Available online at www.sciencedirect.com
SCIENCE DIRECT®
ELSEVIER
Journal of Magnetism and Magnetic Materials 293 (2005) 514–519
Journal of magnetism and magnetic materials
www.elsevier.com/locate/jmmm

Site-directed research of magnetic nanoparticles in magnetic drug targeting

Hua Xu, Tao Song*, Xiuqi Bao, Lili Hu

Department of Biomedical Engineering, Institute of Electrical Engineering, Chinese Academy of Sciences, P. O. Box 2703, Beijing 100080, PR China

Available online 4 March 2005

Abstract

The targeting of ferrofluids composed of 20 nm magnetic particles was studied through simulation and animal experiment. The results showed that some magnetic particles were concentrated in the target area depending on the applied magnetic field. Through theoretical analysis, the retention of the magnetic nanoparticles in a target area is due to large magnetic liquid beads formed by the magnetic field.

Keywords: Magnetic drug targeting; Ferrofluids; Permanent magnet; Magnetic force; MR imaging; NdFeB; Vibrating sample magnetometer; Atomic absorption spectrometer; Sprague–Dawley rats

1. Introduction

Effective drug targeting is vital for the medical treatment of various diseases. Magnetic drug targeting is one of the various possibilities of drug targeting, which aims at concentrating magnetic drugs at a given target site with the aid of magnetic field, so the method enhances drug concentration in the target and reduces the toxicity and side effects in normal tissues. Due to its non-invasiveness and high targeting efficiency, many scientists are engaging in this area from the late 1970s [1,2].

The first worldwide clinical trials of magnetic drug targeting in humans were reported by Lubbe et al. in 1996, who used a ferrofluid (particle size 100 nm) to which the drug epirubicin was chemically bound [3].

The most important point of magnetic drug targeting is how to concentrate magnetic drugs at a given target site, which depends on the drug carrier and magnetic device.

The main drug carriers at present are magnetic liposomes, magnetic albumin microspheres, ferrofluids and carbon–iron alloy which are produced artificially by various ways. Recent development on carriers has largely focused on new polymeric or inorganic coatings on magnetite/maghemite nanoparticles [4].

*Corresponding author. Tel.: +86 10 62558293; fax: +86 10 62558093.
E-mail address: songtao@mail.iee.ac.cn (T. Song).

0304-8853/$ - see front matter © 2005 Published by Elsevier B.V.
doi:10.1016/j.jmmm.2005.01.067

Electromagnets [5] or permanent magnets [1,3,6] can be used as the magnetic device for magnetic drug targeting. The structure of the magnet may be either bipolar or unipolar. A unipolar magnet has a single magnetic polar which is set to one side of target site. A bipolar magnet has two magnetic poles, which are put on both sides of target site, and the two poles should have different shapes in order to generate high-gradient magnetic fields. The non-uniformity of the applied magnetic field is worth emphasizing, because it is necessary for the mobility of the magnetic carriers.

In this paper we focused on the main factors influencing the retention of magnetic nanoparticles in vitro by using a bipolar permanent magnet and the distribution of ferrofluids as drug carrier by MRI in vivo.

2. Materials and methods

Ferrofluid: A water-soluble ferrofluid was purchased from Anhui Jinke Magnetic Liquids Co. Ltd. Its concentration is 9% (V/V), and its specific gravity is 1.34 g/cm^3. The size of the magnetic particles (Fe_3O_4) in the ferrofluid was measured by TEM micrographs. The diameters of the particles are from 10 to 20 nm. According to the hysteresis loop of the ferrofluid (Fig. 1), they are superparamagnetic. When the applied magnetic field strength is higher than 160 kA/m (i.e. the magnetic flux density is more than 200 mT), the mass magnetization (>25 emu/g) is close to the saturation mass magnetization (30.11 emu/g). According to the concentration and specific gravity of the ferrofluid, the saturation magnetization of the ferrofluid obtained is 40.34 kA/m, and the saturation magnetization of magnetic particle is about 448 kA/m.

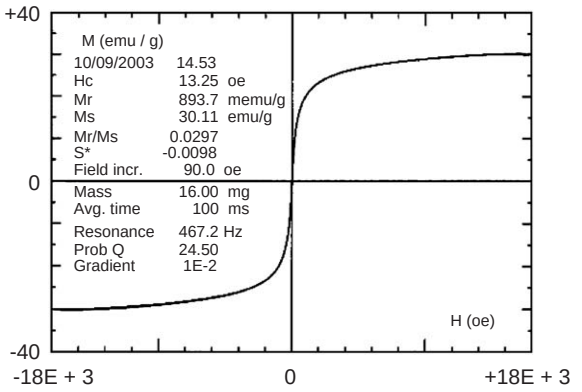

Fig. 1. Hysteresis loop of the ferrofluid measured by a vibrating sample magnetometer.

Permanent magnet: A C-shaped permanent magnet (bipolar) was designed and manufactured for the experiment of magnetic drug targeting (Fig. 2a). In order to generate a high-gradient magnetic field and reduce the target area, one pole is designed as a frustum of rectangular pyramid with a surface of $10 \times 10\,mm^2$. The other pole is

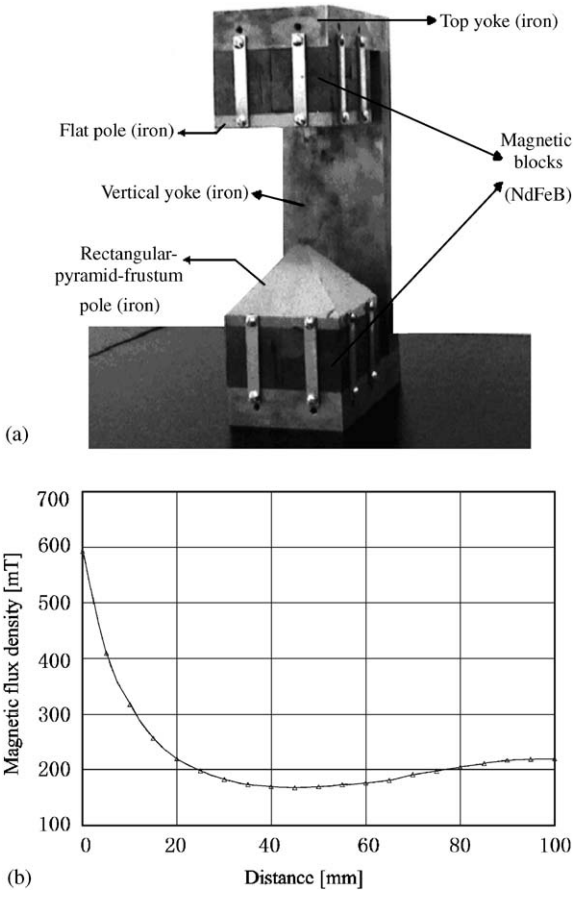

Fig. 2. The C-shaped permanent magnet and its magnetic field. (a) Structure of the magnet. (b) The distribution of the magnetic flux density according to the distance from the rectangular-pyramid-frustum pole.

flat with a surface of $100 \times 100\,mm^2$. The gap between the two poles is 100 mm.

The magnetic flux density of the magnet is shown in Fig. 2b. It was found that both the magnetic field (590–220 mT) and the gradient (27–6 T/m) are high at 0–20 mm distance away from the rectangular-pyramid-frustum pole.

In vitro apparatus: An in vitro apparatus (Fig. 3) simulating human circulatory was used to test the retentions of ferrofluids under various flow speeds of medium, various magnetic fields with different magnitude and gradient. In the Fig. 3, a glass tube (F) simulated a blood vessel, whose diameter is 2 mm. A glass ball (G) simulated a tumour (i.e. the target), whose diameter is 6 mm. The water (simulating the blood) in beaker C could be pumped into beaker D through the glass tube by a peristaltic pump (A). The flow speed could be changed through adjusting the pump. The ferrofluids could be injected at the intake (B). The magnet was set around the target region and the magnetic fields of the target could be changed through moving the glass tube.

The retention of ferrofluids in the target was obtained through measuring the content of magnetic nanoparticles in the beaker D by an atomic absorption spectrometer.

In vivo methods: The targeting of ferrofluids was studied in vivo. The same permanent magnet and ferrofluid were used for the experiment. Healthy male Sprague–Dawley rats of 280–300 g were allocated to experiment and sham groups, 3 rats in each group. Experimental rats were anesthetized by pentobarbital (40 mg/kg, i.p.). The ferrofluids were injected through the femoral veins in both experiment and sham groups, with a dosage of 0.1 ml. The C-shaped magnet was set around the right kidney in vivo, and its rectangular-pyramid-frustum pole was 10–20 mm distance from the right kidney. After the ferrofluids were injected, the magnetic field remained for 1 h. The distribution of ferrofluids in the rat was checked by T_1-weighted magnetic resonance imaging (MRI) 30 min later. The sham group, which was injected with the ferrofluids and without applied magnet, was observed by MRI 1.5 h later.

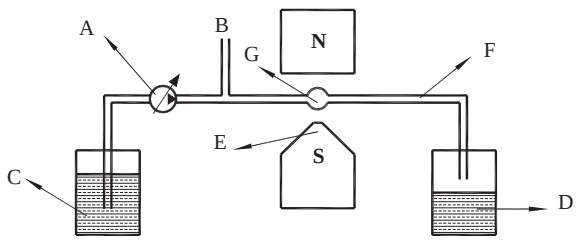

Fig. 3. The in vitro apparatus simulated human circulatory. A-peristaltic pump; B-intake of the ferrofluids; C, D-beaker; E-magnetic pole; F-glass tube; G-targeting.

3. Results

In vitro: The retention of magnetic particles at 3, 17 and 33 mm away from the rectangular-pyramid-frustum pole face when the flow speed changed from 0 to 100 mm/s is shown in Fig. 4. The retention of magnetic particles decreased when the flow speed increased. Particle retention was also related to the applied magnetic field gradient and the magnetic field strength.

In vivo: MRI images of the right kidneys of the rats are shown in Fig. 5. We found a signal change in the right kidney after focusing the magnetic field, pointing at an enhanced magnetic particle concentration in the right kidney because of the external magnetic field.

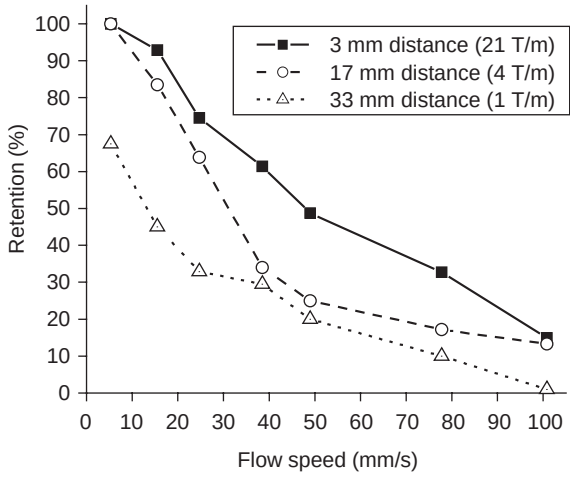

Fig. 4. The retentions of magnetic particles at 3, 17 and 33 mm away from the rectangular-pyramid-frustum pole face at various flow speeds.

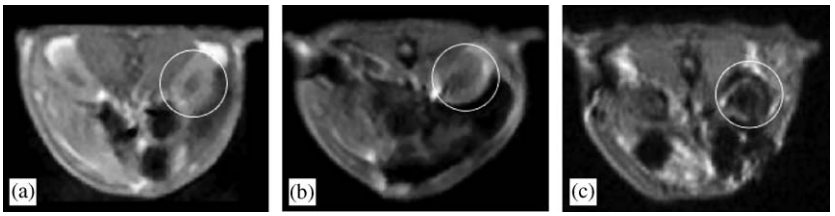

Fig. 5. MRI images of SD rats' right kidneys (within the white circle). (a) The image of kidney before the experiment (without ferrofluids and magnetic field). (b) The image of sham group (injected ferrofluids without magnetic field). (c) The image of experiment group (injected ferrofluids with magnetic field).

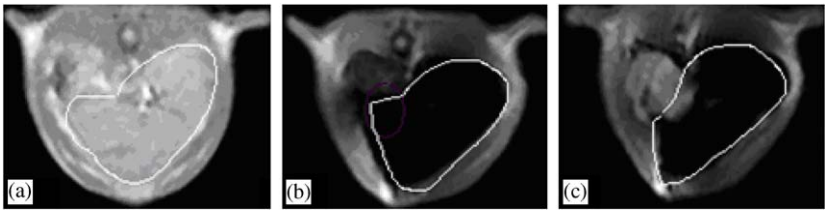

Fig. 6. MRI images of SD rats' livers (within the white line). (a) The image of liver before the experiment (without ferrofluids and magnetic field). (b) The image of sham group (injected ferrofluids without magnetic field). (c) The image of experiment group (injected ferrofluids with magnetic field).

MRI images of a rat's liver before and after the injection are shown in Fig. 6. Many magnetic particles were retained in the rat's liver whether a magnetic field was applied or not. The magnetic particles in the liver of the sham group, however, were more concentrated than in the experimental group.

4. Discussion

4.1. Magnetic force on magnetic particles

The magnitude of the magnetic force on a small magnetic particle is described as [7]

$$F_{\mathrm{mag}} = \mu_0 M \frac{\mathrm{d}H}{\mathrm{d}s} V_{\mathrm{par}}, \tag{1}$$

where F_{mag} is magnitude of the magnetic force; μ_0 is magnetic permeability of vacuum; M is magnetization of the particle; H is magnetic field strength; $\mathrm{d}H/\mathrm{d}s$ is derivative of H; V_{par} is volume of the particle.

According to the results of Senyei et al. [1], the magnet particles can be concentrated in target only when

$$F_{\mathrm{mag}} > 6\pi\eta r v d/L = F_0, \tag{2}$$

where η is fluid viscosity; r is particle radius; v is flow speed of the liquid; d is the distance from the particle to the tube wall near to the magnetic polar; L is the bound of applied magnetic force along with the tube.

For the C-shaped magnet, the magnetic field is almost parallel to the vertical direction (Z-axis). So the magnetic force can be described by

$$F_{\mathrm{mag}} = M \frac{\mathrm{d}B_Z}{\mathrm{d}z} V_{\mathrm{par}}, \tag{3}$$

where B_Z is the applied magnetic flux density along with Z-axis.

According to the magnetic field and the hysteresis loop, the magnetic force is 5.1×10^{-17} N at the highest magnetic field strength and gradient (the diameter of the particle is chosen as 20 nm). Assuming that the particle is at the center (i.e. $d = 1$ mm), the flow speed is chosen as 5.3 mm/s, and the viscosity of water is 1.002×10^{-3} Ns/m^2, we could obtain $F_0 = 8.33 \times 10^{-14}\,\mathrm{N} \gg F_{\mathrm{mag}}$ that means that the particles could not be retained

according to Eq. (3). But in fact the retention of the particles was 100% in vitro under the same conditions (see Fig. 4).

During the experiment, we found that the ferrofluids formed some big magnetic liquid beads in the tube under the magnetic field. So we calculated the forces on the magnetic beads to explain the concentration of magnetic particles:

$$F'_{\mathrm{mag}} = M_{\mathrm{bead}} \frac{\mathrm{d}B_Z}{\mathrm{d}z} V_{\mathrm{bead}}, \tag{4}$$

where M_{bead} is the magnetization of the magnetic liquid bead (assumed it is the same as that of the ferrofluid, i.e. 40.34 kA/m); V_{bead} is the volume of the liquid bead.

4.2. Retention of magnetic particles

From premise (2), we can deduce that the magnetic liquid bead could be concentrated in the target only when $d < F'_{\mathrm{mag}} L/6\pi\eta r_{\mathrm{bead}} v = d_0$, where r_{bead} is the radius of the liquid bead. So the retention can be calculated as

$$R_{\mathrm{ren}} = \frac{S_{\mathrm{seg}}}{S_{\mathrm{round}}}, \tag{5}$$

where R_{ren} is the retention of magnetic particles; S_{round} is the area of the tube section (2 mm-diameter); S_{seg} is the area of the segment of a circle with arch height d_0.

According to the calculation, the calculated retentions coincided with the results of the experiment in vitro if the diameter of the liquid bead is assumed as 9 μm (Fig. 7).

Some discrepancies were found between the measured and calculated results from Fig. 6, especially the results at the larger 17 mm distance. There are two possible reasons for these findings. First, to simplify the calculation, the magnetic flux density that we used to calculate the retentions was chosen as an average among the magnetic flux densities in the bound of applied magnetic force along with the tube. Second, there are some measurement errors in the experiment.

According to our analysis, the retention of the magnetic nanoparticles in a target is due to some big magnetic liquid beads being formed under the magnetic field. It is possible that the liquid beads could be formed only when the concentration of magnetic particles in ferrofluids is high and the route from the injection site to the target is short.

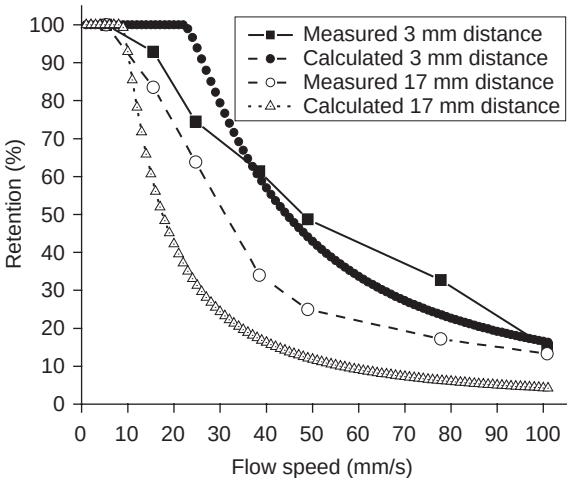

Fig. 7. The measured and calculated retentions of magnetic particles at 3 and 17 mm away from the rectangular-pyramid-frustum pole face at various flow speeds.

4.3. Targeting

From above analysis, it is better to increase the bound of applied magnetic force to concentrate the magnetic particles. But this enlarges the target area. It is a key concept to balance the conflict by optimizing the particles and the permanent magnet.

The in vivo results showed that the 20 nm magnetic particles could be concentrated in the target area (right kidney) by the C-shaped permanent magnet.

Generally the magnetic particles should be modified to make the particles escape from being phagocytosed by reticuloendothelial system (RES) in magnetic drug targeting [6,8]. Because the surfaces of the magnetic particles we used were not modified, many magnetic particles were phagocytosed by liver as MRI shows. That might explain why the particle concentration in the targeted right kidney was less than expected.

Our experimental in vitro and in vivo results for magnetic drug targeting are encouraging and should be investigated further.

Acknowledgements

This study was supported by a grant from Chinese Academy of Sciences (No. KJCX1-09). The authors wish to thank Dr. Jie Ma (Cancer Institute, Chinese Academy of Sciences) for helpful in experiment.

References

[1] A. Senyei, K. Widder, G. Czerlinski, J. Appl. Phys. 49 (1978) 3578.
[2] P.K. Gupta, C.T. Hung, Life Sci. 44 (1989) 175.
[3] A.S. Lubbe, C. Bergemann, et al., Cancer Res. 56 (1996) 4686.
[4] Q.A. Pankhurst, J. Connolly, et al., J. Phys. D 36 (2003) 167.
[5] C. Alexiou, W. Arnold, et al., Cancer Res. 60 (2000) 6641.
[6] C. Alexiou, A. Schmidt, et al., J. Magn. Magn. Mater. 252 (2002) 363.
[7] K.C. Warnke, IEEE Trans. Magn. 39 (2003) 1771.
[8] S. Goodwin, C. Peterson, et al., J. Magn. Magn. Mater. 194 (1999) 132.