Alveolar Airflow and Pulmonary Drug Delivery COMSOL model for Normal and COPD alveolus

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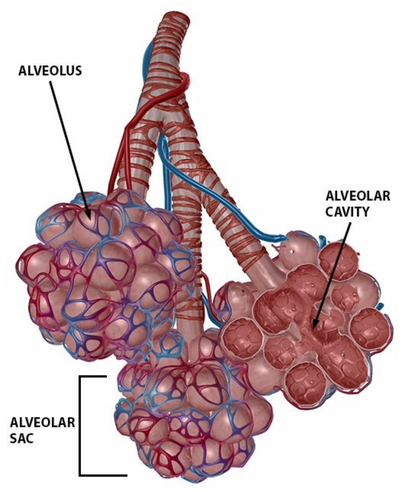
Introduction

Inhaled aerosol drug delivery is an integral component in the treatment of Chronic Obstructive Pulmonary Disease (COPD). Treatment of COPD is accomplished by administering medications directly into the airways that reverse symptoms of the disease. Inhaled drug delivery is currently the most effective method for treating COPD because when inhaled, the medication is delivered directly into the airways and less medication is absorbed by the blood stream.



This project investigated the behavior of air and drug particles in the alveoli. The objective of the project was to **develop a COMSOL model for alveolar airflow and pulmonary drug delivery under the influence of rhythmic alveolar wall expansion and contraction.** The alveoli are small, balloon shaped airways found in clusters at the end of bronchioles where gaseous exchange occurs (Figure 1). COPD causes the destruction of the alveoli leading to the formation of air pockets in the lung. The air pockets (bullae) reduce gaseous exchange as the alveoli permanently loses its ability to inflate and deflate.

Figure 1: Structure of Alveoli

Hypothesis

Drug deposition in the lungs is a function of particle size, shape, density, anatomy of the lungs and breathing parameters such as airflow and inhaled volume.

- Particles with a smaller radius and mass will have maximal deposition for all three models considered compared to particles with a larger radius and mass.
- Damaged alveoli will have reduced airflow and particle deposition.
- Alveolar air pressure is inversely proportional to the velocity.

Materials and Methods

Using COMSOL, an axisymmetric, laminar, steady-state, stationary, 2D model with Newtonian fluid of the alveolus was developed. The baseline geometry consists of a cylindrical tube (alveolar duct) connected to a sphere (alveolus) (Figure 2). The model was constructed using an extra fine mesh for more accurate results. To simulate the permeability of the alveoli as well as their contraction and expansion, the circumferential wall of the sphere was created using a leaking wall boundary condition with r and z spatial velocity components. The velocity of the inhaled air was calculated from average literature values of the tidal volume, total minute volume, and inhaled air flow rate of the alveoli. The walls of the cylindrical tube had a no slip boundary condition while the open end of the cylindrical tube was defined as the inlet with zero pressure. The universal model parameters were defined (table 1). The particle deposition was investigated in 3 alveolar models with varying physical complexities. Water particles of different radii and mass were introduced into the model to investigate the behavior of drug particles with different properties in the alveoli.

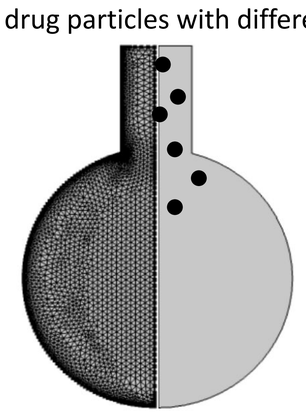


Table 1: Model Universal Parameters

Name	Expression	Value	Description
Rho	0.0012[g/cm^3]	1.2 kg/m^3	Air Density
RhoP	1[g/cm^3]	1000 kg/m^3	Aerosol Density
RT	0.025[mm]	2.5x10^{-5}m	Tube Radius
LT	0.05[mm]	5x10^{-5}m	Tube Length
RB	0.05[mm]	5x10^{-5}m	Ball Radius
Mu	1.8x10^{-4}[g/cm*s]	1.8x10^{-5}kg/(m*s)	Air Viscosity
MuP	0.01[g/cm*s]	1000kg/(m*s)	Aerosol Viscosity

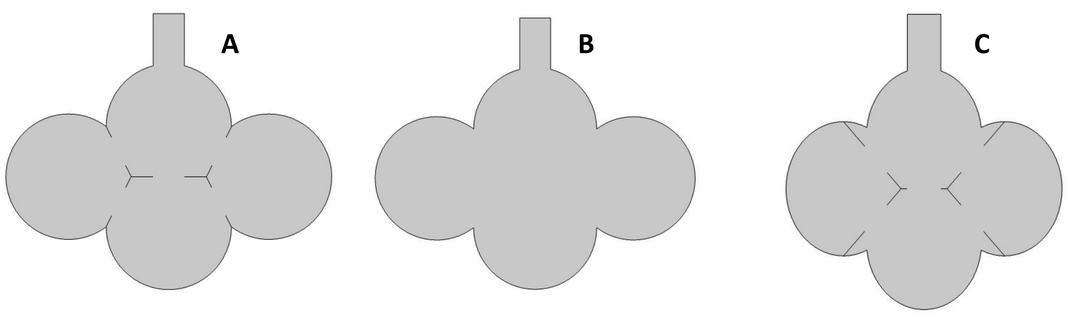


Figure 2: Model Formulation: Model A show the geometry of a healthy, normal alveoli. Model B and C show two variations of damaged alveoli i.e ruptured walls (A) and deflated walls (B).

Navier-Stokes equations

Continuity

$$\frac{\partial \rho}{\partial t}+\frac{\partial(\rho v_x)}{\partial x}+\frac{\partial(\rho v_y)}{\partial y}+\frac{\partial(\rho v_z)}{\partial z}=0$$

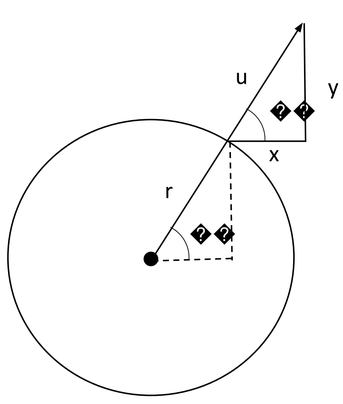
x − momentum

$$\rho\frac{\partial v_x}{\partial t}+\rho\left[v_x\frac{\partial v_x}{\partial x}+v_y\frac{\partial v_x}{\partial y}+v_z\frac{\partial v_x}{\partial z}\right]=-\frac{\partial P}{\partial x}+\mu\left[\frac{\partial^2 v_x}{\partial x^2}+\frac{\partial^2 v_x}{\partial y^2}+\frac{\partial^2 v_x}{\partial z^2}\right]+\rho g_x$$

y − momentum

$$\rho\frac{\partial v_y}{\partial t}+\rho\left[v_x\frac{\partial v_y}{\partial x}+v_y\frac{\partial v_y}{\partial y}+v_z\frac{\partial v_y}{\partial z}\right]=-\frac{\partial P}{\partial y}+\mu\left[\frac{\partial^2 v_y}{\partial x^2}+\frac{\partial^2 v_y}{\partial y^2}+\frac{\partial^2 v_y}{\partial z^2}\right]+\rho g_y$$

$$-\frac{\partial P}{\partial y}+\mu\left[\frac{\partial^2 v_y}{\partial x^2}\right]=0 \qquad -\frac{\partial P}{\partial x}\cdot=0$$



Reynold's Number Calculation

$$Re = \frac{\rho u D}{\mu}$$

The calculated Re = 1.768x10^{-4}

Re ≪ 2000 ⟶ Laminar flow

Fluid flow

$$u = \frac{Q}{N 4\pi r^2}$$

The calculated u = 5.305x10^{-5} m/s

Q = average air flow rate, N = 600 million alveoli

Results

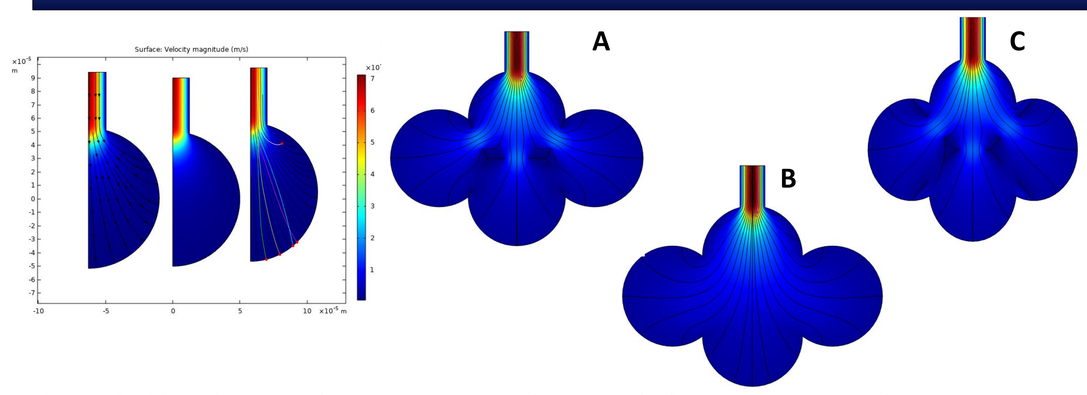


Figure 3: Velocity magnitude and streamline of fluid in a normal alveoli (A), ruptured alveoli (B), and deflated alveoli (C).

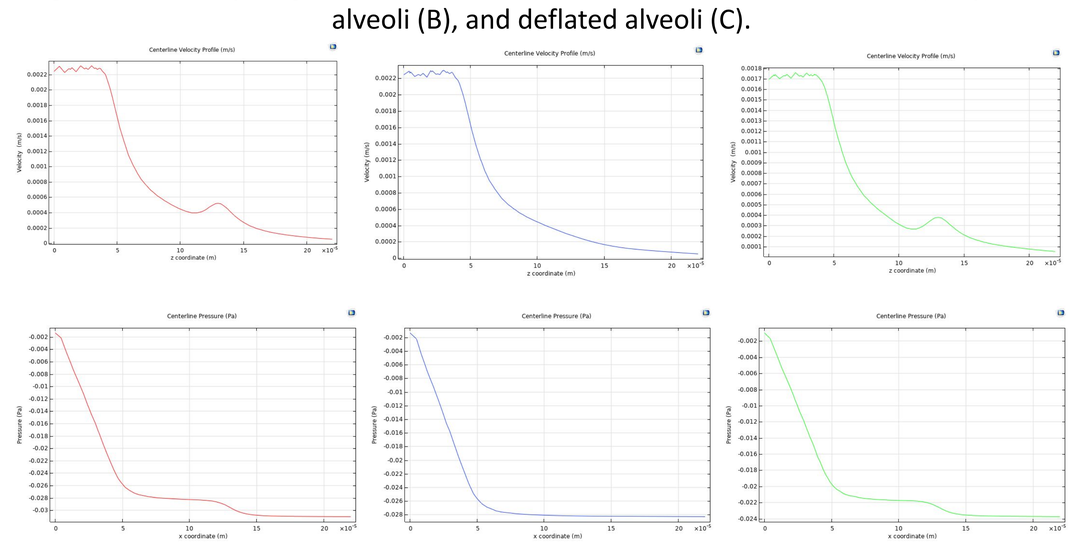


Figure 4: Centerline velocity and pressure profile for normal alveoli (A), ruptured alveoli (B), and deflated alveoli (C).

The direction of airflow in the alveoli changed depending on whether that alveoli was expanding or contracting. During expansion, particles were forced into the alveoli and during contraction, particles were forced out of the alveoli. Particles with masses ranging from 4*10^-15 kg to 2*10^12 kg had different trajectories in the alveoli. Particles with a smaller mass closely followed the streamline of air in the alveoli while particles with a larger mass were randomly distributed in the alveoli. In a normal alveoli, the velocity of air slightly increased as the fluid moved from one alveoli to another. In a ruptured alveoli, the velocity of the air decreased throughout the entire alveoli. The deflated alveoli had the lowest fluid velocity compared to the normal and ruptured alveoli. The general observed trend in all the alveoli was a decrease in pressure and an increase in velocity as pressure decreased.

Conclusions and Discussion

Smaller particles have higher deposition and more efficient delivery in the alveoli because they are able to easily follow the movement of air in the alveoli while larger particles have lower deposition. Although the velocity and pressure of air in the alveoli generally decreases, the pressure is inversely proportional to the velocity as expected. Damaged alveoli have less particle deposition due to reduced air flow and surface area. The results from this study support our initial hypothesis.

Limitations and Applications

For simple computation, the model was developed in 2D. However, for further research, the model should be developed in 3D so as to obtain results than closely represent the actual structure of the alveoli. This model was developed neglecting the effects of other gases such as carbon dioxide and oxygen found in the alveoli because it was outside the scope of this project. The effects of the surfactant, a substance secreted by cuboidal cells within the membrane of the alveolar epithelium was neglected as well. To simplify the model calculations, the effects of gravity were ignored. The model was computed for 4 alveoli but the human lungs contains 600 million alveoli. To model all 600 million alveoli is a tedious task but would be a more reliable evaluation of air flow and drug delivery in the alveoli. The model geometry consists of a tube of diameter 5x10^{-5}m and length 5x10^{-5}m. Based on literature values, an actual alveolar duct has a diameter of 5x10^{-4}m and a length of 1.17x10^{-3}m.The model used a tube radius reduced by a factor of 10 so that the desired shape of the alveoli could be retained. A time depended model would provide more accurate information about the fluid volume and flow rate with respect to time.

Inhalation drug delivery offers exciting potential to enhance the targeting, release, diagnostic, and therapeutic outcomes for medication. The lungs provide provides many advantages over other sites of drug delivery because they provide non-invasive delivery, a large surface area for absorption, quick therapeutic onset and avoid metabolism. With better understanding of drug delivery in the alveoli, pulmonary drug delivery can be adopted for treating other diseases such as Tuberculosis, Alzheimer's, and other non pulmonary diseases.

References

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