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Magnetic targeting of aerosol particles for cancer therapy

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Abstract

An in vitro model was developed to study and demonstrate the potential and feasibility of magnetically targeted deposition of aerosols for potential applications in lung cancer treatment. Also, a numerical particle tracing model was developed to predict the targeting behavior of the in vitro system; the results from the numerical and experimental studies were in agreement.

Keywords: Magnetic drug targeting; Aerosol drug delivery; Magnetic separation; Lung cancer; Bronchial drug delivery; Model for lung therapy; Simulation; Aerosol distribution; Carbonyl iron particles

1. Introduction

In this study, an in vitro methodology is used to examine the feasibility of targeted delivery of chemotherapeutic agents as an inhaled aerosol to the tracheobronchial region of the lung. In most treatable cases of lung cancer, the cancer occurs in the tracheobronchial region [1]. A numerical model of aerosol particle motion in a magnetic field was also developed to predict the targeting pattern of aerosol particles.

In chemotherapy, cytotoxic drugs are used to kill cancerous cells. These drugs are currently administered intravenously or orally. Generally, combinations of chemotherapy and other drugs are used to mitigate adverse side effects, e.g. skin, gastrointestinal, and bone marrow ailments. Such side effects are inevitable, because the drugs used are toxic to healthy cells as well as cancer cells, and circulate throughout the body.

By delivering chemotherapeutic agents for lung cancer as a magnetically targeted aerosol, it may be possible to reduce adverse side effects by

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administering chemotherapy agents directly to the cancerous tissue. With a properly designed magnetic targeting system, the drug particles would be guided to the cancerous tissue by an appropriate magnetic field. The magnetic field also would have to be strong enough to overcome mucociliary clearance. Studies have shown that up to 95% of particles (6.5 μm diameter) deposited in the tracheobronchial region are removed by mucociliary clearance [2].

There is hardly any information available for such a strategy. The only work to the authors' knowledge that has mentioned the concept of using magnetic force to cause site-specific deposition of aerosol particles is an article by Dikanskii and Kiselev [3], where the concept was discussed in the context of nondestructive testing and field visualization. There is no information available in the literature regarding clinical applications, and even in the work of Dikanskii and Kiselev, the methodological aspects are absent.

In contrast to the concept of clinical applications for magnetically susceptible aerosols, magnetically targeted particles administered intravenously have been investigated in the past twenty five years. The works by Lübbe et al. [4] and Goodwin et al. [5] are examples of magnetic targeting in vivo to deliver drug particles to tumors. Others, such as Liu et al. [6], have investigated the use of magnetic particles for blood embolization. Factors affecting magnetic targeting identified in these works, such as fluid flow velocity, field gradient, and magnet positioning, should also be considered for aerosol targeting.

The first step in the development of a magnetic targeting system for lung cancer is to characterize the deposition of aerosols in simulated conditions of the tracheobronchial region. This was done in vitro using a bench top model. In order to facilitate future development of the system, a numerical simulation of particle deposition was also developed and verified using the experimental results. The current work represents a necessary initial step in the development of a magnetic targeting system, and as such, the fundamentals and possibilities of targeted deposition and retention of magnetic aerosol particles in an idealized model representing the conducting airways is considered.

2. Theoretical background

Inhaled aerosols consist of fine particles suspended in air: the flow of air around the particles is characterized by the particle Reynolds number, *Re*. The Reynolds number describes the ratio of the magnitudes of the inertial and viscous forces on the particle. For small Reynolds numbers ($Re<0.5$), the drag force, $\vec{F}_{\mathrm{D}}$, on a particle is purely due to viscosity, and can be calculated using the Stokes expression for drag force on a sphere as

$$\vec{F}_{\mathrm{D}} = 3\pi\mu d(\vec{v}_f - \vec{v}_{\mathrm{p}}), \tag{1}$$

where μ is the viscosity of air, d is the particle diameter, $\vec{v}_f$ is the air velocity, and $\vec{v}_{\mathrm{p}}$ is the particle velocity. For the air flow (0.34 m/s) and particles (1–3 μm diameter) used in these experiments, the particle Reynolds number was less than 0.1, so the Stokes drag equation shown was applicable.

The magnetic force, $\vec{F}_{\mathrm{M}}$, on a small sphere in a nonmagnetic fluid can be calculated as

$$\boldsymbol{F}_{\mathrm{M}} = \tfrac{1}{2}\mu_0\chi V_{\mathrm{p}}\nabla(\vec{\boldsymbol{H}}^2), \tag{2}$$

where μ_0 is the permeability of free space, χ is the magnetic susceptibility of the particle, V_{p} is the particle volume, and $\vec{\boldsymbol{H}}$ is the magnetic field intensity [7].

In aerosols, the density of the particles is typically much higher than that of air, so the buoyancy force can be neglected. Lift is also neglected, as the air velocity can be assumed constant over the particle diameter. Consequently, application of Newton's second law yields the following force balance for a particle:

$$m\frac{\mathrm{d}\vec{v}_{\mathrm{p}}}{\mathrm{d}t} = \vec{\boldsymbol{F}}_{\mathrm{M}} + m\vec{\boldsymbol{g}} + \vec{\boldsymbol{F}}_{\mathrm{D}}, \tag{3}$$

where m is the particle mass, $\vec{\boldsymbol{g}}$ is acceleration due to gravity, and $\vec{\boldsymbol{v}}_{\mathrm{p}}$ is the velocity of the particle. Substituting Eqs. (1) and (2) into Eq. (3) and considering $m/\rho_{\mathrm{p}} = V_{\mathrm{p}}$ and $\nabla(\vec{\boldsymbol{H}}^2) = 2\vec{\boldsymbol{H}}\nabla\vec{\boldsymbol{H}}$ results in the following expression:

$$\frac{m}{3\pi\mu d}\frac{\mathrm{d}\vec{\boldsymbol{v}}_{\mathrm{p}}}{\mathrm{d}t} = \frac{m}{3\pi\mu d}\left(\frac{\mu_0\chi}{\rho_{\mathrm{p}}}\vec{\boldsymbol{H}}\nabla\vec{\boldsymbol{H}} + \vec{\boldsymbol{g}}\right) + (\vec{\boldsymbol{v}}_f - \vec{\boldsymbol{v}}_{\mathrm{p}}), \tag{4}$$