) and manipulation, data acquisition to post-processing (e.g. Paraview) are built into the system. Users with programming skills can improve existent solvers and utilities or even choose to create new ones that better fit their needs, which constitutes the central advantage of OpenFOAM® over other software packages.

2.7.2 Solvers

OpenFOAM® provides a wide range of solvers suitable for applications in the electromagnetics, chemical reactions, turbulent flows or even financial fields of study. In this section, only the solvers that were used in this project will be discussed.

- **simpleFoam** is a steady-state solver of incompressible turbulent flows. The solving procedure is iterative and it follows the SIMPLE algorithm, where SIMPLE stands for Semi-Implicit Method for Pressure Linked Equations.
• *pimpleFoam* is a transient solver of incompressible flows. The solving procedure follows the PIMPLE algorithm, which is a merge result between the semi-implicit method for pressure linked equations (SIMPLE) and pressure implicit with splitting of operator (PISO) algorithms. This specific transient solver provides the possibility of, on run-time, adjusting the time step to meet a predefined Courant number limit.

### 2.7.3 Meshing

Unlike other CFD codes such as *ANSYS Fluent* or *ANSYS CFX*, OpenFOAM® does not incorporate a fully orthogonal all purpose structured mesh generator. Instead it allows the user to choose from a variety of mesh generation processes, some including native mesh generation tools like *blockMesh*, *snappyHexMesh*, and *foamyHexMesh*, and others including third-party opensource software such as *cfMesh* or *SALOME*. This work in particular, followed a mesh generation procedure including the use of *blockMesh* and *snappyHexMesh*.

• *blockMesh* is an OpenFOAM® native mesh generation utility which is able to create multi-block structured meshes. This tool decomposes the domain geometry into one or more three dimensional graded hexahedral blocks. For simple geometries, *blockMesh* can produce fully orthogonal meshes. However it is information intensive (e.g. the user needs to provide the coordinates for the vertices of every block), thus making the task of meshing a complex geometry troublesome and ultimately unpractical in the industrial setting.

• *snappyHexMesh* automatically generates three dimensional hex-dominated unstructured meshes from triangulated surface geometries, in stereolithography (STL) format. The mesh is tailored to the specified surfaces by iteratively refining a starting background mesh (castled mesh phase, Figure 2.13: The complete TwinCaps® computational domain)
2.14c) and morphing the resulting mesh to the surface (snapping phase). The layer addition phase moves the mesh away from the wall and inserts a prescribed number of cell layers. Each phase is an iterative process that stops only when geometric tolerances and predefined quality parameters (e.g. maximum non-orthogonality < 65°) are met.

For this work three unstructured grids, of increasing mesh refinement at the wall, were generated. The level of mesh refinement for each grid was regulated by a snappyHexMesh parameter which defines the overall first cell height relative to the wall. It was assumed that the first cell center height is equal to half the cell height $\Delta y_1 = 2y_1$. Recalling its definition $y^+_1 = u_\tau y_1/\nu$ and the expression for the friction velocity $u_\tau$ from section 2.4

$$y^+_1 = \frac{u_\tau y_1}{\nu} = \frac{y}{\nu} \sqrt{\frac{\tau_\omega}{\rho}}$$ \hspace{1cm} (2.19)

Where $\tau_\omega$ is the shear stress at the wall, which is defined as

$$\tau_\omega = \frac{1}{2} \rho C_f U^2$$ \hspace{1cm} (2.20)

Substituting the expression for $\tau_\omega$ (Equation 2.19) in Equation 2.20 yields
\[
y^+ = \frac{y}{\nu} \sqrt{\frac{\frac{1}{2} \rho C_f U^2}{D}} = \left( \frac{\frac{UD}{\nu}}{Re_D} \right) \frac{y}{D} \sqrt{\frac{C_f}{2}}
\]  

(2.21)

Recognizing the under-braced term as the flow's Reynolds number, \( y \) can be rewritten as function of \( y^+ \), Reynolds number \( Re_D \), a flow characteristic length \( D \) and the skin friction coefficient \( C_f \).

\[
y = y^+ \left( \frac{D}{Re_D} \right) \sqrt{\frac{C_f}{2}}
\]  

(2.22)

The flow's Reynolds number was computed assuming as reference velocity the device outlet velocity, \( U_{out} \), derived from TwinCaps®'s experimentally measured flow rate at a 4kPa pressure drop, and the mouthpiece median diameter \( D_m = 8.38 \times 10^{-3} \text{m} \) as reference dimension.

\[
U_{out} = \frac{Q_{out}}{A_{out}} = \frac{6.3 \times 10^{-4}}{5.52 \times 10^{-5}} \frac{\text{m}^3 \text{s}^{-1}}{\text{m}^2} = 11.42 \text{m} \text{s}^{-1}
\]

(2.23)

\[
Re_D = \frac{U_{out} D_m}{\nu} = \frac{11.42 \times 8.38 \times 10^{-3}}{1.59 \times 10^{-5}} \frac{\text{m} \text{s}^{-1} \times \text{m}}{\text{m}^2 \text{s}^{-1}} = 6024.22
\]

(2.24)

With the Reynolds number calculated, the skin friction \( C_f(Re_D) \) could also be assessed

\[
C_f = 0.575 Re_D^{1/5} = 0.01
\]

(2.25)

Substituting these values into Equation 2.21, the height of the first cell center to the wall \( y \) can be directly computed for each chosen \( y^+ \). Table 2.4 shows the values of \( y \) as well as the three main mesh quality parameters: maximum aspect ratio; maximum skewness; and maximum non-orthogonality (see Figure 2.16) for each generated grid.

<table>
<thead>
<tr>
<th>Table 2.4: Quality parameters of the generated meshes</th>
</tr>
</thead>
<tbody>
<tr>
<td>( y^+ )</td>
</tr>
<tr>
<td><strong>Ideal mesh</strong></td>
</tr>
<tr>
<td><strong>Mesh 1</strong></td>
</tr>
<tr>
<td><strong>Mesh 2</strong></td>
</tr>
<tr>
<td><strong>Mesh 3</strong></td>
</tr>
</tbody>
</table>

Although the meshes have fundamentally different levels of refinement near the wall, they exhibit similar quality parameters. This is because the automatic mesh generation process embed in snap-hexMesh is iterative, closing each loop only after a set of predefined quality parameters is met. In the present case, one of the most important quality controlling parameters is the global maximum non-orthogonality value fixed at 65°. This non-orthogonality upper limit value is the recommended standard, and it is regarded as a compromise between mesh quality and the swiftness of generation. Additionally, OpenFOAM® solvers offer the option of adding extra pressure correction loops to correct non-orthogonality effects on gradients. The other two quality parameters, the maximum aspect ratio and the
maximum skewness, are driven by the latter and consequently vary from one mesh to the other.

![Diagram showing mesh quality parameters](image)

**Figure 2.16:** Main mesh quality parameters: (a) The aspect ratio is a measure of cell elongation $AR = \Delta_y / \Delta_x$; (b) Skewness exists when the line connecting two adjacent cell centers is not concurrent with the face center; (c) Non-orthogonality results from the misalignment between face normal vectors and the line connecting neighbor cell centers (which is included in the calculation of the gradient across the face), adapted from Rhoads (2014)

The increase of mesh refinement level at the wall naturally lead to higher aspect ratio ($AR$) values, as the cell’s height was reduced. These relatively high $AR$ values, if the largest cell size is not aligned with the main flow direction could lead to a smearing of the gradients in that direction. On the other hand, increasing refinement level at the wall reduced cell skewness. Because the cell size at wall dropped, the grid had a better chance at conforming to the complex geometry without distorting its cells as much.

Being an automated unstructured mesh generation engine, `snappyHexMesh` is still information intensive, requiring the definition of a considerable amount of parameters for each meshing phase. The main challenge lies on grasping parameter codependency, i.e. understanding how one alone influences final mesh quality and how its influence is impacted by the remaining parameters when they vary. While `snappyHexMesh` may be relatively fast at producing general purpose meshes, especially in intricate geometries, guaranteeing high quality grids with a low cell count may prove to be both challenging and time consuming.
Chapter 3

Results & discussion

Complementing the existing and ongoing CFD-aided research and development work on the DPI (Coates et al., 2004; Milenkovic et al., 2013) field, this thesis addresses the TwinCaps® flow field problem using an open source CFD toolbox, OpenFOAM®. In section 3.1 and 3.2 the steady-state and transient TwinCaps® flow fields are characterized respectively. Section 3.1 also includes a mesh dependence study and a validation exercise of the proposed model against experimental data. Finally, in section 3.2, a comparison between a transient simulation, with massless particle tracking as a post processing task, and high speed filming of the device operation with a pharmaceutical powder is made.

3.1 Steady flow

One of this thesis’s goals is to evaluate the numerical uncertainty of the computed flow field solution. For this purpose, several cases involving the steady-state internal flow of the TwinCaps® inhaler at different pressure drops, using various grids (see Table 3.1) were studied.

In all these cases (ranging from 1.1 to 5.3) the same methodology was applied, one that comprises the RANS model in conjunction with $k$-$\omega$ SST turbulence model and follows the no wall function approach (discussed in section 2.4). In this methodology it was assumed that, regardless of the pressure drop value, the internal air flow lied on the incompressible regime i.e. the effects of air compressibility on the flow field were considered negligible.

| Mesh 1 | $y^+$ = 0.75 | (1.1) X | (2.1) X | (3.1) ✓ | (4.1) ✓ | (5.1) ✓ |
| Mesh 2 | $y^+$ = 1    | (1.2) X | (2.2) X | (3.2) ✓ | (4.2) ✓ | (5.2) ✓ |
| Mesh 3 | $y^+$ = 1.5  | (1.3) ✓ | (2.3) ✓ | (3.3) ✓ | (4.3) ✓ | (5.3) ✓ |
3.1.1 Iterative convergence

A good practice when computing CFD simulations is to start the iterative process with a discretization method that promotes solution stability and finish with one which provides a higher order of accuracy. With that in mind, each simulation began with the upwind discretization method and finished with the hybrid or linear upwind. It is important to guarantee that the solution using the upwind scheme is converged before switching spatial discretization methods mid-run. Otherwise the newly appointed scheme may not be stable enough and consequently may lead to non-realistic results or ultimately to solution divergence.

According to Ferziger and Peric (2002), solution convergence is achieved when for all flow quantities the following condition, $\phi^{n+1} = \phi^n = \phi$, is true. In other words, a solution is deemed converged when the value of every variable does not change from one iteration to the other. In this scenario the equation residuals, i.e. the difference between solutions of consecutive iterations, are zero. This scenario is not attainable because it would require a high number of iterations, a high quality mesh (both are time consuming) and it would imply zero computer round-off errors (which is never true). Instead a residual threshold value or tolerance (usually $10^{-4}$ but its value is problem-dependent) is defined, below which, $\phi^{n+1} \approx \phi^n$, is considered sufficiently accurate. Figure 3.1 shows the residuals for case 4.3 (see Table 3.1) during the first 3000 iterations.

![Figure 3.1: Equation residuals of case 4.3 run using the upwind discretization scheme. In the legend $U_x$, $U_y$ and $U_z$ are the Cartesian components of the velocity vector, $k$ is $k$, omega is $\omega$, $p$ is pressure and continuity stands for the continuity error](image)

It can be seen that all equation residuals monotonically drop below the $10^{-3}$ threshold value. The lowest residual value belongs to the pressure equation, which is already below $10^{-5}$, due to the fact that the solution is driven by the pressure boundary conditions (discussed in chapter 2).

The equation residuals dropping below a predefined threshold value is a necessary but not sufficient condition for solution convergence. Thus extra investigations must be carried out in order to check the validity of this assumption. In this work, one investigation consisted in defining surfaces, at specific locations of the domain (see Figure 3.2), to probe the flow rates across them and to check if their value
stabilized.

**Figure 3.2:** Control surfaces for flow rate probing. Here $Q_{PCI}$ is the flow rate across the powder compartment inlet, $Q_{FL}$, $Q_{FR}$, $Q_{BR}$ and $Q_{BL}$ are the flow rates at each body side inlet where $F$ designates the two frontal side inlets, $L$ and $R$ the left and right sides respectively and $B$ stands for the backside of the device.

Figures 3.3a, 3.3c and 3.3e show the progression of the flow rate value at the various locations defined in Figure 3.2: outlet; side inlets and powder compartment inlet respectively, with the successive simulation iterations. All of the these quantities reach a plateau before the last iteration which indicates that, in this case in particular 4.3, solution convergence has been achieved.

In an attempt to achieve higher numerical precision of the solution, at the 3000th iteration, the discretization scheme was switched from upwind to linear upwind.

By analyzing Figure 3.5 the effect of changing discretization schemes can be noticed. Figure 3.5a shows the $U_x(y)$ profile at one of the body side inlet channels (which lead into the mouthpiece channel) where the $x$ axis is aligned with channel $y$ is perpendicular to it and $z$ points in the direction of the reader. By comparing this profile, which originates from a numerical solution using UDS, with its LUDS counterpart (Figure 3.5b) it can be seen that the latter exhibits a more pronounced $U_x$ peak whereas the first is more uniform. This difference both in profile shape and peak velocity magnitude is due to the greater predominance of numerical diffusion in the upwind discretization scheme.

The non-uniform profiles of the four side inlet jets in the linear upwind solution (Figure 3.5b) contributed to, as shown in Figure 3.6, a relatively more asymmetric flow field than for upwind the solution.

Additionally, by re-plotting the flow rates at the previously specified locations (Figures 3.3b, 3.3d and 3.3f) it can be seen that these values now fluctuate about a mean value as opposed to the more stable behavior of the upwind solution. This new found instability may be a consequence of the diminished numerical diffusion effect, i.e. fluctuations of the velocity field (for instance in the four jet mixing zone) are now less dampened. In this solution the body side inlet jets do not balance each other out, i.e. the flow rate across each inlet is different, rendering the flow field non-symmetric.

In a problem whose geometry and boundary conditions are symmetric, the solution should also be symmetric. However, to obtain a completely symmetric solution about the $X$ and $Z$ planes, the mesh, the discretization scheme and the discretization error would also need to be symmetric. Since the unstructured meshes are generated automatically by `snappyHexMesh`’s algorithm, satisfying these conditions is impossible.

In order to maintain solution flow field symmetry its iterative convergence has to be thoroughly con-
Figure 3.3: Probed volumetric flow rates, of the upwind and linear upwind solutions respectively, at: (a) and (b) the outlet; (c) and (d) the body side inlets; (e) and (f) the powder compartment inlet.
Figure 3.4: Equation residuals of case 4.3 run using the linear upwind discretization scheme.

Figure 3.5: Body side inlet flow velocity profile when using: (a) upwind; (b) linear upwind as spatial discretization method.

Figure 3.6: Asymmetry of the predicted flow field in the case 4.3.
trolled. A way to control iterative convergence is through solution relaxation.

### 3.1.2 Solution relaxation

When solving a non-linear problem involving fluid dynamics, a sequential solution method is often used as opposed to a simultaneous (or coupled) one where every equation is solved for simultaneously. In sequential equation solving, each equation is treated as if it only has a single unknown, temporarily prescribing the latest available values to the other unknowns (Ferziger and Peric, 2002). Next the "momentarily linear" equations (Equation 2.18) are solved one at a time in inner iterations (e.g. first solving for the velocity $U$ components $U_x$, $U_y$, $U_z$ then for pressure $p$ etc.), and then repeating the cycle (outer iterations) until the entire set of equations is satisfied.

In early calculations, allowing a generic fluid property, $\phi$, to vary by the amount predicted in Equation 2.18 may cause instability and consequently hinder or even prevent convergence. Solution relaxation is a technique applied to these equations, which limits the change in each variable between outer iterations.

Solution relaxation is considered to be implicit if its effect is incorporated into the equation at the beginning of an inner iteration cycle. The algebraic equation for a generic fluid property $\phi$, at a point $P$ and $n$th iteration is written as follows:

$$
\phi^n_P = \phi^{n-1}_P + \alpha_\phi (\phi^{new}_P - \phi^{n-1}_P)
$$  \hspace{1cm} (3.1)

where $\phi^{new}$ is the result of 2.18 and the under-relaxation factor $\alpha_\phi$ satisfies the condition $0 < \alpha_\phi < 1$. Replacing $\phi^{new}$ in Equation 3.1 by its definition in Equation 2.18, results in Patankar's implicit under-relaxation method (Patankar, 1980).

$$
\frac{A_P}{\alpha_\phi} \phi^n_P + \sum_l A_l \phi^n_l = Q_P + \frac{1}{\alpha_\phi} A_P \phi^{n-1}_P
$$  \hspace{1cm} (3.2)

Since $\alpha_\phi < 1$, $A'_P > A_P$ boosting the diagonal dominance of the matrix of algebraic equations, consequently increasing stability of the solution.

Solution relaxation can also be of explicit nature, i.e. it can be applied after the solution of an outer iteration is obtained,

$$
\phi^{new,used}_P = \phi^{old}_P + \alpha_\phi (\phi^{new,predicted}_P - \phi^{old}_P)
$$  \hspace{1cm} (3.3)

where $\phi^{new,predicted}$ is the variable value resulting from Equation 2.18 and $\phi^{new,used}_P$ and $\phi^{old}_P$ are the variable values after relaxation at the current and previous iterations respectively. Setting the relaxation factor to $\alpha_\phi > 1$ results in over-relaxation which will accelerate convergence but can also induce numerical instability. On the other hand, a value of $\alpha_\phi < 1$ leads to under-relaxation that instead slows down convergence (solution may require a relatively greater number of iterations) but increases stability. Finally a relaxation factor equal to $\alpha_\phi = 1$ corresponds to using no relaxation.

In OpenFOAM®, only pressure can be explicitly under-relaxed in the SIMPLE algorithm while other
variables (e.g. \( U, k, \omega \)) are implicitly under-relaxed. Problems where fluid properties, such as the turbulent viscosity, depend on the solution and are iteratively updated, applying explicit under-relaxation to these variables may be crucial to achieving convergence (Moukalled et al., 2015).

Since these particular cases (see Table 3.1) required explicit under-relaxation that was not readily available on OpenFOAM®, a few changes were made to the solver simpleFoam and to the \( k-\omega \) SST model so as to include this type of relaxation for the velocity \( U \), turbulent kinetic energy \( k \) and specific turbulent dissipation ratio \( \omega \) variables.

With the newly added explicit under-relaxation factors given in Table 3.2, the simulation was restarted from the 3000th iteration resulting in a nearly symmetric final solution (depicted in Figure 3.7).

**Table 3.2: The new and former relaxation factors configuration**

<table>
<thead>
<tr>
<th>( \alpha_{\text{imp}} )</th>
<th>( \alpha_{\text{exp}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( U )</td>
<td>( p )</td>
</tr>
<tr>
<td>Former relaxation factors</td>
<td>0.1</td>
</tr>
<tr>
<td>New relaxation factors</td>
<td>0.1</td>
</tr>
</tbody>
</table>

In this solution the side inlets jets balance each other out and it can be seen that the two lines of zero velocity component \( U_x = 0 \), where the two pairs of jets meet (front and back), are aligned.

![Figure 3.7: Body side inlets jets mixing site flow field when using: (a) Exclusively implicit under-relaxation for the velocity and turbulent fields; (b) Implicit and explicit under-relaxation for the velocity and turbulent properties fields](image)

**3.1.3 Numerical error**

Every CFD calculation naturally incurs on a numerical error which is the combined effect of the computer round-off error, the iterative convergence error and the discretization error (Eça et al., 2010). The round-off error is inherent to each computer (e.g. floating point numbers storage precision) and of relatively low significance when compared to the other two sources of error. The non-linear nature of the algebraic equations solved in a sequential iterative process induces an iterative error which, in
simple geometries and flows, can be reduced to the level of computer precision. The discretization error is a by-product of the approximations made in the discretization (spatial and temporal) process which converts the analytical PDE into a system of algebraic equations (see section 2.2). Unlike the round-off and iterative errors, the discretization error becomes less significant as grid refinement level increases (Eça et al., 2010).

For most CFD applications, numerical error is mainly composed of the discretization and iterative errors (Equation 3.4).

\[ U_{\text{num}} = U_{\text{dis}} + U_{\text{iter}} \] (3.4)

Here \( U_{\text{num}} \), \( U_{\text{dis}} \) and \( U_{\text{iter}} \) are the numerical, discretization and iterative error uncertainties respectively. The discretization uncertainty \( U_{\text{dis}} \) can be estimated by comparing the numerical predictions of the selected quantity of interest \( Q_{\text{OUT}} \). In this comparison, each grid’s numerical prediction using the upwind discretization scheme, is plotted against their grid index \((h_i/h_1)^{1/3}\) (Figure 3.8). This index is a measure of grid refinement \( h_i \) when compared to the most refined mesh, in this case Mesh 1 (see Table 3.3).

<table>
<thead>
<tr>
<th>Number of Cells ((h_i))</th>
<th>((h_1/h_i)^{1/3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesh 1</td>
<td>10.93 \times 10^6</td>
</tr>
<tr>
<td>Mesh 2</td>
<td>4.88 \times 10^6</td>
</tr>
<tr>
<td>Mesh 3</td>
<td>1.37 \times 10^6</td>
</tr>
</tbody>
</table>

It is clear to see that there is no monotonic convergence of the \( Q_{\text{OUT}} \) prediction as grid refinement increases towards an infinitely refined grid \( h_i \rightarrow \infty \) where \((h_1/h_i)^{1/3} \rightarrow 0\). Instead \( Q_1 \) is between \( Q_2 \) and \( Q_3 \), thus preventing the extrapolation of \( Q \), via a power series, to \( Q_0 \).

\[ \text{Figure 3.8: Convergence of the outflow numerical prediction with increasing mesh refinement using the upwind scheme} \]

Had a monotonic convergence been achieved, then a estimate of the discretization error\(^1\), \( U_{\text{dis}} \), would have been \( U_{\text{dis}} = Q_0 - Q_1 \). In this situation however, since \(|Q_1 - Q_2| < |Q_2 - Q_3|\) the estimate is given by the maximum difference between outflow predictions in Equation 3.5. For the Case 4.1 using the upwind discretization scheme,

\(^1\)No safety factor is used to convert error estimates into uncertainties (Roache, 1997)
\[ U_{dis_{UDS}} = Q_2 - Q_3 = 1.01 \text{L min}^{-1} \] (3.5)

The uncertainty associated with iterative error visible in figure 3.9 is given by the standard deviation of \( Q \) from its mean value \( \overline{Q} \) over the course of the last \( N = 500 \) iterations of simulation.

\[ U_{iter} = \sqrt{\frac{(Q_i - \overline{Q})^2}{N}} \] (3.6)

\[ \overline{Q} = \frac{\sum_{i=1}^{N} Q_i}{N} \] (3.7)

Table 3.4 summarizes the uncertainty results for the test cases 4.1, 4.2 and 4.3. It can be seen that the discretization uncertainty is several orders of magnitude higher than the iterative one. Thus the numerical uncertainty, while using the upwind scheme, is \( U_{num_{UDS}} \sim U_{dis_{UDS}} = 1.01 \text{L min}^{-1} \).

<table>
<thead>
<tr>
<th>Case</th>
<th>( U_{dis} ) (L min(^{-1}))</th>
<th>( U_{iter} ) (L min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>1.01</td>
<td>1.71 \times 10^{-3}</td>
</tr>
<tr>
<td>4.2</td>
<td>-</td>
<td>2.61 \times 10^{-2}</td>
</tr>
<tr>
<td>4.3</td>
<td>-</td>
<td>5.67 \times 10^{-2}</td>
</tr>
</tbody>
</table>

The same behavior observed while running simulations of the upwind case is present in the linear upwind scheme. The same condition is valid \(|Q_1 - Q_2| < |Q_2 - Q_3|\) only know \( U_{dis_{LUDS}} = Q_2 - Q_3 = 0.89 \text{L min}^{-1} \) is lower that \( U_{dis_{UDS}} \).

![Figure 3.9: Convergence of the outflow numerical prediction with increasing mesh refinement using the linear upwind scheme](image)

Again the iterative error uncertainties for each case run with the linear upwind case, as when run with upwind, are two orders of magnitude lower than the discretization uncertainty and thus \( U_{num_{LUDS}} \sim U_{dis_{LUDS}} = 0.91 \text{L min}^{-1} \).
Table 3.5: Numerical uncertainties for the 4.1, 4.2 and 4.3 test cases ran with the linear upwind scheme

<table>
<thead>
<tr>
<th>Case</th>
<th>$U_{dis}$ (L min$^{-1}$)</th>
<th>$U_{iter}$ (L min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>0.89</td>
<td>1.75 × 10$^{-2}$</td>
</tr>
<tr>
<td>4.2</td>
<td>-</td>
<td>1.11 × 10$^{-2}$</td>
</tr>
<tr>
<td>4.3</td>
<td>-</td>
<td>1.14 × 10$^{-2}$</td>
</tr>
</tbody>
</table>

3.1.4 Experimental methodology

With the purpose of validating the numerical results with experimental data, tests were run on the TwinCaps® inhaler using the dosage unit sampling apparatus (DUSA) for DPIs. The DUSA is generally used to perform Pharmacopoeia-specified tests, which evaluate device performance parameters such as the emitted or delivered dose and their uniformity through container life. In this work however, this testing apparatus was utilized exclusively to measure the volumetric flow rate exiting a powder-less TwinCaps® device when subjected to constant pressure drops.

![Figure 3.10: Experimental tests equipment set-up, adapted from Copley Scientific (2015)](image)

An equivalent test-bench to the one represented in Figure 3.10 was set-up in a laboratory facility at Hovione (Loures, Portugal). The set-up comprises a vacuum pump, which generates the desired pressure drop, a critical flow controller, equipped with a two-way solenoid valve that controls air supply to the inhaler, and the DUSA. Additionally, the inhaler is connected to one end of the DUSA by a mouthpiece adapter which provides an air tight connection between the inhaler outlet and the sampling apparatus. The measuring procedure consists in first regulating pressure drop to constant value by varying the flow rate (with the solenoid valve) and checking the resulting pressure drop measurement at the device outlet (in actuation position, see Figure 3.10). Once the pressure drop value is set, the inhaler and mouthpiece adapter are detached from the DUSA and in their stead a flow meter is placed to finally read the volumetric flow rate. Table 3.6 shows the volumetric flow rate values per pressure drop level.

3.1.5 Inhaler resistance

A DPI's outlet flow rate is a function of the pressure drop level and the device's specific resistance. In their work, Clark and Hollingworth (1993) assuming incompressible airflow within a device, utilized the following relation,
Table 3.6: Measurements of the flow rate passing through ten powder (n = 10) cavities in five TwinCaps® devices

<table>
<thead>
<tr>
<th></th>
<th>N=1</th>
<th>N=2</th>
<th>N=3</th>
<th>N=4</th>
<th>N=5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δp (kPa)</td>
<td>Q₁ (L min⁻¹)</td>
<td>Q₂ (L min⁻¹)</td>
<td>Q₁ (L min⁻¹)</td>
<td>Q₂ (L min⁻¹)</td>
<td>Q₁ (L min⁻¹)</td>
</tr>
<tr>
<td>1</td>
<td>21.8</td>
<td>21.9</td>
<td>21.7</td>
<td>21.2</td>
<td>20.8</td>
</tr>
<tr>
<td>2</td>
<td>28.0</td>
<td>28.0</td>
<td>27.6</td>
<td>27.7</td>
<td>28.2</td>
</tr>
<tr>
<td>3</td>
<td>34.5</td>
<td>34.1</td>
<td>33.4</td>
<td>33.9</td>
<td>33.9</td>
</tr>
<tr>
<td>4</td>
<td>39.4</td>
<td>39.8</td>
<td>38.5</td>
<td>38.8</td>
<td>38.9</td>
</tr>
<tr>
<td>5</td>
<td>44.7</td>
<td>44.5</td>
<td>43.4</td>
<td>43.8</td>
<td>43.5</td>
</tr>
<tr>
<td>6</td>
<td>48.5</td>
<td>49.8</td>
<td>47.7</td>
<td>48.2</td>
<td>48.6</td>
</tr>
</tbody>
</table>

\[ \sqrt{\Delta p} = \sqrt{p_{\text{amb}} - p_{\text{oral}}} = R_D Q \]  \hspace{1cm} (3.8)

where the volumetric flow rate is directly proportional to the square root of the pressure drop developed across it. This relation is a derived form of the renown Bernoulli equation from which is directly deductible that \( \Delta p \propto U^2 \).

Here \( p_{\text{amb}} \) is the ambient pressure, \( p_{\text{oral}} \) is the pressure in the oral cavity, \( Q \) is the outlet volumetric flow rate and \( R_D \) is the device’s specific resistance which is the constant of proportionality.

As expected, Figure 3.11 shows good agreement between Equation 3.8 and the experimental data obtained earlier for the TwinCaps® inhaler. The slope of the linear equation which fits the experimental data represents the experimental device specific resistance, which in this case was found to be \( R_D = 0.0533 \text{kPa}^{-1/2} \text{L}^{-1} \text{min} \).

Figure 3.11: Relationship between pressure drop and flow rate across DPI devices adapted from Clark and Hollingworth (1993)

### 3.1.6 Validation

The physical phenomena in a given problem, governed by a mathematical model are modeled via numerical methods. These models are however unable to capture all parameters which define the real problem and often their equations cannot be solved for exactly, thus a level of uncertainty is incorporated.
into the numerical solution. It must then be acknowledged that the numerical prediction will not exactly correspond to the physical solution. Instead it will consist on an approximation that is as accurate as the model’s conformity with the problem at hand. Validation attempts to estimate the modeling error associated with the mathematical model used (Eça et al., 2010). Validation using experimental results is arguably the most employed method because physical measurements directly show the level of model conformity with reality. It should be noted that every measurement carries a level of uncertainty inherited from the measuring instrument and that the presence of device itself either directly or indirectly disturbs the system being measured. This validation method then involves the mentioned experimental uncertainty, the numerical uncertainty discussed earlier and the parameter uncertainty. The american society of mechanical engineers (ASME) proposed a validation procedure, combining these uncertainties (Eça et al., 2010), in which two quantities are compared:

\[ U_{val} = \sqrt{U_D^2 + U_{num}^2 + U_{input}^2} \]  

\[ E = S - D \]

Where \( U_{num}, U_{input}, U_D \) and \( U_{val} \) are the numerical, parameter, experimental and validation uncertainties respectively, \( S \) is the numerical prediction, \( D \) is the experimental value and \( E \) is the comparison error. This procedure aims to estimate the 95% confidence interval (Equation 3.11) which bounds the modeling error, \( \delta_{model} \) (Eça et al., 2010).

\[ \delta_{model} \in [E - U_{val}, E + U_{val}] \]  

To estimate the validation uncertainty \( U_{val} \), the standard deviation of the measured flow rates of the previously presented TwinCaps® experiment is taken as the experimental uncertainty and the parameter uncertainty is considered to be negligible \( U_{input} \sim 0 \). The standard deviation of the \( n = 10 \) measurements (see Table 3.6) at a 4kPa constant pressure drop, is \( U_D = 0.44\text{L/min} \). Substituting this result and the numerical uncertainty values estimated before \((U_{numUDS} = 1.01\text{L/min} \) and \( U_{numLUDS} = 0.91\text{L/min} \)) in to Equation 3.9 yields a validation uncertainty of \( U_{valUDS} = 1.10\text{L/min} \) for the upwind scheme and \( U_{valLUDS} = 1.01\text{L/min} \) for the linear upwind scheme. Knowing from the experiment that, at a 4kPa pressure drop level, the outlet flow rate is \( Q_{OUT} = D = 38.89\text{L/min} \) and using the predicted values \( S \), the comparison error can be calculated for each case (Table 3.7).

Table 3.7: Calculation of the comparison error between simulation results and experiment

<table>
<thead>
<tr>
<th>Case</th>
<th>( D ) (L/min)</th>
<th>( S_{UDS} ) (L/min)</th>
<th>( S_{LUDS} ) (L/min)</th>
<th>( E_{UDS} ) (L/min)</th>
<th>( E_{LUDS} ) (L/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1</td>
<td>41.33</td>
<td>41.48</td>
<td>2.45</td>
<td>2.60</td>
<td></td>
</tr>
<tr>
<td>4.2</td>
<td>38.89</td>
<td>41.51</td>
<td>2.63</td>
<td>3.34</td>
<td></td>
</tr>
<tr>
<td>4.3</td>
<td>40.50</td>
<td>41.33</td>
<td>1.62</td>
<td>2.45</td>
<td></td>
</tr>
</tbody>
</table>

Now taking both \( E_{LUDS} \) and \( U_{valLUDS} \), the minimum and maximum modeling errors with respect to
the experimental value \( D \) can be estimated,

\[
\delta_{\text{model, min}} = \frac{1.59}{38.89} \times 100\% = 4.1\% \quad (3.12)
\]

\[
\delta_{\text{model, max}} = \frac{3.61}{38.89} \times 100\% = 9.3\% \quad (3.13)
\]

Figures 3.12a and 3.12b both show the experimental data plotted together with the numerical prediction of the outflow, when a 4kPa pressure is applied across the device, for cases run with the upwind and the linear upwind schemes respectively.

There are two potential reasons for the model to over-predict the flow across the device: the turbulence model; and the simplifications made to the geometry. In the present mathematical model, it was assumed that the \( k - \omega \) SST model could capture transition from laminar to turbulent flow within the inhaler. However, this turbulence model is known for anticipating transition (Eça and Hoekstra, 2008), in which case the length of the recirculation zones in the mouthpiece might be under-predicted, arguably equating to a larger numerical outflow prediction, \( Q_{\text{OUT}} \), for the same pressure drop level \( \Delta p \).

Secondly, the geometry simplifications introduced in Section 2.4, however small in number and change, may have affected the pressure drop at the inlets.

Despite these facts, the proposed mathematical model was able to capture an important physical property of the problem, the slope of the \( Q \) vs. \( \Delta p \) curve. Figure 3.13 shows the plot of three operating points 3kPa, 4kPa, 5kPa for the three meshes: Mesh 1; Mesh 2; and Mesh 3 against experimental data of the same points. Moreover, the fitted linear equations formulas are presented in the graph and it can be seen that their slope is similar.

This model could be useful in the context of iterating future device designs by being able to capture the effect of changing their design on their main airflow patterns. However, if a lower modeling error \( \delta_{\text{model}} \) is desired, the mathematical model should be further improved by introducing a transition model alongside the \( k - \omega \) SST turbulence model.
3.1.7 Flow characterization

Throughout inhalation time, the patient generates a pressure drop that, at his/her oral cavity, ranges from 0 to approximately 4 kPa, with the latter value (maximum inspiratory effort) depending on the lung illness type and severity. This pressure drop is the flow’s driving force, drawing surrounding ambient air inwards through the powder compartment inlet and body side inlets. Since TwinCaps® is a passive DPI, i.e. depends exclusively on patient inspiratory effort for drug delivery (see Section 1.2), the total air volume entering the device, the shape of the entrances and how they are disposed relative to each other heavily influence the internal flow field, its flow patterns and its turbulent structures. Ultimately, these flow field characteristics serve as fluidizing, deaggregation and dispersion mechanisms of the dry powder formulation, which directly dictate device performance. To understand how the flow progresses from the atmosphere, through the entrances, and along both powder compartment and mouthpiece lengths till the device’s exit, the flow quantities profiles both in the $x$ and $z$ directions, were sampled at several stages (constant $y$) across the aerodynamic channel (Figure 3.14).

The aerodynamic channel is formed when the device is set into inhalation position and two indepen-
dent volumes: the powder compartment; and the mouthpiece channel are connected with their center axes made collinear. These two volumes encompass distinct two flows, which collectively function as the TwinCaps®’s drug delivery system. To gain insight into both flows a total of twelve stages were studied, five in the powder compartment and seven in the mouthpiece.

3.1.8 Powder compartment flow

Ambient air is essentially at rest before it is drawn in at the device’s bottom inlet of area $A_0$. As the airflow approaches the powder compartment inlet, it is subjected to two consecutive constrictions (see Figure 3.15), of cross-sectional areas $A_1$ and $A_2$, respectively, which accelerate and make the flow uniform before it passes through the inlet. Considering the ratios between these areas $A_0/A_1$ and $A_1/A_2$, recalling the continuity Equation 3.14 and again assuming flow incompressibility, it can be quantified how much the flow’s mean velocity increases form $A_0$ to the powder compartment’s inlet.

$$
\dot{m}_0 = \rho_0 Q_0 = \rho_2 Q_2 = \rho_2 \dot{U}_0 A_0 = \rho_2 \dot{U}_2 A_2
$$

(3.14)

Here $m_0$ and $Q_0$ are the aspirated mass and volumetric flow rates respectively, at the inlet of area $A_0$. With this in mind and knowing that the ratios are $A_0/A_1 \sim 43$ and $A_1/A_2 \sim 7.5$, would mean that the mean flow speed at the powder compartment inlet is $\dot{U}_2 = 332.5 U_0$. This value is overestimated because the surface area $A_0$ is not completely planar, i.e. vectors orthogonal to it are not aligned with the $y$ direction, as implied in Equation 3.14.

![Figure 3.15: Flow streamlines at the powder compartment inlet as seen in a (a) Z plane section cut and a (b) X plane section cut](image)

An uniform airflow of speed $\dot{U}_2$ enters the powder compartment volume through a slit-shaped entrance. Early in the chamber, the flow is unable to follow the surrounding wall surfaces (they form a 90° angle with the previous ones) and separates, forming a slit-shaped jet. Figures 3.16a and 3.16b show the profiles of $U_y$, along both the $x$ and $z$ directions adimensionalized by the compartment’s radius, $R^2$.

The black dashed lines represent the flow right before it enters the compartment whilst the black, dark

---

2The device is manufactured via injection molding and so it is designed with a variable mouthpiece radius $R$, increasing from bottom to the outlet, to ease its extraction from the mold.
blue and light blue full lines define the profiles at 5%, 15% and 25% of its length $L_{PC}$.

The initial $U_y$ peak at the centerline, progressively fades throughout the compartment as the jet transfers momentum to the surrounding fluid. In the $x$ direction (Figure 3.16a), the velocity peak widens as the jet transfers momentum to the fluid at the compartment periphery.

In Figure 3.16b, the $U_y$ value at the edges of the slit-shaped jet. These edges are zones of higher turbulence intensity as they are a site of high velocities gradients ($production of K \propto \nabla U_i$) through which the jet diffuses momentum to the surrounding fluid. Both peaks shift towards the compartment's centerline as the jet is progressively constricted by the recirculation zones, and eventually merge after the flow passes recirculation zone center height. Similarly, two high $K$ value peaks can be identified in Figure 3.17a, however one is clearly shorter than the other. This is mainly due to the jet
being slightly tilted to the side as previously seen in the velocity profiles $U_y(x)$. From Figure 3.17b it is also clear to see that the highest turbulent kinetic energy is registered at 15% of the compartment’s length.

![Streamlines projected in three X-plane cross sections](image)

Figure 3.18: Streamlines projected in three X-plane cross sections: (a) $x = -0.5R$; (b) $x = 0$ and (c) $x = 0.5R$ of the powder compartment

The jet (visible in Figure 3.18b) functions as the primary powder fluidization mechanism, penetrating the gaps of the packed powder bed and impinging momentum to particle agglomerates at the centerline. In many ways this mechanism working principle is similar to the one utilized in fluidized bed technology. A better understanding of powder fluidization within TwinCaps® could then be achieved by tracing parallels between the two technologies as suggested by Tuley (2007). The jet is assisted by a secondary fluidization mechanism, the recirculation zones (visible in Figures 3.18a, 3.18b and 3.18c). These help bring particle agglomerates from the periphery of the compartment to its centerline, thus functioning as a particle feeding system to the primary fluidization mechanism, the jet.

The purpose of the powder compartment flow is first to fluidize the powder packed bed and then to break up large particle agglomerates by promoting particle-wall and particle-particle collisions. It should be noted that the actual flow, within TwinCaps®’s powder compartment, may not be fully represented in this work. Although the identified main flow patterns (the jet and recirculation zones) should be similar, their shape and size could be influenced by the presence of particles, their number and how they interact with the flow.
3.1.9 Mouthpiece flow

Like in the powder compartment flow, still ambient air is aspirated inwards at the body side inlets. This fresh air volume entering the mouthpiece enriches the powder-air mix, maximizing the flow’s entrainment capacity while guaranteeing a comfortable inhalation (Villax et al., 2012). As it travels through the body towards the mouthpiece channel, the flow is constricted due to the abrupt change in channel cross sectional area to $A_1$ (see Figure 3.20). This constriction both accelerates and makes the flow approximately uniform with a $U_x$ velocity profile shown in Figure 3.19. However it is not completely symmetric, featuring a bump at $y/H = 0.8$ which makes the preservation of $x$ and $z$ flow field symmetry in the mouthpiece troublesome.

Upon arriving at the opening leading to the mouthpiece channel, the flow is unable to follow its walls, thus separating and forming four jets, two in the $-x$ direction and the other two in the $x$ direction. Figure 3.20 is a longitudinal cross section (a $Z$ plane) of the mouthpiece compartment, which intersects in half one pair of opposite body side inlet channels, showing the flow streamlines representing the frontal collision of two jets. In an unbounded inviscid flow, this frontal collision between opposite oriented jets, would lead to the formation of a fluid sheet at midway length, where $U_x = 0 \text{ m s}^{-1}$, spreading equally in the $y$ direction with $U_y > 0$ and $-y$ direction with $U_y < 0$. In this particular case however, the collision site is limited at the bottom by the mouthpiece’s channel walls. Thus only a half-sheet (where $U_x = 0$) is formed upwards while the fluid that would form its counterpart recirculates near the powder compartment-mouthpiece passageway in two recirculation zones.

With this in mind it is clear to see why both $U_y(x)$ and $U_y(z)$ velocity profiles at the mouthpiece bottom $y/L_M = 0$ are negative and at $0.05L_M$, the upper limit of the side channels, positive. Moreover, Figure 3.21b shows a nearly constant $U_y = 60 \text{ m s}^{-1}$ profile at $0.05L_M$ which also indicates the existence of the above mentioned fluid sheet.

Figure 3.23b shows two points (circled in blue), at $a \sim 0.35L_M$, bellow which there is reversed flow near the bounding walls and above which the flow travels in the upward direction. This flow feature is captured in the $U_y(z)$ profile, where the previous nearly uniform profile (at $0,05L_M$) now exhibits two inverted humps, with lower velocity magnitude at $z \sim 0.5R_M$.

This indicates the existence of four recirculation zones, which much like in the powder compartment flow, circumscribe a smaller inner flow tube. Figures 3.24a and 3.24b show cross sections ($Y$ planes)
Figure 3.20: Frontal collision between opposite body side inlet jets

Figure 3.21: Flow field velocity profiles across the length of the mouthpiece, adimensionalized by the compartment's radius $R$ in both $X$ and $Z$ directions

Figure 3.22: Flow field turbulent kinetic energy profiles across the length of the mouthpiece, adimensionalized by the compartment's radius $R$ in both $X$ and $Z$ directions
of the mouthpiece channel, at 0, 15L_M and 0, 25L_M respectively, where the four recirculation zones with rotation centers F_1, F_2, F_3 and F_4 in each quadrant, can be seen.

After a height of 0.35L_M, the upper limit of the recirculation zones, the flow tends to uniformize and slow down until the mouthpiece outlet. Figures 3.25a and 3.25b show cross sectional planes at 0, 5L_M and 0, 75L_M where the recirculation zones can no longer be seen and where the above mentioned tendency is observed.

Both in the velocity U_y(x), U_y(z) and turbulent kinetic energy K(x), K(z) profiles this flow behavior is also observable. At this stage the flow is exclusively oriented in the y direction, with the velocity magnitudes in the x and y directions being residual. Accordingly the K(x) and K(z) profiles are mainly dictated by the U_y(x) and U_y(z) profiles respectively (high K values occur where ∂U/∂y is highest).

Finally, in Figures 3.28 and 3.29 the velocity U_y(x), U_y(z) and turbulent kinetic energy K(x) and K(z) profiles at the device’s y = L_M exit are shown. The outlet velocity profiles are clearly smoother whilst the K profiles show relatively low values when compared to those at the early stages of the mouthpiece.

Figure 3.30 shows a cross section of the mouthpiece channel at its exit. Since this cross section consists in a Y plane, and the flow streamlines are fully aligned with the y direction, their projections on the plane all start at a common source at the center and end at the edge.
Figure 3.25

Figure 3.26: Flow field velocity profiles across the length of the powder compartment, adimensionalized by the compartment’s radius $R$ in both $X$ and $Z$ directions

Figure 3.27: Flow field velocity profiles across the length of the powder compartment, adimensionalized by the compartment’s radius $R$ in both $X$ and $Z$ directions
Figure 3.28: Flow field velocity profiles across the length of the powder compartment, adimensionalized by the compartment’s radius $R$ in both $X$ and $Z$ directions (Scale is maintained from the previous figure to enable a direct comparison of the results)

Figure 3.29: Flow field velocity profiles across the length of the powder compartment, adimensionalized by the compartment’s radius $R$ in both $X$ and $Z$ directions (Scale is maintained from the previous figure to enable a direct comparison of the results)

Figure 3.30
The outflow’s velocity profile shape, magnitude and the direction of its streamlines are important as they determine the dispersion and behavior of the particles emitted (Milenkovic et al., 2013). These flow features may influence particle deposition in the oral cavity and consequently determine the amount of particles that reach the upper airways (Milenkovic et al., 2013).

The purpose of the mouthpiece flow is to further deaggregate the particle agglomerates, separating the fine particle (the API) from its carrier (typically lactose monohydrate) by turbulent stress, taking advantage of the high turbulence intensity level originating from the four jet collision site. The recirculation zones prevent the majority of the particles from exiting the device too soon, helping to increase particle residence time and consequently allowing for more fine particles to detach from their carriers.

Unlike the powder compartment flow, the flow characterized above most likely conforms to its real counterpart. Because the total flow rate passing through the mouthpiece is relatively higher than in the powder compartment ($Q_{PC} \approx 0.05Q_{M}$) and the number of particles is approximately the same $^3$, the particle mass fraction drops and the flow falls in the dilute particle flow regime.

In dilute-particle flows, the dynamics of the discrete phase (in this case particles) are influenced by the continuous phase (in this case air), but not the other way around. In other words, the particles follow the flow’s streamlines and do not significantly impact the flow patterns.

### 3.1.10 Flow rate influence

So far we have looked at the axial flow velocity, $U_y$ and turbulent kinetic energy, $K$, profiles along the powder compartment and mouthpiece when a constant 4kPa pressure drop is applied at the device outlet. This specified pressure drop value together with a 4L total inhaled volume make up the standard Pharmacopoeia (Council of Europe, 2014; United States Pharmacopeial Convention, 2015) test conditions, which are representative of the inhalation properties generated by the average patient and are often required for regulatory approval. It is also useful to analyze the device’s flow field under different pressure drop levels, in order to capture the effect of flow rate increase. Figure 3.32 shows the same $U_y$ and $K$ profiles, for simulations of the cases 3.2, 4.2 and 5.2, at 15% (Figures 3.31a and 3.31b) and at 100% (Figures 3.32a and 3.32b) of the mouthpiece’s length.

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$^3$depending on particle retention within the powder compartment
It can be seen that overall the profile shapes are maintained while their values \( (U_y \text{ and } K) \) increase with the pressure drop level. This means that by increasing the flow rate through the device, the mean velocity and turbulence intensity level increase but only at the cost of extra patient inspiratory effort. Another way to visualize the effect of increasing the flow rate on the flow, is by plotting the spatially averaged values \( U_y \) (Figure 3.33) and \( K \) (Figure 3.34) along both powder compartment and mouthpiece lengths with varying pressure drop level.

In the powder compartment, the flow’s mean velocity \( U_y \) rapidly drops from an initially high value (corresponding to the jet velocity) due to the sudden change in cross-section area. Its value then remains approximately constant throughout most of the compartment’s length until it increases slightly as another constriction approaches (passageway between the powder compartment and mouthpiece).

In the mouthpiece (see Figure 3.33a), the flow’s mean velocity \( U_y \) increases from the mouthpiece’s bottom until 5% of its length, the upper limit of the body side inlets, due to upward acceleration impinged by the side jets. Next, \( U_y \) steadily decreases as the flow develops, along the slowly expanding mouthpiece, to the mean outlet value.

Figure 3.33a shows little difference between \( U_y \) profiles of the three cases (3.2, 4.2 and 5.2) whereas Figure 3.33b shows a significant increase in the mean velocity value of cases 4.2 and 5.2 relative to the case 3.2. On one hand, this is due to the relatively low flow rate (approximately 4% of the outlet flow rate) passing through the powder compartment and the corresponding low increase of \( \sim 0.2 \text{ L min}^{-1} \) from one
case to the other. On the other hand, the flow rate passing through each side inlet increases in average 1.4 L min\(^{-1}\), making a total of \(4 \times 1.4 + 0.2 = 5.8\) L min\(^{-1}\) average increase per pressure drop level naturally escalating the average velocity value since the cross-sectional area remains constant.

Table 3.8: Inlet/Outlet flow rate ratio in three cases of increasing pressure drop across the device (3 kPa, 4 kPa, 5 kPa)

<table>
<thead>
<tr>
<th>Case</th>
<th>(\Delta)p (kPa)</th>
<th>(Q_{OUT}) (L min(^{-1}))</th>
<th>(Q_{FR}) (L min(^{-1}))</th>
<th>(Q_{BR}) (L min(^{-1}))</th>
<th>(Q_{FL}) (L min(^{-1}))</th>
<th>(Q_{BL}) (L min(^{-1}))</th>
<th>(Q_{PCI}) (L min(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2</td>
<td>3</td>
<td>36.2</td>
<td>8.7</td>
<td>8.5</td>
<td>8.7</td>
<td>8.7</td>
<td>1.6</td>
</tr>
<tr>
<td>4.2</td>
<td>4</td>
<td>42.2</td>
<td>10.2</td>
<td>9.9</td>
<td>10.1</td>
<td>10.2</td>
<td>1.8</td>
</tr>
<tr>
<td>5.2</td>
<td>5</td>
<td>47.4</td>
<td>11.4</td>
<td>11.1</td>
<td>11.4</td>
<td>11.4</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Figure 3.34: Averaged turbulent kinetic energy, \(\kappa\), value on various (a) powder compartment and (b) mouthpiece channel cross-sections (Y planes)

In the powder compartment, turbulent kinetic energy \(\kappa\) reaches its peak average value at 25% of the compartment’s length. It then decays along that volume, as the average velocity stabilizes, to a residual value of \(\approx 1.5\) m\(^2\) s\(^{-2}\). Although increasing the flow rate did not have a significant impact on the average velocity magnitude, Figure 3.34a shows three \(\kappa\) which are an offset (with maximum value of \(5\) m\(^2\) s\(^{-2}\)) of each other until 50% of the compartment’s length where they overlap. This means that by increasing the pressure drop level, the turbulence intensity inside the powder compartment rises, potentially boosting the flow’s fluidizing power.

In the mouthpiece, turbulent kinetic energy \(\kappa\) reaches its peak average value at 15% of the compartment’s length, overlapping with the maximum average velocity \(U_y\) value at a stage where this velocity component is already dominant. Much like in the powder compartment, \(\kappa\) decays once the velocity field develops and \(U_y\) begins to slowly decrease towards the outlet value. Moreover, the three profiles are also offsets of each other throughout the entire mouthpiece length (of maximum value \(50\) m\(^2\) s\(^{-2}\)), again demonstrating the scalability property of the mouthpiece flow. Incrementing the pressure drop level scales up the turbulence intensity level, increasing the flow’s deaggregating (e.g. fine particle - coarse particle deaggregation by turbulent stresses, see Figure1.8) and dispersive power.

Aside from the potential benefits mentioned above, increasing the flow rate across the device not only requires extra inspiratory effort but also may change the flow regime and affect the device’s performance in an yet unknown way. Upon stating the TwinCaps® internal flow problem (in Chapter 2), it was generally assumed that the air speed was low enough (all over the domain) so that flow could
be considered incompressible. This early assumption can be ratified by evaluating the maximum flow velocity in the domain and later computing the corresponding Mach number. The Mach number, \( M \), is the ratio between the object’s (in this case air) velocity \( v \) and the speed of sound \( a \) of the medium (in this case also air) in which it travels.

\[
M = \frac{v}{a} \tag{3.15}
\]

Here \( v \) is the flow velocity (in this case the maximum flow velocity) and \( a \) is the speed of sound in the fluid (air) at the same conditions (e.g. Temperature) of the actual flow. For ideal gases and air \( a \) is given by Equation 3.16,

\[
a = \sqrt{\gamma R_{\text{air}} T} \tag{3.16}
\]

Where \( \gamma = C_p/C_v = 1.4 \) is the specific heats ratio of air at constant pressure \( C_p \) and volume \( C_v \), \( R_{\text{air}} = R/M_{\text{air}} = 287.09 \text{JK}^{-1}\text{kg} \) is the molar gas constant and \( T \) is the absolute temperature. Assuming an ambient temperature of \( 20^\circ \text{C} \),

\[
a = \sqrt{\gamma R_{\text{air}} T} = \sqrt{1.4 \times 287.09 \times (273.15 + 20)} = 343.24 \text{m s}^{-1} \tag{3.17}
\]

In the three cases 3.2, 4.2 and 5.2 the maximum flow velocity, was found to be at the exit of each body side inlet, where the velocity vector is aligned with the \( x \) direction and \( U_{\text{max}} = U_x \). With the maximum flow velocities \( U_x \) and the speed of sound \( a \) calculated above, the Mach number \( M = U_x/a \) was computed with the results shown in Table 3.9.

<table>
<thead>
<tr>
<th>Case</th>
<th>( \Delta p ) (kPa)</th>
<th>( U_x ) (m s(^{-1}))</th>
<th>( M )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2</td>
<td>3</td>
<td>100.14</td>
<td>0.29</td>
</tr>
<tr>
<td>4.2</td>
<td>4</td>
<td>116.67</td>
<td>0.34</td>
</tr>
<tr>
<td>5.2</td>
<td>5</td>
<td>131.34</td>
<td>0.38</td>
</tr>
</tbody>
</table>

If a fluid travels at a speed lower than the speed of sound \( M < 1 \) (see Figure 3.35), the flow is designated as a subsonic flow. For subsonic flows, compressibility effects (i.e change in air density) become more relevant as flow speed increases and Mach number approaches unity. However for lower speed flows where \( M \ll 1 \), compressibility effects are negligible and these flows are deemed as incompressible. The Mach number value which splits these two regimes apart is generally accepted to be \( M = 0.3 \), meaning all of the cases are susceptible of being affected by air compressibility. However it should be noted that, throughout most of the domain, air velocity magnitude is relatively lower than the one registered in the four jets mixing-zone and \( M \sim 0 \). In technical applications, such as the present case, which concern incompressible fluid flows slightly influenced by compressibility effects, neither compressible nor incompressible schemes can be applied without modifications (Roller and Munz, 2000). Therefore future work aiming to study air compressibility effects on the device’s flow field should comprise a math-
mathematical model which is able to compute solutions for flows with both compressible and incompressible regions. For instance, one incompressible approach is the subsonic approximation used by Bijl and Wesseling (1996). This is an approach accurate for Mach numbers ranging from $0$ to $O(1)^4$, wherein pressure, $p$, is split into a constant part to fulfill the equation of state and a relatively smaller variation which guarantees the divergence-free velocity constraint when $M \rightarrow 0$ (Bijl and Wesseling, 1996).

![Flow regimes according to the Mach number](image)

Figure 3.35: Flow regimes according to the Mach number

### 3.2 Transient flow

In the previous section solutions of steady-state flows, at various fixed pressure drops (Table 3.1), were characterized. Although these results have been useful for understanding the main flow patterns and for potentially identifying the device’s powder dispersion mechanisms, they do not fully represent the actual patient generated flow. This is due to the time-dependency of patient inspiratory effort i.e. the flow rate across the device varies from beginning to end of the inhalation time. The problem of inspiratory flow development inside TwinCaps® throughout inhalation time, is thus transient (time-dependent) in nature. Fortunately, the formulation of this transient problem is similar to that of the steady-state problem, except now both time discretization and time dependent boundary conditions need to be taken into account.

#### 3.2.1 Time discretization

As already discussed in Section 2.2, the first term of Equation 2.6 stands for the rate of change in time of the fluid property $\phi$ and is null for steady flows. On the other hand in transient problems this term is different from zero and therefore it must be preserved and included in the discretization process. Further integrating Equation 2.6 over a finite time step $\Delta t$ yields the equation for transient convection-diffusion problems,

\footnote{on the order of magnitude of one}
\[
\int_{CV} \left( \int_{t}^{t+\Delta t} \frac{\partial (\rho \phi)}{\partial t} \, dt \right) \, dV + \int_{t}^{t+\Delta t} \left( \int_{A} \mathbf{n} \cdot (\rho \phi \mathbf{u}) \, dA \right) \, dt = \\
\int_{t}^{t+\Delta t} \left( \int_{A} \mathbf{n} \cdot (\nabla \phi) \, dA \right) \, dt + \int_{t}^{t+\Delta t} \int_{SV} \phi \, dV \, dt \tag{3.18}
\]

Besides the scheme used for space discretization of the CV (see Section 3.2), another method is needed to discretize the governing equations over a time range \(\Delta t\). The exact form of the final discretized equation depends on discretization method used. With the explicit method, on the RHS of Equation 3.18, only property values, \(\phi^0\), at the old time level, \(t\), are used to compute \(\phi\) at the new time level \(\Delta t + t\). Whereas implicit schemes weigh the influence of property values at the new and old time levels to evaluate \(\phi^0\). The two most common implicit schemes are the Crank-Nicolson scheme, which equally weighs old and new property values influencing on \(\phi\), and the fully implicit scheme which disregards influencing from past time levels. Table 3.10 summarizes a properties comparison between these three methods.

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Stability</th>
<th>Accuracy</th>
<th>Positive coefficient criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explicit</td>
<td>Conditionally stable</td>
<td>1\textsuperscript{st} order</td>
<td>(\Delta t &lt; \frac{\rho (\Delta x)^2}{2T})</td>
</tr>
<tr>
<td>Crank-Nicolson</td>
<td>Unconditionally stable</td>
<td>2\textsuperscript{nd} order</td>
<td>Always positive</td>
</tr>
<tr>
<td>Implicit</td>
<td>Unconditionally stable</td>
<td>1\textsuperscript{st} order/2\textsuperscript{nd} order</td>
<td>Always positive</td>
</tr>
</tbody>
</table>

The stability limitation in Table 3.10 can also be quantified via Courant-Friedrichs-Lewy (CFL) condition,

\[
C = \Delta t \sum_{i=1}^{n} \frac{u_{xi}}{\Delta x_i} \leq C_{max} \tag{3.19}
\]

where \(C\) is the Courant number, which is a measure of the amount of flow information convected \(u\) through a computational grid cell, \(\Delta x\) within a given time step \(\Delta t\).

Because explicit schemes rely exclusively on information at the old time level, they are bounded by the Courant number upper limit of \(C_{max} \leq 1\). Moreover, while using the fully explicit method, improving spatial accuracy becomes extremely expensive because the maximum possible time step needs to be reduced with the square of \(\Delta x\) (Versteeg and Malalasekera, 2005). Accordingly, this scheme is usually not recommended for general purpose applications.

Generally, implicit schemes are unconditionally stable (Table 3.36). However, when applied to the Navier-Stokes equations, the non-linearities in these governing equations often limit stability. Still, they allow a relatively larger Courant number \(C \geq 1\) with the upper limit \(C_{max}\) being a case dependent
value. Depending on the number of solution time levels used the fully implicit scheme can be first-order (two time levels) or second-order (three time levels) accurate in time. Due to both its robustness and unconditional stability, the implicit method is recommended for general purpose transient engineering problems.

3.2.2 Time dependent boundary condition

DPI devices either rely exclusively (passive) or partially (active) on patient inspiratory effort to deliver the label dose to the lungs. Therefore, especially for passive DPIs, the device’s inhalation technique and patient compliance are decisive for a successful inhaled drug delivery. The total inhaled volume, the peak inspiratory flow (PIF) and the time at which it is attained are important inhalation technique parameters and are generally device and patient dependent. Each DPI design is tailored to achieve fluidization and dispersion mechanisms needed to aerosolize a specific powder formulation with a specific set of characteristics (e.g. cohesiveness). Thus there exists a variety of techniques, among different DPIs, which prevents device interchangeability, under the premise that changing DPI without consulting his/her physician could significantly reduce the amount of drug reaching the lower airways and consequently hinder the desired therapeutic effect. In the case of TwinCaps®, to the author’s knowledge, there is no available clinical data that provides a patient inspiratory profile specific to the device. For demonstration purposes however, a simplified example can be built based on the generic inspiratory effort profile introduced by Chrystyn and Price (2009) and depicted in Figure 3.36.

![Figure 3.36: Patient inspiratory effort pressure drop vs. inhalation time, adapted from Chrystyn and Price (2009)](image)

On account of TwinCaps® being a passive reservoir-type DPI, the inhalation technique should consist in a relatively short PIF time, $0,1s \geq t_{PIF} \leq 0,2s$ coupled with a high PIF to impart sufficient energy to the flow for particle fluidization, deaggregation and dispersion. This is the time range of interest, from a flow development standpoint, that allows the characterization of the flow patterns identified as the fluidization and dispersion mechanisms in the previous steady-state test cases. In this work, time-dependency of the airflow across the device is emulated via a simplified $\Delta p(t)$ function (Figure 3.37).

The function is a pressure drop ramp, increasing from rest at $0kPa$ to $4kPa$ corresponding to the PIF in a time of $t_{PIF} = 0,1s$. The pressure drop value of $4kPa$ is then maintained to allow the flow to reach a
Figure 3.37: Time-dependent pressure boundary condition: pressure drop level rises from 0 to 4 kPa in an peak inspiratory flow rate time of $t_{PIF} = 0.1$ s and then is kept constant to allow the flow field solution to reach steady-state final steady-state.

3.2.3 Transient case configuration

The TwinCaps® transient problem formulation is similar to its steady-state counterpart except for the outlet pressure boundary condition and the incorporation of a time discretization scheme. The remainder of case parameters are re-utilized based on experience gathered from the previous steady-state studies.

Because it features the lowest number of volumes (saving computing time) and allows for a solution of numerical precision comparable to those of Mesh 1 and Mesh 2, Mesh 3 was the grid chosen for this case. Linear upwind was the selected spatial discretization scheme, as it is associated to a lower discretization uncertainty than the regular upwind and is less likely to impart numerical diffusion into the final solution field. The selected temporal discretization scheme was the fully implicit one. This scheme allows the selection of a Courant number larger than unity, thus affording a relatively larger time step (for the same grid cell size), without compromising the stability of the resulting flow field solution. However, increasing $\Delta T$ inherently deteriorates the numerical precision of the solution in time. Therefore, the choice of the Courant number $C$, and consequently the time step, must consider the trade-off between numerical stability and precision and computing time.

The solver used to carry out the simulation, pimpleFoam, includes the feature of limiting the maximum Courant number $C_{max}$ by adjusting the time step $\Delta t$ accordingly (the cell size $\Delta x_i$ is constant). After iterating the value of this Courant number upper limit within a range of $1 \leq C_{max} \leq 100$, it was found that $C_{max} = 100$ provided the fastest solution while maintaining stability.

In Figure 3.38 the volume maximum and mean Courant number history values are plotted along the successive outer SIMPLE + PISO loop iterations. As their values rise with the increasing pressure drop value, the time step size $\Delta t$ increases accordingly to the value of $5 \times 10^{-4}$ s, and when they reach the respective plateau values of 100 and 5, $\Delta t$ is continuously adjusted until the final value of $3.6 \times 10^{-5}$ s is reached.
3.2.4 Powder compartment flow

Just before inhalation, at \( t = 0 \) s, both the air surrounding and within the device is at rest. As the patient actuates the device, he/she exerts at first a small pressure drop that drives the internal air volume towards his/her mouth. When \( t = 0.001 \) s have elapsed the pressure drop is \( \Delta p = 40 \) Pa, a value which generates a "perfect fluid" like flow field (Figures 3.39a and 3.39e) where the streamlines at powder compartment's entrance are able to follow its bounding walls. At the second time step \( t = 0.002 \) s however, the outside air is drawn in at a speed which does not permit it to follow the compartment's walls as before thus flow separation occurs and a slit-shaped jet is formed. With the inception of this flow feature, two other arise, two recirculation zones circumscribing the jet (Figures 3.39b and 3.39f).

As time progresses so does the pressure drop level \( \Delta p_{i+1} = \Delta p_i + 40 \) Pa and consequently the magnitude of the velocity field and size of the recirculation zones.

The maximum length of the recirculation zone is reached at the \( t = 0.007 \) s time step. From then on until \( t = 0.1 \) s when \( \Delta p = 4 \) kPa the jet fluctuates about its upright centered position (in the \( x \) direction) with
the recirculation zones varying in width accordingly. This upright position about which the jet fluctuates corresponds to the symmetric steady-state solution discussed in Chapter 2.

Until $t = 0.1\text{s}$, the amplitude and frequency of the flow patterns oscillation about their steady-state states are both a function of the pressure drop gradient $\Delta p/t_{PIF} = 40\text{kPa s}^{-1}$. The steeper the gradient the larger in magnitude and number the fluctuations. The real flow generated by the patient's inspiratory effort, the curve's gradient is time dependent $\Delta p/t \neq \text{constant}$ and is generally more accentuated at the beginning of inhalation gradually tending to zero as PIF is reached (see Figure 3.37). A steeper initial gradient imparts more power, $P$, to the flow (Tibbatts et al., 2010).

$$P = Q\Delta p$$ (3.20)

Where $\Delta p$ and $Q$ are the pressure drop and fluid flow rate across the device. This power conjugated with the above mentioned flow pattern fluctuations constitute the driving force behind powder fluidization within the TwinCaps® inhaler. Ultimately this limits the device’s range of applicability, i.e. if the patient is unable to generate a high pressure drop gradient (e.g. patients suffering from severe COPD) which guarantees the minimum required energy to properly fluidize the powder bed, then device performance may be hindered. It is then important when conceiving DPI devices, particularly a passive DPI, to aim for a design which both promotes a high turbulence intensity level and a low internal device resistance.

By re-plotting the graphs, seen in subsection 3.1.10, for the present transient case, the influence of increasing pressure drop an consequently the flow rate on the spatial averages of velocity $\overline{U_y}$ and turbulent kinetic energy $\overline{K}$ over a powder compartment cross-section and over time can be studied.

In the following figures the time steps $t = 0.025\text{s}, t = 0.05\text{s}, t = 0.075\text{s}$ and $t = 0.1\text{s}$ correspond to $\Delta p = 1\text{kPa}, \Delta p = 2\text{kPa}, \Delta p = 3\text{kPa}$ and $\Delta p = 4\text{kPa}$ respectively, allowing a comparison between these states and previously studied steady-state solutions at the respective pressure drop levels. Figure 3.57a shows once again that, except for the entrance, once $t \neq 0$ the average velocity value does not change neither across the length of the powder compartment nor time.

At the powder compartment entrance, where $A_{y=L=0} \ll A_{y=L}$ and consequently velocity magnitude

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5if the jet is shifted to the right the left recirculation zone is necessarily larger than the right one
Figure 3.41: Averaged velocity component, $U_y$, value across time $t$ on various (a) powder compartment and (b) mouthpiece cross-sections (Y planes)

is relatively higher, $U_y$ increases, not linearly but quadratically with time (Figure 3.57b). Because the time-dependent boundary condition defines a linear variation of the pressure drop level $\Delta p$, the average velocity on a a given mouthpiece cross-section $U_y$ varies according to the following relation,

$$\Delta p \propto U^2$$  \hspace{1cm} (3.21)

In the powder compartment, turbulent kinetic energy $\overline{K}$ reaches its peak average value at 25% of the compartment’s length. It then decays along that volume, as the average velocity stabilizes, to a residual value of $\sim 1.5 \text{m}^2 \text{s}^{-2}$ at its exit. The $\overline{K}$ profiles at $t = 0.075 \text{s}$ and $t = 0.1 \text{s}$ (Figure 3.42a), when $\Delta p = 3 \text{kPa}$ and $\Delta p = 4 \text{kPa}$, are similar in shape to their steady-state counterparts but lower in their peak magnitude by $\sim 5 \text{m}^2 \text{s}^{-2}$.

Figure 3.42: (a) Averaged velocity $U_y$ and (b) turbulent kinetic energy, $\overline{K}$, values across time $t$ on various powder compartment cross-sections (Y planes)

Past $t = 0.1 \text{s}$ however, the $\overline{K}$ peak shifts from $y/L = 0.25$ to $y/L = 0.5$ at $t = 0.15 \text{s}$. Additionally, in Figures 3.42a and 3.42b it is clear to see that even after the pressure drop value has reached its final value of $\Delta p = 4 \text{kPa}$ at $t = 0.1 \text{s}$, the $\overline{K}$ profiles have yet to stabilize when $t = 0.15 \text{s}$. Thus the airflow inside the powder compartment did not reach a steady-state within simulation time.
3.2.5 Mouthpiece flow

Like in the powder compartment flow, still ambient air is aspirated inwards at the body side inlets as the patient begins to inhale. However unlike in the latter flow, at the earliest time step, $t = 0.001s$, when the pressure drop level is $\Delta p = 40Pa$, the flow is unable to make the turn around the four sharp corners, $S_1$ to $S_4$ of internal angle $\theta > 270^\circ$ (see Figure 3.43) and it separates. As a consequence four recirculation zones appear, one per each side inlet, at the mouthpiece’s walls in between side openings. At their highest point, there are two "stagnation points" $E_1$ and $E_2$, that belong to the streamline diving the recirculating flow from the free-flowing one. Additionally, at the mouthpiece centerline, there exists a third stagnation point $E_3$ that sits at the intersection of the four stagnation lines which correspond to the interfaces where the four flows, originating from each side inlet, meet.

![Figure 3.43: Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.001s$](image)

Once $t = 0.002s$, outside air is drawn in at such a speed that does not allow it to follow the compartment's walls at the signaled locations, $S_5$ to $S_8$ (internal angle $\theta \sim 120^\circ$) in Figure 3.44b, as before and thus the flow separates and four jets are formed.

With the inception of these flow features, four other arise, four recirculation zones of centers $F_1$, $F_2$, $F_3$ and $F_4$ depicted in Figure 3.39b. Also, with the increase in flow speed, the previously mentioned four recirculation zones of centers $F_1$, $F_2$, $F_3$ and $F_4$ grew in length leaving $E_1$ and $E_2$ closer to the centerline.

At $t = 0.003s$ with a new increase in flow speed, the recirculation zones 1, 2, 3 and 4 grow in length pushing $E_1$ and $E_2$ further towards the centerline. Moreover, the four jets $FL$, $FR$, $BR$ and $BL$ no longer meet at the centerline on stagnation point $E_3$ and instead collide pair in pair ($FL$ with $FR$ and $BL$ with $BR$) giving rise to two new "stagnation points" $E_4$ and $E_5$.

There is then a system of four "stagnation points" circumscribing the centerline, whose configuration in a symmetric flow field solution is represented in Figure 3.47. The dots represent the various "stagnation points" while the black arrows give the flow direction relative to each "stagnation point".

With a computational domain, boundary and initial conditions symmetric about the $x$ and $z$ axis the flow field solution ought also to be symmetric. Instead when the aforementioned system is unbalanced (Figure 3.52) the air intake at each body side inlet is uneven-ed and more air flow passes through the right side inlets $FR$ and $BR$ on time step $t = 0.06s$ (Figure 3.48) and through the left side inlets $FL$ and $BL$ on time step $t = 0.08s$ (Figure 3.49) for instance.

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6 Although the flow is three-dimensional and $U_y \neq 0$, the points of "junction" of streamlines, where cross-stream velocity is zero ($U_x = U_z = 0$) are going to be designated as "stagnation points"
Figure 3.44: Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.002s$

Figure 3.45: Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.003s$

Figure 3.46: Streamlines projected on to a Y cross-section of the mouthpiece, at the four body side inlets half-height and time step $t = 0.004s$

Figure 3.47: Symmetric configuration of the "stagnation points" system
At these time steps, the "stagnation points" system takes the following configurations in Figures 3.50a and 3.50b.

By time step $t = 0.05s$ the final system configuration was achieved. More air volume enters the $BL$ and $FR$ side inlets unbalancing the system by pushing both $E_4$ and $E_5$ away from the centerline and consequently creating a vortex at the center (Figure 3.52).

It is clear to see in Figure 3.53 that the flow field configuration has been maintained since time step $t = 0.05s$ till time step $t = 0.16s$. Figure 3.54 shows a contour plot of the turbulent kinetic energy $k$ of the
same cross-section where the streamlines were projected in previous figures. The four side inlet jets are readily identified as the zones, inside the mouthpiece channel, colored in dark blue where \( k < 5 \text{m}^2 \text{s}^{-2} \) (zones 4). This is due to the fact that, from the body side inlet to the respective mouthpiece channel entrance, there are no large velocity gradients and eddy-viscosity \( \nu \tau \) is of the order of the kinematic viscosity \( \nu \).

The lines where \( U_x = 0 \) at the site of collision between the two pairs of jets (zones 2) are naturally zones of high turbulence intensity due to the velocity gradients \( \partial U_y / \partial x \) and \( \partial U_x / \partial x \) in the \( x \) direction. Zone 1 at the mouthpiece centerline, registers the highest turbulent kinetic energy value \( k > 500 \text{m}^2 \text{s}^{-2} \). These zones, mainly zones 1 and 2, are responsible for deaggregating the fine drug particles from their carriers by turbulent stress (see Chapter 1) and later dispersing them. The white dashed line represents the source of particle agglomerates exiting the powder compartment and entering the mouthpiece channel.

Both the spatial averages of the turbulent kinetic energy \( \overline{k} \) and velocity in the \( y \) direction \( \overline{U_y} \) reach
their peak value downstream of four jets mixing-zone at $y/L = 0$, 15 being the highest values throughout the entire inhalation time. Both the values then decay as the flow approaches the device’s outlet. As in the flow rate influence section, it is remarkable the scalability of both $U_y$ and $R$ profiles. Also, in Figures 3.55a and 3.56a, the profiles of time steps $t > 0$, 1s overlap showing that a steady-state solution has been achieved.

Figure 3.56: Averaged turbulent kinetic energy, $R$, value across time $t$ on various (a) powder compartment and (b) mouthpiece channel cross-sections (Y planes)

### 3.2.6 Particle visualization

Recent work in the DPI field of investigation has focused on the prediction of particle behavior and deposition within the device. For this purpose, researchers have generally utilized one of the following methods:

i) Lagrangian particle tracking as post-processing operation: A method where the fluid flow field is first solved with the particles being introduced after as point sources.

ii) Euler-fluid/Lagrangian-particle: A method that addresses the particles as a disperse phase in a Lagrangian reference frame and the fluid as a continuum phase in an Euler reference frame.

iii) CFD + DEM: A method that couples CFD for the flow field solution and DEM for the solution of each particle’s momentum equations. The coupling can be one-way, where only the fluid exerts influence on particle behavior, or two-way where both fluid and particles influence each others behaviors.

The above methods are ordered from least (method i)) to most (method iii)) computationally expensive with a naturally increasing level of detail between them. In the Euler-fluid/Lagrangian-particle approach particle clouds are often represented by a single particle in order to save computational time. In the third method, adding to the CFD computing effort of the flow field, linear and angular momentum equations are resolved for the six degrees of freedom (three translational and three rotational) at each time step sharply increasing the computational time.

Due to the limited time frame of this work, none of the mentioned methods was undertaken. Instead a purely qualitative comparison, between the first seconds of the real multiphase particle-airflow and its transient simulation, is presented. Figures 3.57a, 3.57b and 3.57c show post-processed time frames of

Footnote: The complete set of time frames is presented as an annex.
a high-speed film featuring a powder loaded TwinCaps® compartment shot in a laboratory at Hovione’s facilities. To enable a comparison with the real flow, massless spherical particles where introduced in a random fashion at several heights of the powder compartment.

Figure 3.57: Powder bed fluidization in the real: a); b) and c) and simulated flow: d); e) and f)

In this case the particles simply follow the flow’s streamlines (Figures 3.57d, 3.57e and 3.57f). The only information that can be extracted from this comparison is the visible tendency in both cases of the particles lifting first in center and later shifting to side of the powder compartment. In the real flow, this can be due to an eventual non-symmetric geometry of the device used (e.g. surface irregularities ate slit-shaped powder compartment entrance), to a misalignment between its powder compartment inlet and its body bottom inlet or even to one side of the powder bed being more densely packed than the other. In the flow simulation, this can also be due to geometric imperfections (e.g. non-symmetric mesh) or to the discretization method and the numerical diffusion it introduces. However, to gain a better understanding of the real multiphase flow a test case employing one of the previously mentioned methods would need to be undertaken.

8The complete set of time steps corresponding to the time frames extracted from the video is presented as an annex
Chapter 4

Conclusions and suggestions for future work

This thesis presents the use of OpenFOAM®, an open-source CFD toolbox, to determine the complex internal airflow within the TwinCaps® dry powder inhaler. Besides characterizing the main flow patterns, this work comprised a mesh dependency study to estimate the solution's numerical uncertainty and a comparison of the solution with experimental data.

A set of nine steady-state test cases was simulated, using three different meshes Mesh 1, Mesh 2 and Mesh 3 of increasing refinement, under three constant pressure drop levels 3, 4, and 5 kPa across the device. For an operating pressure drop of 4 kPa it was found that increasing mesh refinement did not lead to a monotonic convergence of the outflow numerical prediction for both linear and linear upwind discretization schemes. The discretization uncertainty for Mesh 1 is then majored by the maximum difference between predictions for both methods. The uncertainties associated to the iterative error were negligible when compared to the discretization error, thus the numerical prediction uncertainty for the above mentioned pressure drop condition was found to be 2.4% and 2.2% for the upwind and linear upwind schemes respectively. The set of results for each mesh showed good agreement with experimental results, as the corresponding numerical flow rate vs. pressure drop curve exhibited a similar slope to that of the experimental one. However, the simulations under-predicted the head loss, i.e. the device's internal resistance, resulting in comparison errors, $E$, of 6.7%, 8.6% and 6.3% for the 3, 4, and 5 kPa pressure drop levels respectively. As a result, the modeling error is estimated to be between 4.3% and 9%. On this note, should future work require a lower modeling error, then a transition model should be included in the mathematical model as opposed to allowing the SST $k$-$\omega$ turbulence model deal with transition on its own accord. On the other hand, should it require a more precise estimate of the modeling error, i.e. a narrower interval $[\delta_{\text{model,min}}, \delta_{\text{model,max}}]$, future studies could include second-order accurate discretization schemes in space and time. Additionally, investing in a multi-block structured mesh generator (e.g. GridPro) could sharply increase mesh quality and consequently the accuracy of numerical predictions.

These simulations also uncovered the flow patterns behind the fluidization, powder deaggregation
and dispersion mechanisms. Two nearly independent sub-flows were identified, one consisting of a jet inside the powder compartment which provides fluidizing power and a second comprising a high turbulent mixing zone formed by the frontal collision of two pairs of jets that deaggregate and disperse the powder. The maximum flow field velocity predicted at each pressure drop level reached Mach numbers near the upper limit of the incompressible flow regime \((M = 0, 3)\). Potential compressibility effects could be investigated by carrying out a similar study which accounts for air compressibility.

With the information acquired from the steady-state stage a transient test case, and by applying a time-dependent pressure boundary condition, representative of patient inspiratory effort, was simulated. Further insight on the actual development of the flow patterns could be gained by applying a pressure boundary condition derived from a real patient inspiratory effort profile such as the ones presented in the work of Chapman et al. (2011).

Finally, a purely qualitative comparison is made between time frames of a high speed film featuring a drug filled TwinCaps® powder compartment and the transient simulation with massless spherical particles placed as a post-processing task. As the real flow inside the powder compartment is a dense particle flow, no conclusions can be drawn from this comparison besides the tendency of the particles to be lifted towards one of the sides of the compartment observed in both real and simulated flows. To gain understanding on particle trajectory, their collision with the device’s inner walls and other particles a CFD-DEM study, using OpenFOAM®’s DPMFoam solver for instance, should be undertaken.


Bijl, H. and P. Wesseling (1996), A numerical method for the computation of compressible flows with low Mach number regions.


Villax, P., I. G. McDerment, and M. Bunce (2012), Simple Inhaler.


Appendix A

(a) $t = 0.004\text{s}$  (b) $t = 0.005\text{s}$  (c) $t = 0.006\text{s}$  (d) $t = 0.007\text{s}$  (e) $t = 0.008\text{s}$

(f) $t = 0.009\text{s}$  (g) $t = 0.010\text{s}$  (h) $t = 0.011\text{s}$  (i) $t = 0.012\text{s}$  (j) $t = 0.013\text{s}$

(k) $t = 0.014\text{s}$  (l) $t = 0.015\text{s}$  (m) $t = 0.016\text{s}$  (n) $t = 0.017\text{s}$  (o) $t = 0.018\text{s}$
Figure A.0: High speed filming frames of the TwinCaps® powder compartment.
Figure A.0: Fluidization of a massless particle bed in a transient simulation
Appendix B

Figure B.1: Powder compartment flow streamlines in the: a), b), c) and d) Z mid-plane and e), f), g) and h) X mid-plane at the first four time steps
Figure B.2: Powder compartment flow streamlines in the: a), b), c) and d) Z mid-plane and e), f), g) and h) X mid-plane at several time steps.