Numerical Simulation of In-Vitro Dispersion and Deposition of Nanoparticles in Dry-Powder-Inhaler Aerosols

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Aerosol dispersion and deposition inside an idealized mouth-throat has been numerically simulated using a stochastic Lagrangian model accounting for Brownian motion and particle-wall interaction. Delivery of nanoparticles to the lungs is extremely difficult, mainly due to their low inertia, and for this reason they are often loaded into larger carrier particles. Bearing in mind the potentialities of nanoparticles in advanced drug delivery, a set of monodisperse particles with diameters in the nanosize range, as well as in the respirable and carrier ranges, were considered in the present simulations. Deposition patterns were obtained by tracking a total of 16,000 particles for each diameter. The results have shown that similar patterns were obtained in the mouth-throat for 400 nm particles and larger. A clear correspondence between secondary flow structures in the fluid and these deposition patterns was observed, demonstrating the role of the convective transport processes for this size range. In contrast, a much more uniform distribution of the particles adhering to the walls was noted for a size of 200 nm. It was also found that a very large amount of these particles (nearly 80%) is lost by deposition on the mouth-throat, thus recommending the use of larger carrier particles.

Keywords:

1. INTRODUCTION

Aerosols are widely recognized as an effective method for the delivery of therapeutic agents to the respiratory tract. Several devices are commonly used to meet this purpose, namely dry-powder-inhalers (DPIs), pressurized metered-dose-inhalers, and nebulizers. Although each class of devices presents unique strengths and weaknesses, DPIs are often referred to as more efficient and easy to use because they are typically formulated as single-phase, solid particle blends, and require little or no coordination of actuation and inhalation.

Local delivery of medication to the lungs is highly desirable in patients with specific pulmonary diseases including tuberculosis, still a leader killing disease in the world. However, inhaled particles must overcome a number of obstacles and defense mechanisms before reaching the deep lung. It is generally accepted that the size of particles targeted to this region must be contained within a certain diameter range in order that these may have the ability to pass through the mouth and throat, and penetrate the tracheobronchial tree. This is the so-called “respirable” or “fine particle” range, usually reported as corresponding to aerodynamic diameters between 1 and 5 \( \mu \text{m} \). Still, a major part of the particles successfully depositing in the upper bronchial area will be transported away from the lungs by mucociliary clearance. Particles reaching the deep lung also face other defense mechanisms, such as the alveolar macrophages and the enzymatic activity.

New drug-targeting strategies using nanoparticles for pulmonary delivery may be able to avoid mucociliary clearance and macrophage uptake, delivering drugs directly to the target tissue or target cells. Altogether, available studies have provided clear indications that drug particles engineered in the nanosize range may lead to enhanced bioavailability. However, the introduction of (solid) colloidal drug delivery systems has brought about additional analytical difficulties to an already complex subject as the physical behavior and the transport mechanisms...
of colloidal systems differ significantly from those found in classical aerosols, which are generally in the micrometer diameter range. For instance, due to their low inertia, nanoparticles essentially move by Brownian motion and settle very slowly, thus severely hindering an efficient lung deposition.\(^2\) However, it has been demonstrated that this task may be accomplished by loading nanoparticles (or other colloids) into larger carrier particles (or aggregates) via spray-drying.\(^5\)–\(^8\)–\(^10\)

The development of a dry powder aerosol delivery system involves powder production, formulation, dispersion, delivery and deposition of the aerosol particles. Although most of these stages have been traditionally based on empirical considerations, numerical simulations have recently proved to be a powerful and valuable tool in the field of particle engineering.\(^11\)–\(^13\) The performance of powder formulations has been considerably improved over the last decade and advanced computational modeling can further assist the engineering effort in the design of optimized drug particles.\(^7\) Due to the fact that each patient presents unique physiological characteristics and respiratory patterns, in-vitro studies emerge as a preliminary but systematic manner to contribute to the aforementioned objective.

In the present work, numerical simulations using a stochastic Lagrangian model have been employed to improve our understanding about the delivery of dry powder aerosols containing monodisperse nanoparticles. The dispersion and deposition of aerosols in the mouth-throat section of a glass twin-impinger\(^14\) was studied for particles within the nanosize, respirable, and carrier diameter ranges. The numerical model includes the effect of Brownian motion in which variances of random forces exerted on nanoparticles are identical to those on a single isolated particle, as given by the Langevin equation. Particle-wall interaction was carefully modeled and wall deposition accounted for van der Waals forces. Present and future developments of this numerical model are aimed at contributing to the compromise between optimization of the respirable fraction\(^15\) and minimization of the drug dose in order to avoid the toxicological hazards of inhaled nanoparticles.\(^16\)

Taking into account the forces of inertia, aerodynamic drag, gravity, buoyancy and virtual mass, the particle trajectory may be described by the following set of first-order ordinary differential equations:

\[
\frac{d\vec{X}}{dt} = \vec{V}
\]

\[
\frac{d\vec{V}}{dt} \left( 1 + \frac{1}{2} \frac{\rho_f}{\rho} \right) = F_D \left( \vec{U} - \vec{V} \right) + \vec{F}
\]

where \(\vec{X}\) is the particle position vector, \(\vec{V}\) and \(\vec{U}\) stand for the velocity vectors of the particle and the fluid, respectively, \(t\) is time, \(F_D\) is an aerodynamic drag force coefficient, \(\rho\) and \(\rho_f\) are the particle and fluid densities, respectively, and \(\vec{F}\) is a generic force per unit mass to bring the remaining body forces into the analysis. For particles characterized by a diameter \(d \geq 500\) nm, Brownian diffusion may be neglected, thus leading to:

\[
\vec{F} = \left( 1 - \frac{\rho_f}{\rho} \right) \vec{g}
\]

\[
F_D = \frac{3}{4} \frac{C_D}{d} \frac{\rho_f}{\rho}
\]

In Eqs. (3–4) \(\vec{g}\) stands for the gravitational acceleration and \(C_D\) is a drag coefficient calculated from:

\[
C_D = \max \left[ 0.44, \frac{24}{Re} \left( 1 + 0.15R_e^{0.687} \right) \right]
\]

where \(R_e\) denotes a relative Reynolds number calculated using the dynamic viscosity of the fluid \(\mu\), as follows:

\[
R_e = \frac{\rho d |\vec{U} - \vec{V}|}{\mu}
\]

Other forces such as Magnus, Saffman or Basset forces were not considered because their relative importance is expected to be much smaller than that of the previous ones. However, for particles characterized by a diameter \(d < 500\) nm, Brownian diffusion must be taken into account. In this case, the generic force \(\vec{F}\) and the aerodynamic drag force coefficient are alternatively expressed by:

\[
\vec{F} = \left( 1 - \frac{\rho_f}{\rho} \right) \vec{g} + \vec{\zeta} \left( \frac{216 \mu \sigma T}{\pi \rho \rho_f d^3 C_C \Delta t} \right)
\]

\[
F_D = \frac{18}{d} \frac{\rho_f}{C_C \rho}
\]

where \(T\) is the temperature, \(\sigma\) stands for the Boltzman constant and \(\vec{\zeta}\) denotes a pseudorandom vector.\(^11\) The amplitudes of the components of Brownian forces are thus computed at all time steps \(\Delta t\), during the calculation of the particle trajectory. In Eq. (8) \(C_C\) stands for the well-known Cunningham factor given by:

\[
C_C = 1 + \frac{2\lambda}{d} \left[ 1.257 + 0.4 \exp \left( -1.1 \frac{d}{2\lambda} \right) \right]
\]

where \(\lambda\) is the mean free path of fluid (gas) molecules.

**2. THEORETICAL AND NUMERICAL MODELLING**

**2.1. Particle Transport and Dispersion**

Due to the fact that the flow of the continuous phase in dry-powder-inhalers is usually turbulent, Lagrangian stochastic modeling based on an Eddy Interaction Model\(^17\) (EIM) was employed to simulate the transport and dispersion of aerosol particles. The mechanisms considered included particle inertia and convection, Brownian and turbulent diffusion, and gravitational settling.

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The numerical solution of Eqs. (1–2) was obtained iteratively via a modified version of the “regula falsi” method for the solution of the non-linear algebraic equation resulting from their discretization in time using a backward Euler method. A constant value of the fluctuating (turbulent) velocity component of the fluid was assumed in the EIM model within each (variable) time step \(\Delta t\), which was determined by the characteristic lifetime of eddies in the turbulent flow. These velocities were obtained by randomly sampling a Gaussian distribution with a standard deviation of \(\sqrt{2\kappa/3}\). In this model, each individual particle interacts successively with different turbulent eddies along its trajectory. Hence, the interaction time was calculated using an approach that relates eddy time and velocity scales via \(k - \varepsilon\) modelling.\(^{19}\) In the present case the dissipation rate \(\varepsilon\) of the turbulent kinetic energy \(k\) is estimated using the low-Reynolds-number model developed for wall boundary layers,\(^{19}\) as follows:

\[
\varepsilon = \frac{k^{1/2}}{l_e}
\]  
\[(10)\]

where \(l_e\) is a length scale characterizing the turbulent dissipation expressed by:

\[
l_e = \kappa C_{\mu}^{-3/4} D \left[ 1 - \exp(-0.261 Re_p) \right]
\]  
\[(11)\]

In Eq. (11) \(Re_p\) is a local Reynolds number based on the wall distance \(D\) and the turbulent eddie velocity scale \(\sqrt{\kappa}\), \(\kappa\) denotes the von Kármán constant and \(C_{\mu} = 0.09\). The characteristic length \(L_e\) and time \(T_e\) of the turbulent eddies is finally given by:

\[
L_e = \frac{C_{\mu}^{3/4} L^{3/2}}{\varepsilon}
\]  
\[(12)\]

\[
T_e = \frac{L_e}{\sqrt{2\kappa/3}}
\]  
\[(13)\]

The foregoing procedure must be applied on tracking of a statistically high number of particles so that the effects of turbulence may be stochastically accounted for. The present model for transport and dispersion of particles was validated against the experimental data available in the literature\(^{20,21}\) and good agreement has been obtained between numerical predictions and experiments.\(^{22}\)

### 2.2. Particle-Wall Interaction and Deposition

In the numerical modeling, the particles were assumed to be dispersed enough so that the interactions between them may be neglected, which is consistent with typical mass streams from dry-powder-inhalers. However, the interaction of the particles with walls is considered a key mechanism in the present study, namely the inelastic impact. This has been simulated employing a simple model based on the use of normal and tangential coefficients of restitution, which display a cubic dependence on the impact angle.\(^{23}\) Further, it is predicted that the particles will stay adhered to the wall when their kinetic energy after impact is not sufficient to compensate van der Waals forces.\(^{24}\) This may be translated in terms of a minimum particle velocity for escape, via energy balance, as follows:

\[
V_{\text{min}} = \sqrt{\frac{A}{\pi d^2 Z_0 \rho}}
\]  
\[(14)\]

where \(V_{\text{min}}\) is the minimum velocity of impacting particles required to avoid adhesion, \(A\) is the Hamaker constant (assumed here as \(1.15 \times 10^{-20}\) J) and \(Z_0\) is the separation distance between particle and wall (taken as \(0.4 \times 10^{-9}\) m). The effect of electrostatic forces may also be easily included in Eq. (14), but these were not currently considered due to the uncertainty associated to the electric properties and charges of the materials used in this study.

When a particle is moving far from the walls, it is assumed that the velocity gradients in the continuous phase are small. Consequently the fluid velocity may be taken as constant inside each mesh volume used in the discretization of the computational domain, thus not requiring an exact determination of the particle position within the volume. However, when a particle is moving in the vicinity of walls, say inside a mesh volume containing an external boundary, large velocities gradients are observed in the continuous phase and therefore it is no longer acceptable to assume a piecewise-constant evolution for the fluid velocity. In such areas, a near-wall law\(^{25}\) involving an inverse-distance weighted interpolation in the local velocity field was used instead.\(^{22}\)

### 3. RESULTS AND DISCUSSION

#### 3.1. Mouth-Throat Model

An idealized mouth-throat based on the geometry of the first chamber of a classical glass twin-impinger\(^{14}\) has been considered in this work. Figure 1 illustrates its geometrical details as well as the curvilinear, structured, numerical mesh used, formed by a total of \(32 \times 32 \times 70\) volumes.

An air flow rate of 60 liters/min was used, corresponding to standard operation conditions of the aforementioned impinger. The mean and turbulent flow fields inside the mouth-throat model for this condition have been experimentally characterized in detail in a previous study.\(^{26}\) Figures 2(a) and (b) portray the projection of the mean flow streamlines, respectively in a meridional and an equatorial plane of the spherical bulge in the model. It can be observed that part of the fluid establishes a recirculation on the top region of the bulge (meridional plane), and another part impinges on the wall surface facing the entrance section. The remaining fluid seems to be drawn directly through the exit section. However, the equatorial
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3.2. Dispersion and Deposition

Monodisperse spherical particles of different sizes (200 nm, 400 nm, 800 nm, 2 μm and 25 μm), but sharing the same density $\rho = 1.55 \text{ g cm}^{-3}$, have been considered in this investigation. The first two diameters are characteristic of submicron particles approaching the nanoscale, the next two values reach for the so-called respirable range of diameters usually desirable for drug particles, and the larger value of the set may be seen as a typical dimension often used for carrier particles. The micrograph in Figure 3 provides a practical example of a large carrier particle with small drug particles attached to it, with the aim of improving their transport efficiency in pulmonary delivery as previously discussed.

Deposition patterns were obtained by tracking a total of 16,000 particles, employing the stochastic Lagrangian model described in the previous section. These were released at the entrance of the mouth-throat, uniformly distributed on a cross-section equivalent to that of the mean flow pattern demonstrates that this portion of fluid forms two Dean vortices inside the spherical bulge, which are also associated to the establishment of a strong secondary flow across the vertical duct. The same figures further display the contours of turbulent kinetic energy $k$, showing that the maxima of turbulent fluctuations is well correlated with the location of strong vortical motion. These features are expected to significantly influence the behavior of aerosol particles as these are transported and dispersed by the air flow. However, such behavior also exhibits a strong dependence on particle size, with a particular emphasis when the nanoscale is approached, as will be discussed in the next subsection.

Fig. 1. Perspective view of the mouth-throat model and numerical mesh.

Fig. 2. Mean streamlines and turbulent kinetic energy contours in the fluid flow inside the mouth-throat model for an air flow rate of 60 liters/min: (a) meridional plane; (b) equatorial plane.

Fig. 3. Micrograph of a large carrier particle with small drug particles attached.
mouthpiece of a Rotahaler® (GlaxoSmithKline) dry-powder-inhaler. All particles were tracked until adhesion to the mouth-throat walls or exhaust through the exit section occurred and, in general, smaller diameters demanded larger computational times.13 Figures 4(a), (b) and (c) show the corresponding results for \( d = 200, 400 \) and \( 800 \) nm. The basic pattern obtained from the analysis of larger diameters did not differ significantly from that obtained for \( d = 800 \) nm, except for the fact that the number of adhered particles was reduced. In contradistinction, evident changes were observed for the smaller diameters. Whereas for \( d = 200 \) nm the deposition of particles on the mouth-throat surface is predominantly random (hence more uniform), displaying only a mild effect of the structures in the air flow, the computed patterns for \( d = 400 \) and \( 800 \) nm exhibit the increasing role of these structures in the process. This is in agreement with previously reported simulations of the deposition of 300 nm particles in a model of a human oropharynx. Although the number of adhered particles diminishes considerably from Figures 4(a to c) as a result of the four-fold increase in diameter, it can be seen that for \( d = 800 \) nm the deposition occurs mainly in the air flow impingement areas on the back and exit of the spherical bulge. In the latter region, the footprint left by the secondary flow associated to the previously mentioned vortex pair is clearly observable (both in Figs. 4(b and c)), thus providing new evidences of the correspondence between those flow structures and particle deposition sites.27

Naturally, as the number of particles lost by adhesion to the walls reduces, the amount of particles showing the ability of traveling further is increased. A quantitative assessment of the dependence of such behavior on particle size is presented in Figure 5 for the complete set. It can be observed that a continuous increase occurs from only about 20% for \( d = 200 \) nm to approximately 50% for \( d = 800 \) nm. Interestingly enough, the amount of particles escaping from the mouth-throat seems to stay nearly unchanged in the so-called respirable range. However, a dramatic increase is seen for large particles, namely for

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**Fig. 4.** Deposition patterns on the surface of the mouth-throat model for various particle diameters: (a) \( d = 200 \) nm; (b) \( d = 400 \) nm; (c) \( d = 800 \) nm. Particles are not to scale.

**Fig. 5.** Effect of particle size on the ability of the particles to escape adhesion to the mouth-throat model.
As expected, the efficiency of the transport of aerosol particles by the air flow becomes too small for nanoparticles, thus recommending the use of larger carrier particles.6

It is also relevant to analyze how the particles abandoning the mouth-throat model are distributed across the outlet section. This may be appreciated in Figure 6 for \(d = 25 \mu m\). The resulting pattern for \(d = 2 \mu m\) does not differ much from that obtained for the smaller diameters, except for the density of particles. Consequently, it may be concluded that up to the so-called respirable range the particles leave the mouth-throat predominantly distributed across a broad central region, with its center slightly displaced towards the back surface (Figs. 6(a, b and c)). This observation is consistent with the thought that many of these particles are approximately following the fluid paths. The foregoing behavior would not be expected from large particles, such as those characterized by \(d = 25 \mu m\). In fact, the particles seen in Figure 6(d) are mostly located in the vicinity of the opposite surface, probably as a result of particle rebound on the back surface. However, the majority of these large particles are dragged by the air flow along the walls of the outlet section, avoiding adhesion only because of their size. It must also be noted that this situation might be radically changed if a mucosal surface was considered instead. In this case, the latter particles would most likely be trapped in a surface displaying such characteristics.

4. CONCLUSIONS

A numerical method using a stochastic Lagrangian model has been developed for the prediction of in-vitro dispersion and deposition of aerosol particles. The method was applied to study the behavior of monodisperse particles inside an idealized mouth-throat operating at a constant air flow rate of 60 liters/min. Particles within the nanosize, respirable and carrier diameter ranges have been considered in the analysis. Deposition patterns were obtained by tracking a total of 16,000 particles for each diameter. The principal findings of this work may be summarized as follows:

1. In general, smaller particles demanded larger computational times, mainly as a result of slower settling;
2. Similar deposition patterns were obtained for particles characterized by \(d = 400 \text{ nm}\) and larger, though the amount of particles adhered to the walls varied;
3. These patterns exhibited a clear correspondence with the large-scale flow structures, namely those associated to secondary flow;
4. A much more uniform deposition pattern was obtained for particles characterized by \(d = 200 \text{ nm}\), mainly as a consequence of Brownian diffusion becoming the prevalent mechanism;
5. A continuous decrease of the amount of particles lost by adhesion in the mouth-throat was observed from about 80% for \(d = 200 \text{ nm}\) to approximately 50% for both \(d = 800 \text{ nm}\) and \(d = 2 \mu m\), followed by a sharp decrease when the diameter was increased to \(d = 25 \mu m\).
6. However, in the outlet section of the mouth-throat the majority of these large particles were dragged along the walls, whereas the smaller particles were mainly transported in the central region.
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References and Notes


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