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Theoretical Design of High-gradient Magnetic Systems for Drug and Gene Targeting to Lung*

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Abstract: Engineered magnetic nanoparticles and microparticles represent a cutting-edge tool in medicine because they can be simultaneously functionalized and guided by a magnetic field. We have theoretically analyzed their possible applications in the lung therapy in this study. We have proposed several equipments for more efficient delivery of drugs, DNA and siRNA into the lung epithelium. This study provides the theoretical fundamentals needed for development of a targeted magnetic drug delivery system for inhaled therapeutic aerosol particles.

1. Introduction

Magnetic field based drug delivery methods are one of the most attractive approaches for localizing a drug in the body, because magnetic forces act at a relatively long range and do not affect most of biological tissues. Magnetic drug delivery by particulate carriers is a very efficient method of delivering a drug to a localized disease site. Very high concentrations of chemotherapeutic or radiological agents can be achieved near the target site, such as a tumour, without any toxic effects to normal adjacent tissue or to the whole body. Fig. 1 highlights the concept of magnetic targeting by comparion of the systemic drug delivery with magnetic targeting. In magnetic targeting, a drug or therapeutic radioisotope is bound to a magnetic compound, injected into a patient's blood stream, and then stopped with a powerful magnetic field in the target area (see arrow in Fig. 1).

Depending on the type of drug, it is then slowly released from the magnetic carriers (e.g. release of chemotherapeutic drugs from magnetic micro-spheres) or confers a local effect (e.g. irradiation from radioactive microspheres; hyperthermia with magnetic nanoparticles). It is thus possible to replace large amounts of freely circulating drug with much lower amounts of drug targeted magnetically to localized disease sites, reaching effective and up to several-fold increased localized drug levels [1–6].

Aerosolization therapy for lung diseases has been applied for a long time. However, it has now become clear that the lung is a perfect point of entry not only for local therapy, but also for the systemic delivery of therapeutic substances. It provides a surface area of 100 m^2 and is separated from the pulmonary capillary blood by a barrier of less than 1 mm. Furthermore, there is no 'first pass effect', as is found in the intestinal tract. Recent technical improvements, with regard to both the production and the delivery of aerosols, indicate that the development of appropriate inhalation techniques may be the therapeutic way

*) *Dedicated to Professor Peter Lukáč on the occasion of his 70th anniversary.*

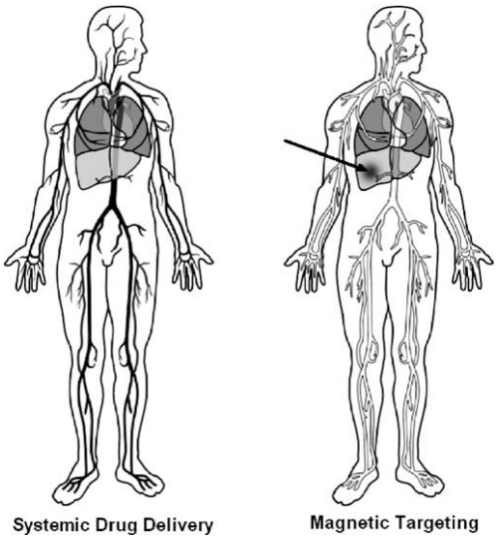

Fig. 1. Influence of the magnetic field on the distribution of magnetic nanoparticle bearing drug.

forward for a variety of diseases. Systemic delivery of hormones via the lung will be on the market in the very near future, and new substances such as antisense oligonucleotides and siRNA are in development. Because the nanocarrier systems maybe administered to the airways easily, a number of respiratory diseases may be approached using nanoparticles: obstructive lung diseases, genetic disorders affecting the airways, infectious diseases including tuberculosis, and cancer. Cystic fibrosis is a particularly inviting target for aerosolized gene therapy, as it is a single-gene disease and the critical target cells, airway epithelial cells, are directly accessible to the environment. However, achieving genetic correction by airway administration of vectors has proven to be difficult. Extracellular and intracellular barriers (Figs. 2, 3) limit the gene transfer efficiency of viral and non-vi-

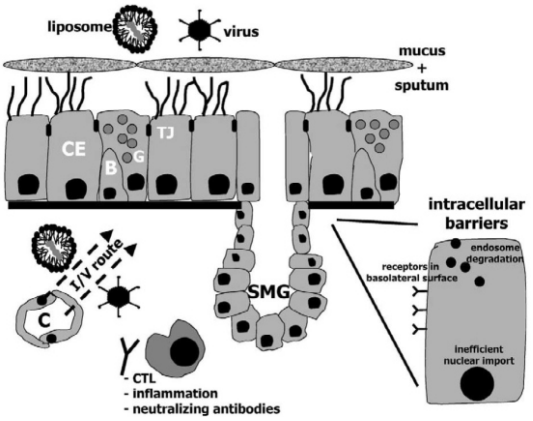

Fig. 2. Routes and barriers in airway epithelium.

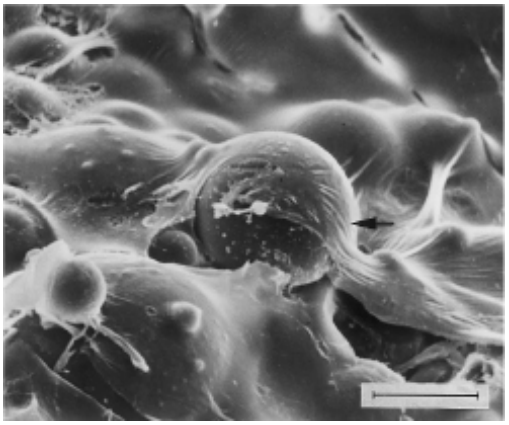

Fig. 3. Particles submerged in lung mucus.

ral vectors to airway epithelial cells. Extracellular barriers include the presence of infected mucus and sputum, mucociliary clearance and tight junctions between the cells, which limit the access of viral vectors to the receptors localised on the basolateral membrane.

2. Results and discussion

One possible approach to increase the efficiency of drug delivery to lung is the magnetic targeting (Fig. 4):

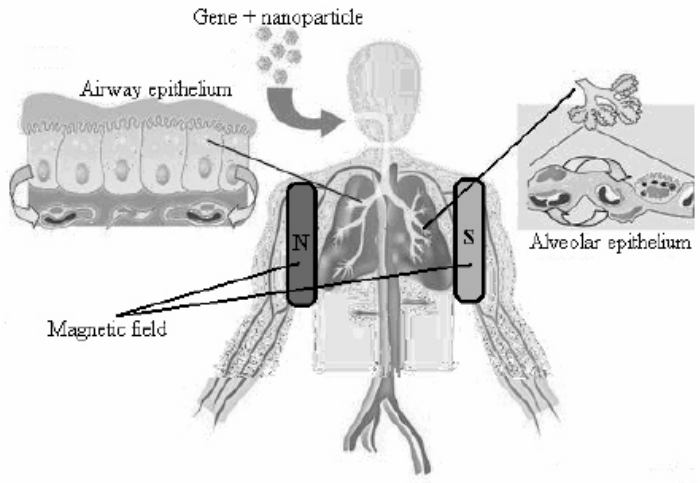

Fig. 4. Magnetically enhanced gene delivery.

Magnetostatic problems are those in which the fields are time-independent. In this case, the field intensity (**H**) and flux density (**B**) must obey equations

$$\mathbf{H} \quad \mathbf{J},$$
$$\mathbf{B} \quad 0,$$

with a constitutive relationship between B and H for each material

$$\mathbf{B} \quad \mathbf{H}.$$

If a material is nonlinear (e.g. saturating iron or alnico magnets), the permeability, μ, is actually a function of B:

$$\frac{B}{H(B)}.$$

The Finite Element Method Magnetics (FEMM) goes about finding a field that satisfies all these 3 equations via a *magnetic vector potential* approach. The flux density is written in terms of the vector potential, A, as:

$$\mathbf{B} \quad \mathbf{A}.$$

Then the first equation can be rewritten as:

$$\frac{1}{(\mathbf{B})} \quad \mathbf{A} \quad \mathbf{J}.$$

For a linear isotropic material (*const*.) will reduce the previous expression in Coulomb gauge ($\mathbf{A}$ 0) to

$$\frac{1}{} \quad \mathbf{A} \quad \mathbf{J},$$

in that ($\mathbf{A}$) = ($\mathbf{A}$) $\mathbf{A}$.

We consider the solved problems as planar ones, flux density defined in x-y plane, i.e. we regard the z-coordinate of magnetic flux density, Bz, equal to zero, which means that the magnetic vector potential is equal to **A** = (0, 0, A). We also confine to current density parallel to the z-direction of the coordinate system. In this simplification, the last equation leads to the scalar elliptic partial differential equation

$$\frac{1}{} \quad A \quad J,$$

that solution using finite elements method is the basis of David Meeker FEMM [7] program used in this study.

Simple magnet blocks typically generate field gradients in the order of 1–6 Tm^{-1} across the diameter of standard 15–50 ml laboratory test tubes. High-gradient magnet separators generate field gradients that are significantly higher than this, through the use of optimally designed magnetic circuits. Across 15–50 ml test tubes, such systems may generate gradients ranging from 10 to 100 Tm^{-1}. Even higher gradients can be achieved with smaller bore containers and separator systems. For the purposes of aerosol targeting in the

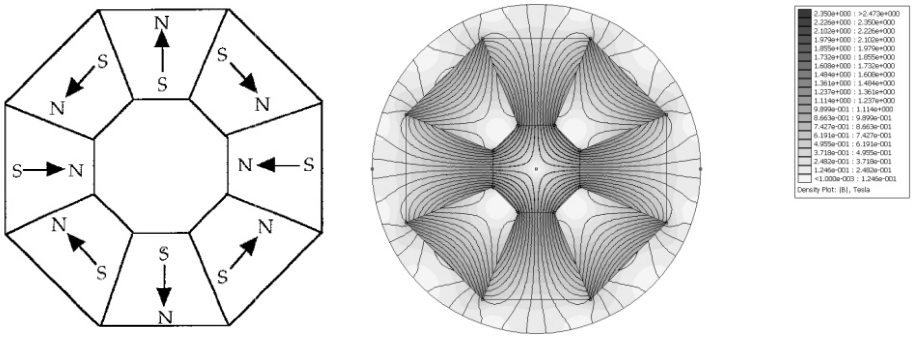

Fig. 5. Octapolar magnet.

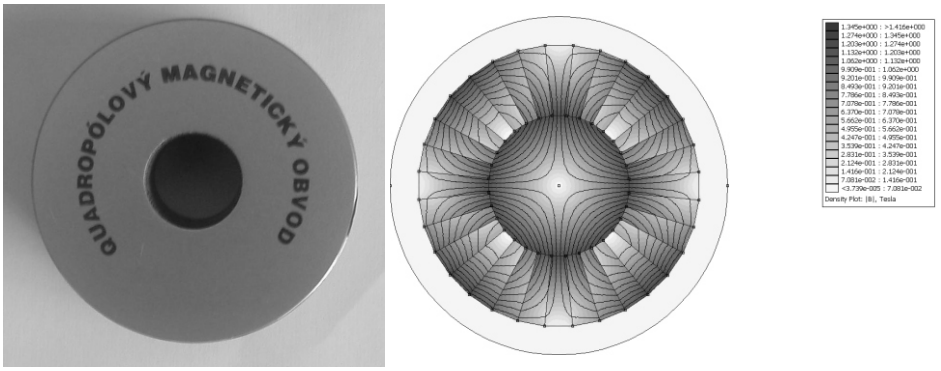

Fig. 6. 32-Spolar magnet.

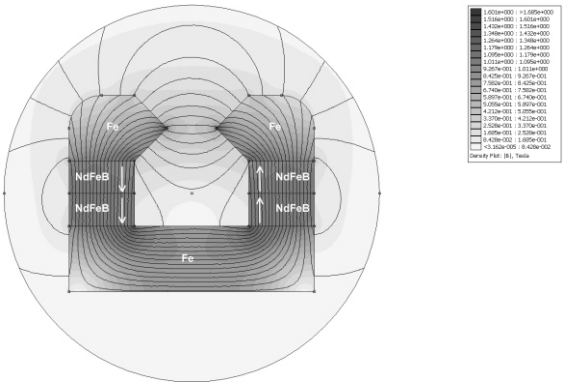

Fig. 7. Simple closed magnetic circuit.

lung we have found, as an optimal, quadrupolar configurations build using 8 (Fig. 5) and 32 magnets (Fig. 6) from Nd-Fe-B magnetic alloy, with surface magnetic induction B = 1.34 T. Due to the shielding the magnet is magnetic only inside the central hole. The highest gradient in this device is almost 100 T/m. In the hole with a diameter of 3 cm a mouse can be inserted, and aerosol with magnetic microbeads carrying drug, gene or siRNA can be applied for the in vivo testing of the device using mice. We have also developed several simple closed magnetic circuits (e.g. Fig. 7).

Motion of magnetic particle in the plane in magnetic field with flux density B in viscous nonmagnetic and nonmoving fluid ambient, if we consider only magnetic and Stokes drag force of moving particle, is determined by the Newton's law and can be described by the system of ordinary differential equations:

$$\frac{dx}{dt} \quad v_{p,x},$$

$$\frac{dy}{dt} \quad v_{p,y},$$

$$\frac{dv_{p,x}}{dt} \quad \frac{1}{m_p} \quad \frac{V_p}{f} f(B(x,y)) \quad B_x(x,y)\frac{B_x(x,y)}{x} \quad B_y(x,y)\frac{B_x(x,y)}{y} \quad 6 \quad R_p v_{p,x},$$

$$\frac{dv_{p,y}}{dt} \quad \frac{1}{m_p} \quad \frac{V_p}{f} f(B(x,y)) \quad B_x(x,y)\frac{B_y(x,y)}{x} \quad B_y(x,y)\frac{B_y(x,y)}{y} \quad 6 \quad R_p v_{p,y},$$

where R_p, m_p and V_p are the radius, the mass and the volume of the particle, $_f$ and are the permeability and viscosity of the fluid ambient, respectively; and function $f(B(x,y))$ is determined according to [9], from magnetization model of particles based on self demagnetization and magnetic saturation of magnetite particles, as:

$$f(B) \quad \begin{array}{ll} 3 & B/ \ _f \quad M_{sp}/3 \\ M_{sp} \ _f / B & B/ \ _f \quad M_{sp}/3 \end{array},$$

where M_{sp} is saturation magnetization of the particle.

We have solved equations of magnetic nanoparticle motion using the numerical solver in Matlab® for many different initial positions of the magnetic beads, and we have found that lung represents a unique opportunity, as compared with e.g. magnetic drug targeting in bloodstream, because the viscosity of air is ~10–100 times lower than that of liquid, and for gene delivery magnetic beads with dimension of 1–10 m can be safely used (instead of 10–100 nm). The behavior of a fine aerosol particle inside the lungs is determined by the balance between magnetic force, gravity and aerodynamic forces that are exerted on the particle, if we neglect gravity, the ratio of magnetic force and Stokes drag force may be enhanced theoretically by the factor of 10 000!

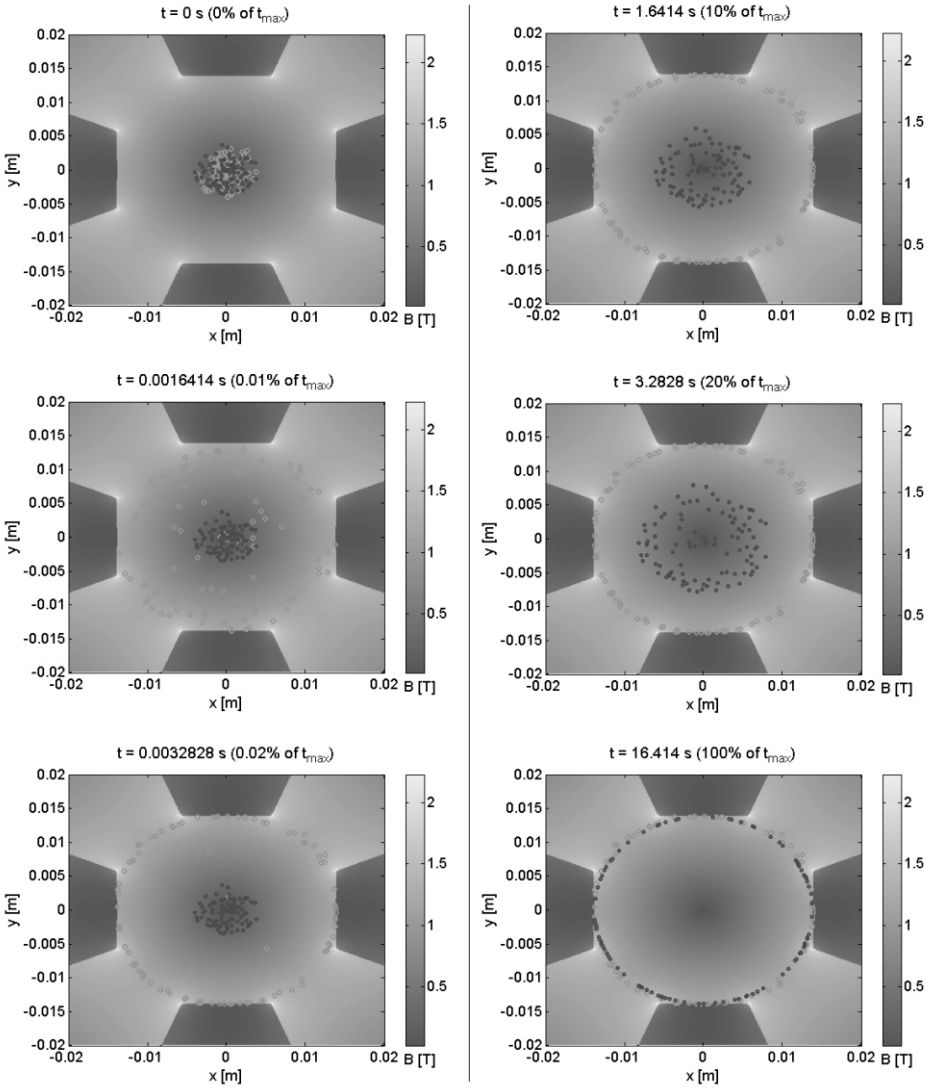

Fig. 8. Snapshots of trajectory of magnetite (Fe_3O_4) particles (green – microparticles with radius 10 m; red – nanoparticles with radius 50 nm) in the air in the magnetic field of permanent quadrupole – octapolar magnet.

In conclusion, we can say that the lung represents one of the most promising targets for magnetically enhanced drug and gene delivery and retention.

Acknowledgement

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