STOCHASTIC TRACKING AND DEPOSITION OF PARTICLES INSIDE A COMPLEX GEOMETRY

Pedro J. Mendes†*, João F. Pinto† and João M. M. Sousa*

* Departamento de Engenharia Mecânica, Instituto Superior Técnico,
Av. Rovisco Pais 1049-001 Lisboa, Portugal
e-mail: pjmendes@navier.ist.utl.pt, msousa@alfa.ist.utl.pt

† Departamento de Tecnologia Farmacêutica, Faculdade de Farmácia de Lisboa
Av. Prof. Gama Pinto 1649-003 Lisboa, Portugal
e-mail: pjmendes@ff.ul.pt, jfpinto@ff.ul.pt

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Abstract. The development of new medicines for inhalation requires a series of procedures including in-vitro tests using special testing devices, which simulate the human airways to assess the local deposition of drugs. Such tests require samples of the new drugs and the series of tests are costly and time-consuming. A numerical model for the two-phase flow inside the first chamber of one of these special devices, the Twin Impinger (TI), has been developed. Due to the effects of drag, gravity and virtual mass forces, computer-generated particles travel through the virtual TI, which was discretised using a structured mesh. An Eulerian model has been used to simulate the continuous phase and a Lagrangian stochastic eddy-interaction model (EIM) has been chosen to simulate the behaviour of the discrete phase. Aiming to reduce the uncertainty associated to turbulence modelling of the continuous phase in a complex flow, detailed experimental data has been taken for the mean and turbulent air velocity fields. These data have been obtained by the use of a 2D Laser Doppler Anemometer, employing the continuity concept to generate the third velocity component. The interaction between particles was not considered because it was supposed that the particles were already dispersed enough inside the TI. Finding the Eulerian control volume where the particle was after each Lagrangian time-step was attained in a circular search around the previous particle position, in preferential directions, for the closest mesh node. The Eulerian cell values for the mean and turbulent velocity fields were assumed everywhere except near the wall, where the gradients are larger, and corrections in both the flow model and the EIM were required. The interaction between the particles and the walls of the TI considered a coefficient of restitution depending on the angle of impact of the particles, which were considered adhered if their kinetic energy after impact was not sufficient to compensate the van der Waals forces between the wall and the particle. A simple procedure to compute the distance between the particle and the near-wall velocity led to preferential deposition in lines orientated along the mesh, and the formation of unphysical particle clusters. Major improvements to the global model performance were obtained by the use of near-wall corrections in the EIM and employing a more elaborate algorithm for the wall distance. However, these changes increased the computational cost of the numerical simulations.
1 INTRODUCTION

Delivery of drugs to the lungs as an aerosol is regarded as an excellent route for local or systemic delivery of drugs due to the high efficacy and acceptability by both patients and physicians. Aerosols have been used traditionally on the treatment of illnesses of the lungs and the respiratory tract, such as asthma, and most recently the pulmonary route has been chosen for the administration of proteins as well. For example, insulin is the latest protein to be delivered by an aerosol.

Often, the design of new drug formulations and inhaler devices must be assisted by a series of in-vitro tests. In order to assess the quality of the aerosols, samples containing the drug are produced and evaluated in testing devices such as cascade impactors (e.g. Andersen multi-stage impactor), or multistage liquid impingers (e.g. Twin Impinger, TI). These devices are designed to simulate the movement and location of deposition of particles in the respiratory tract and their use is compulsory once the design, production and evaluation of an aerosol are considered. Correlations between the locations of drug deposition in the devices with their counterparts in the respiratory tract, and the size of particles, are thus established.

Unfortunately these tests are costly and time-consuming. Furthermore, the concept is rather empirical and predictions are difficult to carry out. Thus, alternative methods to evaluate the performance of aerosolised medicines, together with mathematical models to predict the deposition pattern of the particles of an aerosol are of most interest.

By the application of such models to devices, such as the TI, it is possible to a) characterise and understand the fluid flow within the device and b) predict the particles’ flow (either a liquid or a solid in air). Once these goals are reached, the process of designing drug particles and devices is expected to become easier and less empirical.

In order to develop numerical models for an equipment as the TI it is necessary to considerer a curvilinear coordinate system adjusted to the equipment, and the complexity of the device geometry requires the discretisation into an irregular mesh using Eulerian control volumes with various dimensions. On the other hand, the complexity of the flow pattern in these devices requires the application of complex mathematical models. For this reason and to minimize the uncertainty associated with the prediction of a complex recirculating, turbulent flow, the direct measurement of the flow inside the device seems to be a better approach than the use of computational models to predict the behaviour of the continuous phase. These measurements can be carried out by several techniques, namely Laser Doppler Anemometry (LDA), Particle Image Velocimetry or Hot-wire Anemometry. The use of an optical technique (e.g. LDA) is preferable because it does not require physical contact with the flow.

The aim of the present work is the development and evaluation of a computer model to predict the trajectory, mass fluxes and deposition of particles from a Dry Powder Inhaler in a TI, using LDA data to characterise the continuous phase in the flow.

2 METHODOLOGY

The mean and the turbulent fields inside a TI (Figure 1) were measured employing a two-component Laser Doppler Anemometry (LDA) system (DANTEC, DK) operating in
backward-scatter mode. Due to the fact that the TI is made in DURAN® glass (refractive index $n = 1.47$) and its pieces display a complex geometry with high curvatures, a procedure for refractive index matching in the course of the measurements was required. Ideally, the TI should have been submerged into a liquid showing a refractive index $n$ very close to the one corresponding to the DURAN® glass. Subsequently, in order to achieve dynamic similarity with the air flow case, the same value of the Reynolds number must be prescribed. However, usable fluids characterized by the demanded value of $n$ (e.g. oils) usually display high viscosity, leading to the requirement of high pumping power, which in turn leads to significant heat generation and, thus, stability problems. A compromise was found by using water as working fluid ($n = 1.34$). Nylon particles ($5 \mu m \pm 1.5 \mu m$ in diameter and density of $1.02 \text{ g/cm}^3$) were used as seeding in the LDA measurements. LDA measurements were carried out at 1011 locations. Mean and turbulent quantities were obtained using ensemble averages of about 5000 particles at each location.

A numerical stochastic model of the two-phase flow inside the first chamber of the first stage of the TI was developed to determine the trajectories of the particles and their locations of deposition in the chamber, based on the results of the LDA measurements for the continuous phase. This model is based on a mesh with $32 \times 32 \times 70$ nodes in $i$, $j$ and $k$ directions, respectively (Figure 2). The mean flow velocity and the kinetic turbulent energy in each one of the nodes of the mesh were obtained by interpolation of the results from the LDA measurements. The third component of the velocity has been derived from the equation of continuity, as explained in detail by Sousa\textsuperscript{4}.

For the continuous phase and for the discrete phase, Eulerian and Lagrangian models were used, respectively. Namely, a Lagrangian stochastic eddy-interaction model (EIM) has been employed to simulate the behaviour of the discrete phase\textsuperscript{5}, where the characteristic length,
time and velocity scales of turbulent eddies were estimated according to $k$-$\varepsilon$ turbulence modelling.

![Planar representation of the numerical mesh used to simulate the chamber under the study: a) side view (control plane shown in red); b) view of the plane $k=1$](image)

The simulated particles move inside the numerical model of the TI due to inertial, drag, gravitational and virtual (added) mass forces, according to the following expression:

$$\frac{d\vec{V}}{dt} \left( 1 + \frac{\rho_f}{2 \rho_p} \right) = \frac{3 \rho_f}{4 D_p \rho_p} C_D \left( \vec{U} - \vec{V} \right) + \ddot{g} ,$$

where $\vec{V}$ is the velocity of the particle, $\vec{U}$ the velocity of the fluid, $t$ is time, $C_D$ is the drag coefficient, $D_p$ is the diameter of the particle, $\rho_f$ and $\rho_p$ are the fluid and the particle’s densities, respectively, and $g$ is the gravity acceleration. Data for particles of lactose (density of 1.55 g/cm$^3$, diameter 5 µm ± 1 µm, normally distributed) were used in the model and samples with $15 \times 10^3$ particles were considered. Other forces such as Magnus, Saffman or Basset forces were not considered because their relative importance is much smaller than the other forces. In addition, it is assumed in the model that the dispersion of the particles is sufficient enough to avoid the interactions between them.

The impact of the particles to the walls of the TI was simulated according to a model that uses coefficients of restitution, and depends on the angle of impact. The particle is considered adhered to the wall when the value of the velocity of the particle, after impact, to which corresponds a value of the particles’ kinetic energy, is not sufficient to compensate the van der Waals forces.
where $V_{\text{min}}$ is the minimum velocity of the particles need to avoid adhesion, $A$ is the Hamaker constant (assumed here as $1 \times 10^{-20}$ J) and $Z_0$ is the separation distance between the particle and the wall (taken as $0.4 \times 10^{-9}$ m).

To find the Eulerian control volume where the particle was after each Lagrangian time step, a circular search around the previous position of the particle was carried out, in a preferential direction. Mesh nodes characterised by the same value of $k$ form plans where the search scheme is applied. According to the signal of the internal product of the two vectors, it is possible to find out in which side of the plane the particle is. The first of these two vectors is the vector defined from the closest node of the mesh to the particle in the previous Lagrangian time step and the actual position of the particle. The second vector is a vector that belongs to plane $k$ of the closest node of the mesh in the previous Lagrangian time step (defined by two nodes of the mesh in this plane). So, the search has only to be carried out on the side of the plane where the particle is. Figure 3 illustrates this procedure: $A$ is the node of the mesh closest to the particle in the previous Lagrangian time step, $P$ is the position of the particle, $B$ is another node with $k$ equal to $A$. In this case,

$$\overrightarrow{AP} \cdot \overrightarrow{AB} > 0,$$

thus $P$ is on the right side of the plane. If the internal product is negative, $P$ must to be on the left side of $k$. The distance between the nodes of the mesh close to the particle in both the Lagrangian time steps must be smaller than the distance between the actual position of the particle and the closest node of the mesh in the previous Lagrangian time step plus the distance between two consecutive nodes. It follows that by knowing the dimension of the boundaries of the control volumes it is possible to limit the search for the location of the particle. One value for $k$ was already defined, and by following this procedure, the other value for $k$ and two values for $i$ and $j$ are defined. Figure 4 shows $A$ as the closest node of the mesh to the particle in the previous Lagrangian time step, $B$ as the next node of the mesh and $P$ the actual position of the particle. In this case,

$$1 < \frac{\overrightarrow{AP}}{\overrightarrow{AB}} < 2,$$

so that the search considers the limit of two nodes from the location $A$ to both $D$ and $C$.

Searching for the closest node of the mesh, instead of searching for the centre of the Eulerian control volume, simplifies the calculation and saves time. Following this procedure, another mesh is virtually considered, in which the nodes of the first mesh are the centres of the Eulerian control volumes of the new mesh. The velocity considered for the fluid is the one

$$V_{\text{min}} = \sqrt{\frac{A}{\pi D_p^2 Z_0 \rho_p}},$$

(2)
of the node in the mesh closer to the particle. Only when the particle is close to the wall (namely within the three control volumes closer to the wall), the model verifies exactly in which Eulerian control volume the particle is, and checks if the particle is outside the virtual piece.

![Figure 3](image)

**Figure 3:** Schematic showing the side of the plane $k$ where the particle can be found

When a particle is not close to the walls of the simulated volume, it is considered that the gradients of the velocity of the fluid are small and the velocity is constant in each one of the Eulerian control volumes. For this reason, it is not necessary to determine exactly in which control volume the particle is. In regions close to the walls (on the Eulerian control volume that contain the external boundary), large gradients of the velocities are observed and therefore it is not acceptable to consider a piecewise-constant velocity. To simulate the flow in these regions two different approaches were tested, as follows:

a) In the first one, when a particle was located in these regions, the velocity of the fluid was calculated taking into consideration the distance between the particle and the point in the wall that was closer to the particle, and between the particle and the seventeen nodes around the closest node to the particle, using the velocities of each one of these points in an interpolation method. The weight of each point in the interpolation scheme depends on its inverse distance to the position of the particle. In this approach, the distance between the particle and the wall that was considered was the distance between the particle and the plane that contains the surface of the boundary of the Eulerian control volume where particle is.

b) In the second approach, the velocity of the air varies according to a near-wall law. As shown in Figure 5, the determination of the velocity of the fluid in the location of the particle
uses the point of the wall located closer to the particle and the point of interception of the line that simultaneously passes through the particle and through the point of the wall closer to the particle, counting the first surface of an Eulerian control volume from the wall. As this interception point is located between the four nodes of the surface from which it belongs, the velocity of the fluid in this point was determined by interpolation of the velocity using the four neighbouring nodes only. In the determination of the distance of the particle to the wall the model considers the Eulerian control volume where the particle is located and the eight Eulerian control volumes around it, searching for the shorter distance and verifying if the point belongs to the boundary.

Figure 5: Schematic representation of the determination of the second point to apply the near-wall law, P-position of the particle, A-closest point on the wall, B-second point to calculate the velocity of the fluid in the position of the particle, c and d-boundaries; bold lines define the limits of the Eulerian control volumes

The passage of the particles from the first to the second chambers of the TI (i.e. from the mouth to the trachea, in a clinical perspective) is critical to the success of the medicine. Thus in order to understand how particles move between the two chambers, a plane (control plane shown in Figure 2, red line) was defined. In order to validate the model, computational tests were carried out with computer-generated particles approximating the physical properties of Ventilan Rotacaps™ (GlaxoSmithKline) and the experimental results were compared with the predictions of the present model.

3 RESULTS

Results from the LDA measurements show the flow fields of mean velocity and turbulent kinetic energy. Figure 6a illustrates the mean velocity field and Figure 6b the turbulent field in the central plane of the first chamber of the first stage of the TI, after the three-dimensional reconstruction. These figures show a complex flow pattern with several recirculation and stagnation zones and different local turbulence intensities. Figure 7 shows the same data displayed in Figures 6 viewed from the top. The most distinctive characteristic of the flow is the presence of two large, counter-rotating vortices inside the chamber.
Figure 6: Flow in the central plane of the first chamber of the first stage of the TI:
(a) mean velocity and (b) turbulent kinetic energy

Figure 7: Top view of the flow in the first chamber of the first stage of the TI:
(a) mean velocity and (b) turbulent kinetic energy
Based on the particle tracking model proposed, Figure 8 shows a few examples of calculated trajectories for the particles described in the previous section. Although the sample considered to obtain the results shown in this figure was small (288 particles), and thus its statistical significance may be questionable, it is possible to realize that a large number of particles impact on the walls of the device, partially confirming the high loss known to occur in the respirable fraction (percentage of drug that reaches the second stage of the TI and has clinical effect) of Dry Powder Inhalers. The results for deposition, considering the complete set of $15\times10^3$ individual particles, are shown in Figures 9 and 10.

The particles that enter the first chamber of the first stage of the TI can be divided into two groups: the first one is related to the particles that adhere to the walls of the device and the second one to the particles moving on to the next chamber. Figures 9 and 10 show the distribution of particles (computer-generated) that have adhered to the walls of the device. Whereas Figure 9 shows the pattern of deposition obtained for the first approach described in the previous section, which considers a simpler calculation of near-wall velocities and wall distance, Figure 10 displays the pattern of deposition for the second approach. In both figures the largest concentrations of particles can be observed at the side zones located at the end of the inlet tube (A), on the wall at the opposing side of the entrance (B) and at the entrance of the exit tube (C). In Figures 9 and 10 (a and c) it is possible to see the footprint of the particles at the exit tube, in consequence of the secondary flow established in this tube, due to the two vortices inside the chamber (see Figure 7) and the change on flow direction. In Figure 9 it is possible to see that, in region (B), the particles are preferentially arranged along lines parallel to the mesh, while in Figure 10 this abnormal behaviour of the particles is no longer observed. The clusters seen in region (C) are also larger in Figure 9 than those observed in Figure 10.
Figure 9: Deposition of particles with a simple determination of near-wall flow velocity and wall distance:
a) side view, b) top view and c) front view

Figure 10: Deposition of particles with a more precise determination of near-wall flow velocity and wall
distance: a) side view, b) top view and c) front view
As a conclusion, the second methodology considered to calculate the distance between the particle and the wall and to determine the velocity of the fluid at the particle’s location produced more realistic results. This stems from the observation that the particles were distributed more randomly along the walls and the particle clusters formed show a more continuous distribution. An improvement in the uniformity of the particles’ deposition in the main regions of deposition, (A), (B) and (C) was obtained, but those regions remained the same for both cases. However a small increase in the number of deposited particles has been observed (from 35%, for the simple scheme, to 38%, with the more precise determination) and the time of calculation increased almost four times.

Employing the first approach for the calculation of the near-wall velocity, when a particle is traveling parallel to the wall, its distance to this element is constant, independently of the distance to a node. Therefore, the closer the particle is to the closest node, the more important is the first node from the wall in the direction of the node that is closer to the particle in the determination of the velocity of the fluid at the location of the particle. The importance of the other sixteen nodes does not vary much, because the distance of the particle to these points is almost constant. Hence, the calculated velocity of the flow in the position of the particle will show the smaller value when the particle is in the middle point between two modes. For this reason, such location is also the point where the velocity of the particle will be smaller, and the point where the particle will show a larger tendency to be deposited.

Figure 11 shows the trajectories of two particles close to the wall. These trajectories are circular and parallel to a circular surface, as occurring in the TI. While the trajectory of particle 1 is located in the interior of the circumference, particle 2 travels in the exterior. The point A of the surface is the closest point to particle 1 when this particle is at position $A_1$, and also the closest point to particle 2 when it is in position $A_2$. However, while the closest point to the simulated wall of the trajectory of particle 1 is point $A_1$, point $A_2$ is the farthest point to the simulated wall of the trajectory of particle 2. When particle 1 is in position $B_1$, the closest points in the wall are both points $B$ and $B'$. The points of the wall between $B$ and $C$ and between $C$ and $B'$ are never the closest points to particle 1. By the contrary, the points between $B$ and $C$ are the closest points to the trajectory of particle 2 between $B_2$ and $C_2$, and the points between $C$ and $B'$ are the closest points to this trajectory between $C_2'$ and $B_2'$. Moreover, it can be noted that point $C$ is the closest point to particle 2 when this particle is between $C_2$ and $C_2'$. 

![Figure 11: Examples of trajectories of particles close to the wall](image)
Using the first approach for the calculation of the near-wall velocity along a concave surface (particle 1 in Figure 11) the two above-referred effects will work together and the particles became deposited between the nodes (Figure 9). In a convex surface it is possible that equilibrium exists. Predominance of the first effect occurs with smaller distance between a node of the wall with its closest node outside the wall or larger areas of the surfaces (of the Eulerian control volumes), which belong to the boundary of the virtual piece. Predominance of the second effect occurs with large angles between the two surfaces of the boundary (the angle is measure from the interior). In this situation equilibrium does not occur and the particles adhere preferentially between the nodes, even when the angles between the particles are larger than $\pi$ rad, leading to the formation of unphysical clusters in region (C) of Figure 9. Along a plane surface the second effect does not take place and the adhesion of the particles occurs preferentially in between the nodes of the mesh.

Using the second approach, particle 1 (Figure 11) will be affected by slower fluid in point A1. This occurs for particle 2 between C2 and C2’, and for a longer period. Particle 1 will be affected by faster fluid in point B1, and particle 2 in point A2. As a result, the velocity of the particles will be smaller or larger, respectively, in each one of these points. Therefore, along a concave surface, the particle will show the same tendency not to deposit very close to the nodes or to the lines that separate the Eulerian control volumes, and in a convex surface the particles form clusters in this points or closes to it. These effects increase with the increment of the angle between the surfaces. Along a plane surface these effects do not occur and a particle that travels parallel to the surface will not show the above-described mesh dependency for deposition. Using this approach the simulation of the flow is more realistic. As observed in the deposition results portrayed in Figure 10, the second approach led to a more realistic deposition of the particles in the walls of the TI. In region (B) the particles are more randomly distributed and in region (C) the clusters are less intense, so that the transition between these to other regions is smoother.

![Figure 12: Distribution of the particles’ mass flux across the control plane (shown in Figure 2)](image)
Regarding the particles that move on to the next chamber, Figure 12 shows the mass flux of the particles that cross the control plane (Figure 2). The areas in red reflect the zones at which the mass flux was higher, in contrast to the areas in dark blue showing the lowest fluxes through this plane. From these results, it can also be concluded that the crossing of particles is not symmetrical. Whereas the distribution of the mass flux in Y-direction is almost symmetrical as anticipated, the distribution in Z-direction shows that the concentration of particles crossing the plane is higher at side A than at side B (Figure 2). Naturally this mainly reflects the presence of the secondary flow inside the exit duct.

The analysis of the control tests used for validation of the present model show the distribution, by percentage, of the drug spread through the capsule shell, the device and the various chambers of the TI presented in Figure 13 (left column). If only the particles that left the Dry Powder Inhaler and were able to reach the TI are considered (Figure 13, right column), it is possible to recalculate the distribution in the different chambers. It follows that the fraction corresponding to the first chamber (the one predicted by the numerical model) is about 37%. Noting that the proposed numerical model takes only into consideration the first chamber, the agreement between this value and the predicted mass fraction (38%) gives good indications regarding the capabilities of the model to predict the fraction of particles deposited in the first chamber, as well as about their movement to the following chamber.

4 CONCLUSIONS

- A numerical model based on Lagrangian stochastic tracking of particles was developed to predict the movement and deposition of drug particles in a Twin Impinger. The model uses experimental data (LDA) to characterise the flow field of the continuous phase.

![Graph showing the distribution of the drug in different sites.]

Figure 13: Control tests for model validation: percentage of the drug in the different sites considered
The numerical model enabled the identification and quantification of the surfaces of impact and adhesion of particles to the walls of the Twin Impinger. Furthermore, the model identified the preferable pathways of the movement of the particles to the following chamber.

A more precise determination of the distance from the particles to the walls and an improved numerical scheme to simulate the near-wall flow led to the alleviation of the mesh dependency for the deposition pattern of the particles. Better agreement with control test results was obtained for this case. However, a nearly four-fold increase in computational time was also obtained.

The numerical predictions made by the model were validated by real measurement experiments, run according to the European Pharmacopoeia and thus demonstrating the capabilities of the proposed numerical model.

REFERENCES