ANALYTICAL STUDY OF NANO MAGNETIC DRUG DELIVERY AND TARGETING IN COMPARISON WITH EXPERIMENTAL RESULTS

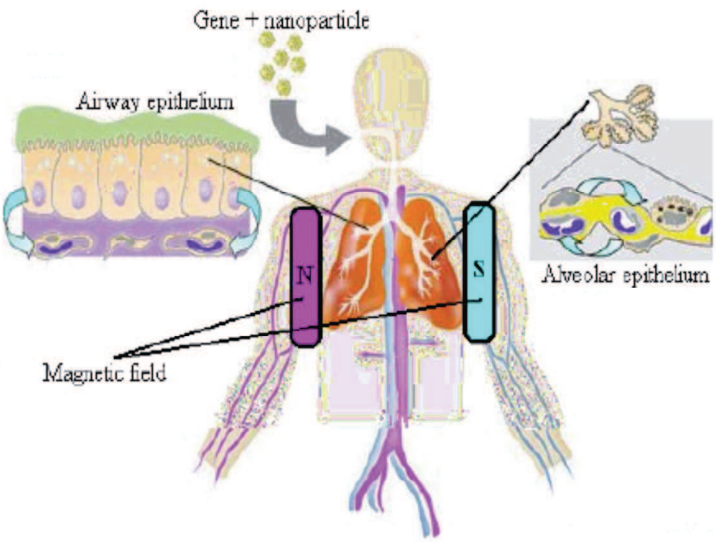
C.R UTHRA, DR.R.VASANTHAKUMARI

Abstract: Theoretical analysis and possible application of engineered magnetic nano particles and micro particles in the lung therapy has already been studied. Several equipment for more effective delivery of drugs into the lung epithelium has been proposed earlier. This study provides an analytical method needed for development of drug targeting to lung in comparison with experimental results.

Keywords: Aerosolizationtherapy,Drugtargeting,magneticnanoparticle,Quadrapole magnet.

Introduction: One of the basic requirements in drug management is that sufficient quantities of the drug reach the desired site in the body. The main aim is to decrease the amount of drug to the non target sites as it can harm the healthy organs and cells of the body. This is achieved by attaching the drugs to the magnetic nano particles which act as carrier particles and are controlled externally by magnetic fields. This is done by locating the permanent magnets directly over the affected sites in the body.

Aerosolization therapy for lung diseases has been applied for a long time. The lung is a perfect point of entry not only for local therapy but also for systematic delivery of therapeutic substances. Recent technical improvements, with regard to both the production and delivery of aerosols indicate that appropriate inhalation techniques may be the therapeutic way forward for a variety of diseases. Since the nano carrier system may be administered to the airways easily, a number of respiratory diseases may be approached using nano particles.



Principle of magnetic drug targeting to the lungs:
Methods:
Theoretical Model: There are several forces acting on magnetic particle in viscous environment and magnetic field, such as magnetic force due to all field sources, Stokes' viscous drag force, inertia,buoyancy and gravity, thermal kinetics (Brownian motion) particle fluid interactions and interparticle effects such as magnetic dipole interactions, electric double layer interactions, and van der Walls force. Except magnetic, inertial, and viscous drag force the other interactions are negligible for magnetic micro- or nanoparticles. For this reason, we suppose in this paper only these dominant effects. The trajectory of motion of magnetic particle in magnetic field and viscous fluid ambient using Newton's law:

$m\,d\mathbf{v}/d\mathbf{t} = \mathbf{F_m} + \mathbf{F_s}$ **(1)**

wheremp and vp are the mass and velocity of the particle,andFm and Fs are the magnetic and stokes drag force respectively.

Magnetic Forces: A magnetic particle is replaced by"equivalentpoint dipole moment $\mathbf{m}_{peff}$ localized at the center of particle.According to this method, force acting on the dipole is given by

$$\mathbf{F_m} = \boldsymbol{\mu}(\mathbf{m_{p,eff}} \cdot \boldsymbol{\nabla})\mathbf{H_a} \quad (2)$$

whereμ is permeability of fluid ambient, $\mathbf{m}_{p,eff}$is “effective”dipole moment of the particle, which depends on externally applied magnetic field intensity **H***a* at the center of particle, where the dipole momentis localized.A magnetic force is therefore a function of external magnetic field gradient and the magnetization of the particle. Below the saturation the particles are linearly magnetized with their magnitude of magnetic moment increasing in the direction of external field. Beyond the saturation point,magnetic moment magnitude tends to a constant value.According to this magnetization model of particles basedon self demagnetization and magnetic saturation developed by Furlani group the effective dipole moment canbe expressed as

$$\mathbf{m}_{p,eff} = \mathbf{V_p f(H_a) H_a}. \qquad (3)$$

We consider magnetic particle with radius R_p and volume V_p and a function

$$f(H_a) = \frac{3(\aleph p - \aleph f)}{(\aleph p - \aleph f)+3} \quad Ha < \frac{(\aleph p - \aleph f) + 3}{3\aleph p} M_{sp}$$

$$= \frac{Msp}{Ha} \quad H_a \geq \frac{(\aleph p - \aleph f) + 3}{3\aleph p} M_{sp} \qquad (4)$$

Where $\chi p$and $\chi f$are the magnetic susceptibilities of the particle and ambient fluid, respectively, *Msp*is saturation magnetization of the particle, and $H_a = |\mathbf{H_a}|$.We assume nonmagnetic fluid ($\aleph_f \approx 0$) and high susceptibility of magnetic particles, i.e.$\aleph_{p>1}$, which is in the case of water or air as fluid ambient, and magnetite Fe_3O_4 as particles accomplished; hence

$F(B) = 3 \qquad B/\mu < M_{sp}/3$

$= M_{sp}\,\mu/B \qquad B/\mu \geq M_{sp}/3 \qquad (5)$

where*B* is magnetic flux density of external field and isvalid:$B/\mu = H_a$.

As an illustration we could calculate trajectory of magnetite particles in the magnetic field of permanent quadrupole.Magnetic flux density was modelled as magnetostatic problem in which the fields are time-independent. In this case, the field intensity (**H**)and flux density (**B**) must obey equations

$\nabla \times \mathbf{H} = \mathbf{J}$,

$\nabla \cdot \mathbf{B} = 0$

with a constitutive relationship between *B* and *H* for each material

$\mathbf{B} = \mu\mathbf{H}$.

If a material is nonlinear (*e.g.* saturating iron or alnicomagnets), the permeability, μ is actually a function of *B*:$\mu = B/H(B)$.

Quadrupole

Mathematical model: A planar model which is not 3D, but it representsthe distribution of flux density in transversal planeof infinite long permanent magnets arranged to quadrupolewith zero value of perpendicular component of fluxdensity was created. The quadrupole consists of eight sphenoid blocks,in the section, of uniformly magnetized Neodymium rareearthmagnets with magnetic energy product 37 MG.Oe(megagauss-oersted; NdFeB N37) and with magnetizationorientation revolved in 135° between adjacent blocks. Thegeometry of quadrupole is determined by the radii of inscribedand circumscribed circle, i.e. 1.4 and 4.5 cm in our case, respectively. The purposes of magnetic targeting intolung, is illustrated in the Fig1.In this model we consider in addition to magneticforce, fluidic force acting on a moving particle in fluidmedium. Its magnitude is determined by Stokes’ law forthe drag on a sphere with radius *Rp*in uniform flow,

$$F_s = -6\pi\eta Rp(vp - vf) \qquad (6)$$

whereη and **v***f*are the viscosity and the velocity of thefluid, respectively, and **v***p*is the velocity of the particle. Inthis case is the fluid ambient quiescent, i.e.$v_f = 0$ m. s^{-1}.

Calculating Flux Density Components Of A Quadrapole: In the next step magnetic f**lux density of permanent quadrupole**is computed bydetermining the **B**-field outside an infinitely long cylindricalmagnet that has an alternating radial polarization and a linear second quadrantdemagnetization curve of the form

$\mathbf{B} = \mu\mathbf{H} + \mu_o \mathbf{M_s}(\varphi)$

Let $R_1$and R_2 denote the inner and outer radii of the cylinder, respectively.As the magnet is infinitely long, the problem reduces to a 2D boundary value problem (BVP). We use the solution method presented in [2]with the magnetization inside the cylindergiven by

$\mathbf{M}_s(\varphi) = M(\varphi)\,\overline{r}$ where

$$M(\varphi) = \sum_{i=1}^{\infty} M\varphi \cos(i\varphi)$$

$$Ms/i\pi \textstyle\sum_{\downarrow}(k=1)^{\uparrow} Npole$$

$$(-1)k\,[sin\text{-}[\,((2k-1)i\pi)/Npole] - \sin[(2k+1)i\pi/Npole$$

M_i=]]

N_{pole} is the number of poles

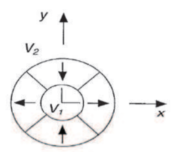


FIGURE 4.19 Infinite cylinder with radial magnetization.

A solution is sought for the region V_2 outside the cylinder.The coefficients of interest are $V_i^{(2)}$ and$U_i^{(2)}$. From the Orthogonalityof $\sin(i\phi)$ and cos (iϕ) we find that $V_i^{(2)} = 0$ for all i. The coefficients $U_i^{(2)}$ are given by $U_i^{(2)}(M_i, R_1, R_2, \mu)$ which is calculated numerically as per [2] .

The field components $B_r^{(2)}(r,\phi) = \mu_o \sum_{i=1}^{\infty} i r^{-(i+1)} U_i^{(2)} \cos(i\phi)$

$$B_\phi^{(2)}(r,\phi) = \mu_o \sum_{i=1}^{\infty} i r^{-(i+1)} U_i^{(2)} \sin(i\phi) \qquad (7)$$

are calculated.Movement of magnetic particles in the plane inmagnetic field with flux density *B* in fluid ambient withviscosity *η*, which is not moving, is described by systemof **ordinary differential equations (ODE):**

$$dx/dt = v_{p,x}$$

$$dy/dt = v_{p,y}$$

$$dv_{p,x}/dt= \frac{1}{mp}\left\{\frac{Vp}{\mu} f(B(x,y))\left|Bx(x,y)\,\partial Bx\frac{x,y}{\partial x} + By(x,y)\frac{\partial Bx(x,y)}{\partial y}\right| - 6\pi\eta Rp\ vp,x\right\}$$

$$dv_{p,y}/dt= \frac{1}{mp}\left\{\frac{Vp}{\mu} f(B(x,y))\left|Bx(x,y)\,\partial By\frac{x,y}{\partial x} + By(x,y)\frac{\partial By(x,y)}{\partial y}\right| - 6\pi\eta Rp\ vp,y\right\}$$

(8)

wheremp = $V_p\rho_p$ and $V_p = 4/3\pi r^3$ are the mass and volume of the particles respectively

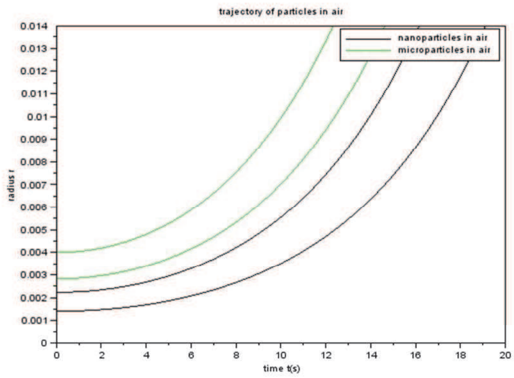
This system of equations is obtained by combinations of expressions from (1) to (6)

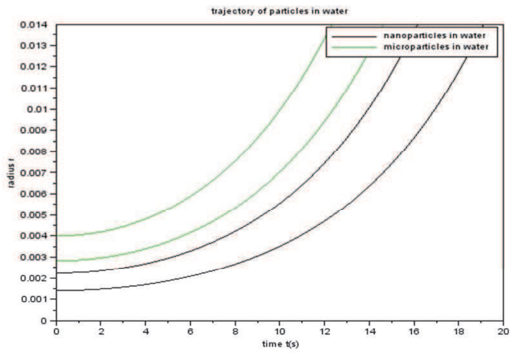
Gradient of flux density components is calculated usingequation (7).

The field is expressed as $B_o = (B_r^2 + B^2_\phi)^{1/2}$ where B_o is both the field coefficient and gradient of the Quadrapole.Setting the trajectory of magnetite (Fe_3O_4) particles, with density ρ = 5000 kg.m−3 and a saturationmagnetization M_{sp}= 4.78 x 10^5 A.m-1, in the magneticfield created by quadrupole consisting of permanentNdFeB N37 magnets, which is calculated analytically using,eqn(7) in nonmovingand nonmagnetic fluid, with viscosity equal tothat of water or air, i.e. $\eta = 1.003 x.10^{-3}$ N.s.m-2 or$\eta = 1.82x\ 10^{-5}$ N.s.m-2, respectively.For this particle B_o was found to be 0.018T.

Computations Using Scilab: Scilab 5.4 numerical solver was used for solving the set of equations (8). Computations were done for nanoparticles with radius 50 nm, which are often used in magnetic drug targeting, as well as microparticles with radius 10 μm, which can be used for magnetic separation. The trajectories of magnetite particles of each size in the air as fluid ambient as shown by [2] was solved analytically and the trajectory traced.

Initial conditions for calculationswere: randomly position in the circle with radius 0.4 cm from the center of quadrupole and zero initial velocity.Computation of trajectory for each particle was stoppedafter it reached internal boundary of quadrupole, approximatelyat a distance 1.4 cm from the center.Wecansee microparticles were captured faster than nanoparticles.Also small nanoparticles were attracted in a longer, butstill reasonable time approximately after 16s. Trajectories of magnetite particles with different sizes, microparticleswith radius 10 μm and nanoparticles with radius 50 nm, in the field of permanentquadrupolein the air and in water in different times are traced using scilab.. Mean capturetime is in this case shorter than ones in viscouslywater medium, due to smaller drag force. Capture timeof magnetic particles in magnetic field of quadrupole,can be also decreased by increasing magnetic flux densitiesand field gradients of studied configuration replacingpermanent magnets by pulsed electromagnets, similar to those pulsed quadrupole lenses using for focusing heavy ion beams in accelerator physics. These results equally apply also to magnetic separation of proteins, DNA, and whole cells.





Conclusions: The trajectories of magnetite particles of different sizes in the field of permanent quadrapole in the air and water were traced in different times with the help of numerical solver. The tendency of the particle to be captured by the magnet increases when air is chosen as the medium.The analytical model presented here was compared with the experimental model [3] and found to be correct.This model presented here is ideal for parametric analysis of magnetic targeting invivo.The numerical procedure proved to be a powerful tool for further development of the magnetic drug targeting technique for patient specific clinical studies.

References:

1. Basic design and engineering of normal-conducting, iron-dominatedElectromagnets-Th.Zeckler- CERN Geneva Switzerland.
2. Permanent magnet **and** Electromechanical Devices,EdwardP.Furlani,Academic Press series in Electromagnetism.
3. Magnetic drug delivery and targeting principles and applications,MelaniaBabincova,PeterBabinec, biomed 2009 Dec;153(4);243-250.
4. Mathematical modelling of magnetically targeted drug delivery,AndrewD.Grief,Giles Richardson,JMMM,293 (2005),455-463.
5. Modelling magnetic carrier particle targeting in the tumour microvasculature for Cancer treatment,OvidiuRotairu, Norwal J.C Strachan,JMMM 293(2005) 639-646.
6. Applications of magnetic nanoparticles in biomedicine,Q.APankurst,J Connolly J. Phys. D: Appl. Phys. **36** (2003) R167–R181 PII: S0022.
7. **A** Model for Predicting Magnetic Targeting of Multifunctional Particles in the MicrovasculatureE. J. Furlani and E. P. FurlaniInstitute for Lasers, Photonics and Biophotonics,University at Buffalo (SUNY), Buffalo, NY, 14260
8. Pankhurst QA, Connolly J, Jones SK, Dobson J. Applicationsof magnetic nanoparticles in biomedicine.J Phys D2003;36(13):R167–81

***

ResearchScholar,ManonmaniumSundaranar University, Tirunelveli,
AssociateProfessor,KMPGRCentre,Pondicherry.