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Use of Ultrasonic Radiation Torque to Align High Aspect Ratio Particles for Targeted Pulmonary Drug Delivery

Stacey Yuen[1‡], Warren H. Finlay[1] ([1]Univ. of Alberta)

1. Introduction

Inhaled pharmaceutical aerosols (IPAs) are an effective and fast-acting form of drug delivery due to the physiological properties of the peripheral airways and alveoli. While IPAs are most commonly known for the treatment of asthma and chronic obstructive pulmonary disease, they have more recently been explored as a form of drug delivery for antibiotics to treat lung infections and chemotherapeutic agents to treat lung cancers. In particular, due to the toxic effects of chemotherapeutic agents and the localized nature of lung cancer, it is desirable to reduce harmful side effects to healthy lung tissue and to be able to target affected areas of the lung for improved drug deposition.

In comparison to spherical aerosol particles, high aspect ratio particles (HARPs) demonstrate better penetration through the upper airways of the lung due to their aerodynamic properties and improved deposition by interception in smaller, peripheral airways [1)]. However, deposition by interception of particle tips with airway walls is dictated by the orientation of the elongated particles, which predominantly align aerodynamically with the long axis parallel with the direction of flow [2)].

Noting that the airways of the lung are randomly oriented, HARPs that are uniformly aligned with an external field may also be described as randomly oriented with respect to the airways of the lung. This increases the probability of deposition by means of particle tip – airway wall interceptions. Previously, enhanced deposition has been achieved by loading ellipsoidal particles with paramagnetic nanoparticles and controlling particle orientation with the application of an external magnetic field [3)]. To eliminate the need for magnetically active particles, the present work explores the use of an ultrasound field in place of a magnetic field.

2. Aerodynamic Torque and Ultrasonic Radiation Torque

To achieve particle alignment with an external ultrasound field, the exerted ultrasonic radiation torque must be sufficient to overcome the aerodynamic torque exerted on elongated particles in a shear flow. An ellipsoidal particle in shear flow has it's greatest angular velocity when the major axis of the particle is perpendicular to the direction of fluid flow, and it's lowest angular velocity when the particle is parallel with the fluid flow [4)]. Thus, it may be interpreted that the aerodynamic torque on an ellipsoidal particle predominantly acts to orient the long axis of the particle to be parallel with the streamlines of fluid flow as shown in **Fig. 1**. Conversely, the ultrasonic radiation torque exerted on an ellipsoidal particle in an ultrasound field acts to align the long axis of the particle to be perpendicular to the direction of the sound waves as shown in **Fig. 2** [5)]. That is, if the fluid flow and ultrasound waves are travelling along the same axis, the aerodynamic torque and ultrasonic radiation torque compete to align a particle in perpendicular orientations.

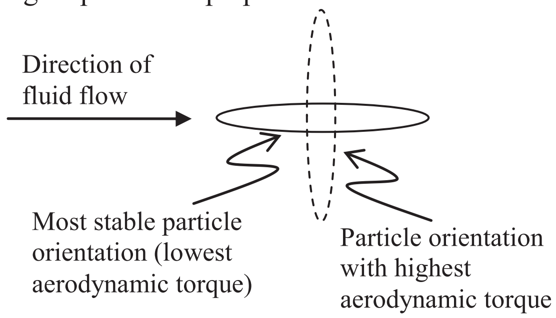

Fig. 1 Principal orientations of an ellipsoidal particle in laminar fluid flow.

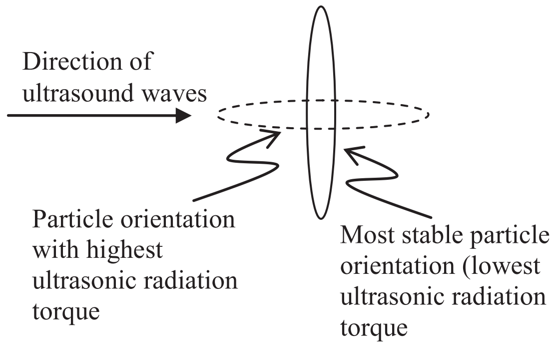

Fig. 2 Principal orientations of an ellipsoidal particle in an ultrasound field.

The aerodynamic torque on ellipsoidal particles is calculated as a function of the average fluid velocity gradient, particle geometry, and particle orientation θ (angle between major axis of particle and direction of fluid flow) [4]. Given a typical inhalation flow rate of 18 l/min. and assuming Poiseuille flow, a typical average velocity gradient in the peripheral airways of the lung is found to be 548 s^{-1} [6,7]. The dotted line in **Fig. 3** shows the aerodynamic torque for θ=π/2 (maximum torque) plotted as a function of particle aspect ratio (length/diameter).

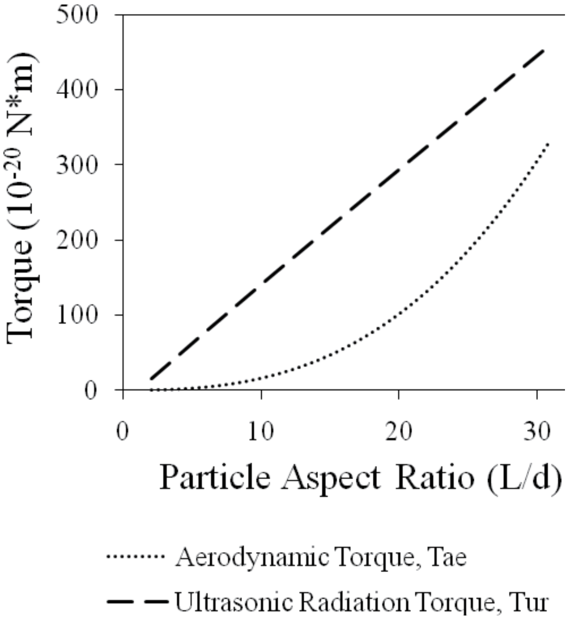

Fig. 3 Torque plotted as a function of particle aspect ratio.

An object in an ultrasound field experiences a radiation force as a result of the changes in energy density which is characteristic of acoustic fields [8]. Non-spherical objects, such as ellipsoids, also experience an ultrasonic radiation torque. This study focuses on the ultrasonic radiation torque caused by plane progressive ultrasound waves on ellipsoidal particles suspended in air as was first calculated by König [5]. The ultrasonic radiation torque on an ellipsoid is dependent on the following parameters: ultrasound intensity, ultrasound frequency, particle diameter and length (and aspect ratio), particle material properties, and fluid properties. The ultrasonic radiation torque is compared to the aerodynamic torque to determine ranges for the aforementioned variables such that the particles align in accordance with the acoustic field. The dashed line in Fig. 3 represents the ultrasonic radiation torque plotted as a function of the particle aspect ratio for an ultrasound intensity of 0.5 W/cm^2, while **Fig. 4** shows the ratio of ultrasonic radiation torque to aerodynamic torque plotted as a function of particle aspect ratio. Since the ultrasonic torque exceeds the aeroodynamic torque by a large factor for certain aspet ratios, this demonstrates the capacity for ultrasound to be used as a technique to align HARPS with an external field and to enhance their deposition in the lung.

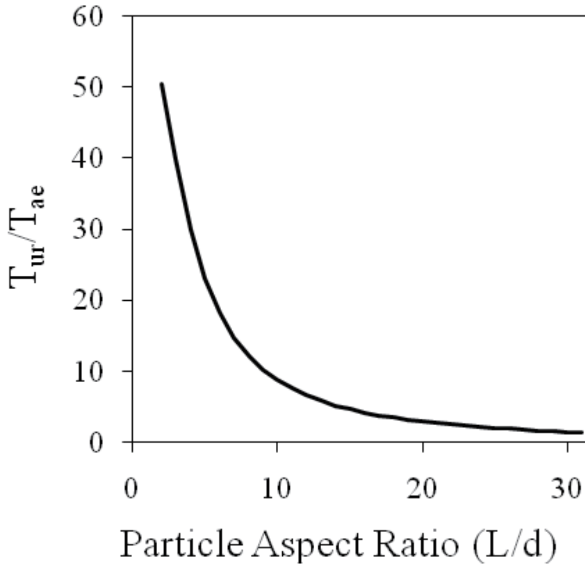

Fig. 4 Ratio of ultrasonic radiation torque to aerodynamic torque for various particle aspect ratios.

3. Experimental Work

Experiments being performed utilize a flow apparatus designed to direct the fluid flow and ultrasound field along the same axis such that the aerodynamic torque and ultrasonic radiation torque compete to align a particle in perpendicular orientations. Shadowgraphy will be employed to visualize particle orientations in the absence and presence of varying ultrasound fields. This experimental study is in progress to further validate the theoretical work discussed here.

Acknowledgment

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