

The guidance of magnetic colloids in simulated tissues for targeted drug delivery

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The delivery of anticancer agents delivered by magnetic carrier particles (MP) is an exciting new prospect in treating cancer. Here an experimental model is used to investigate the physical guidance of magnetic carrier colloids through simulated tissues. Using a gradient magnetic field, it was found that magnetic particles could be dispersed within a simulated diseased tissue in < 120 minutes. This treatment time depended on the magnetic field, the MP properties and the kind of tissue (interstitial space between the cells). These results indicate that the magnetic guidance of colloids has the potential for treating sub-surface cancers within the human body.

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1. Introduction

The systemic administration of chemotherapeutic agents has as its main drawback the distribution of the drug within the whole body resulting in cytotoxic effects on healthy cells. The magnetic drug targeting (MDT) technique offers the possibility to concentrate the cytotoxic agents within the diseased tissues thus minimizing the amounts of drug dispersed into the rest of the body. This new method uses the innovative idea of reversible binding therapeutic agents to magnetic carrier particles (MPs), injecting them into the blood stream and concentrating the MP-drug complexes within the target tissue using either high or medium gradient magnetic fields [1]. The efficiency of this therapy depends upon physical and physiological parameters including the intensity and the gradient of the magnetic field, the volume and the magnetic properties of the particles, the rate of the blood flow, the distance between the affected area and the magnetic field source, the uptake rate of the particles by the reticulo-endothelial system, the extravasation of the MPs in the tumour tissue, their cellular uptake, the strength of the binding between MPs and drugs, the volume of the tumors and the degradation rate of the carrier matrices in which the drug is enclosed [2].

This work presents an experimental model to analyse the guidance of magnetite particles (MP) through agar gels which simulates the magnetic targeting of carrier particles in human tissues. The agar gels are used because their structure and porosity resembles the interstitial space from real tissues. MPs are chosen as carrier support because they are already used routinely in humans as a contrast agent in MRI. The properties of MP (magnetization, particle size distribution) are analysed. The movement MP through the gels is studied as function of the gel porosity,

the properties of the magnetic field (intensity, gradient) and the volume of MP colloid.

2. Experimental

2.1. Preparation of magnetite

An aqueous solution of Fe(III) (4ml) and Fe(II) (1 ml) ions was prepared from 1M FeCl₃ 6H₂O and 2 M FeCl₂ 4 H₂O. 50 mL of 1.0 M aqueous NH₃ solution was added drop-wise over a period of 5 minutes under continuous stirring. The precipitated magnetite was magnetically settled, rinsed five times with distilled water (50 ml), and then treated with 2 mL of 25% tetramethylammonium hydroxide under continuous stirring for 5 minutes. The size distribution of MP suspended in water and the magnetic characteristics of the magnetic colloid suspension were analysed by dynamic light scattering (DLS) and balance force methods [3], respectively.

2.2 The guidance of MP through gels

Agar gels (plate count agar, Merck, Germany) with a range of solid concentrations (0.275 to 0.375 %) were prepared by heating agar-deionised water solution at 90° C for 15 minutes, with vigorous magnetic stirring, followed by cooling at 4° C for 24 hrs. Before cooling, the agar solutions were poured in "Plexigals" rectangular containers (20 × 20 × 23 mm) and a 2.5 mm diameter vertical well (13 mm long) was formed by inserting a cylindrical plastic pin in the solution (Fig. 1). The obtained well simulates a "reservoir" (e.g diseased blood vessel) which can accommodate various amounts of colloidal MP (0.5 to 3.5 µl). A non-uniform magnetic field generated by a magnetized ferromagnetic rod (1 cm –diameter, 15 cm-

long) placed underneath the container and the MP were guided through the gel toward its bottom surface, where the magnetic field is highest. The position of magnetic particles was registered by video-recording and their velocity through the gel was determined by image analysis.

The ferromagnetic rod was magnetized perpendicularly on its axis using a background magnetic field which was generated by a bi-polar magnetic circuit. The experimental values of the magnetic field intensity, measured using a portable Hall effect Gaussmeter (MG-5DP, Walker Scientific Inc., Worcester, USA) were compared with theoretical predictions for a linear distribution of magnetic moments [4].

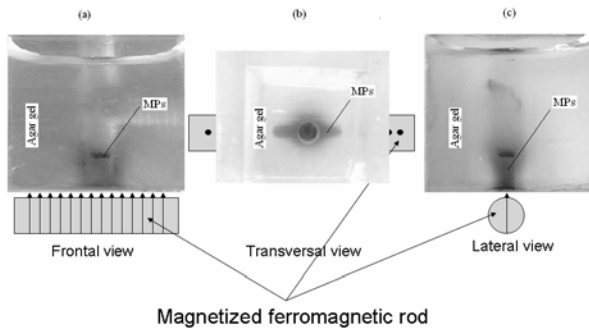


Fig. 1. Guidance of colloidal MPs through agar gels, which simulate in vitro the interstitial space from tissues. A ferromagnetic rod (diameter - 1 cm, length - 15 cm) magnetised perpendicularly on its axis generates a non-uniform magnetic field which pulls the colloidal magnetic particles towards the surface of the rod: (a) frontal view; (b) transversal view; (c) lateral view.

3. Results and discussion

The size of the MPs follows two log-normal distributions, one with particles being $< 0.12 \mu m$ (average size $x_c \sim 0.08 \mu m$) (Fig. 2 a) and the other one with particles between 0.15 to $0.5 \mu m$ (average size $x_c \sim 0.28 \mu m$) (Fig. 2 b).

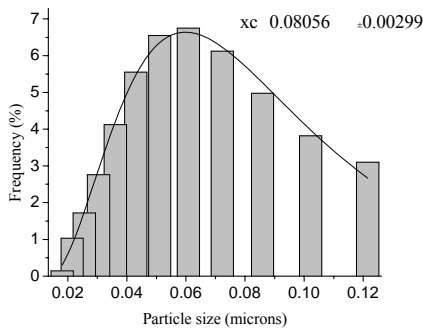


Fig. 2a. The size distribution of magnetite particles suspended in water. for low size MP (average size $x_c \sim 0.08 \mu m$).

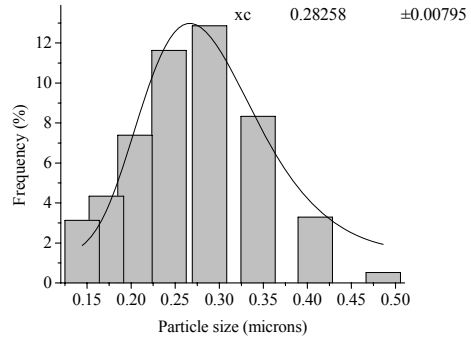


Fig. 2b. The size distribution of magnetite particles suspended in water. for large size MP (average size $x_c \sim 0.28 \mu m$).

The magnetisation of the MP colloid (M) increases increasing the magnetic field intensity and attains a saturation value of 115 Gs. Whereas, the magnetic susceptibility decreases from an initial value of 0.27 to a saturation value of 0.023 (Fig. 3).

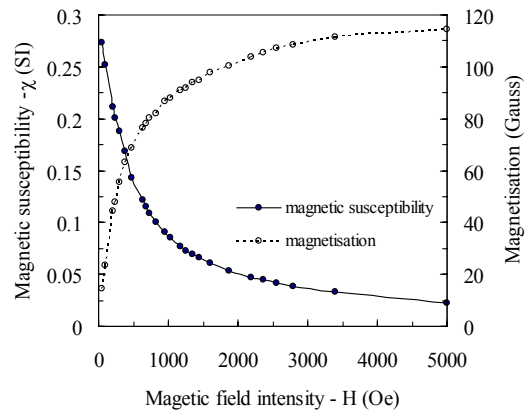


Fig. 3. The magnetic susceptibility and magnetization curves of the magnetite colloid.

The vertical component of the intensity of magnetic field (H_z) (Fig. 4), used for MP guidance through the agar gel, decreases when the distance r from the axis of the ferromagnetic rod increases [4],

$$H_z = H_o \left(1 + r_{rod} / r^2\right) \quad (1)$$

where H_o is the intensity of background magnetic field used to magnetize the ferromagnetic rod of radius r_{rod} . Equation (1) is valid when the ferromagnetic rod has length much longer than its radius, and the intensity of the background magnetic field is not high enough to saturate the rod ($H_o < M_{srod} / 2 = 18000 \text{ Gs} / 2 = 9000 \text{ Gs}$).

The magnetic force acting on MPs is

$$F_{mz} = \mu_0 V_{MP} M_{MP} \nabla H_z = -2\mu_0 V_{MP} M_{MP} H_o r_{rod} / r^3 \quad (2)$$

where V_{MP} and M_{MP} are the volume and the magnetization of the MPs, respectively.

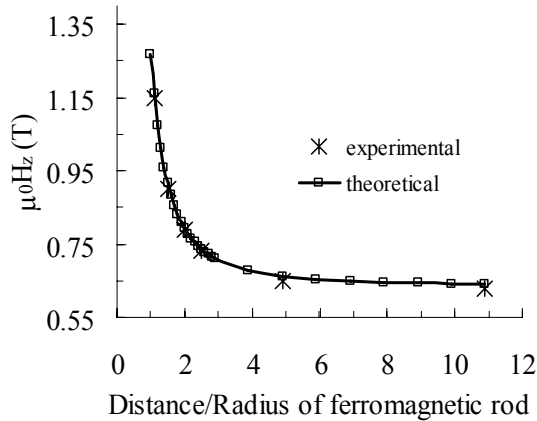


Fig. 4. The vertical component of the magnetic field for a ferromagnetic rod magnetized perpendicular on its long axis: The saturation magnetisation of the rod is $M_{srod} = 18000$ Gs and the background magnetic field is $H_o = 6000$ Oe.

According to eq. (2) the velocity of MPs (which is proportional with the magnetic force) must decrease when the distance r from the rod increases. However, the velocity of the fastest particles measured by imaging techniques (Fig. 5) is constant along the MP path through the gel (Fig. 6). Moreover, the MP velocity further depends on the initial amount of colloid from the “reservoir” (Fig. 7).

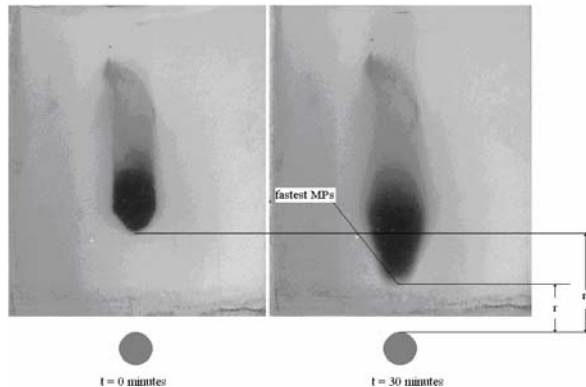


Fig. 5. The velocity through the gel for the fastest magnetic particles is calculated by video-recording of their positions at different time moments: (a) initial position (r_i) of the MP, $t = 0$ minutes; (b) the position (r) of MP after $t = 30$ minutes.

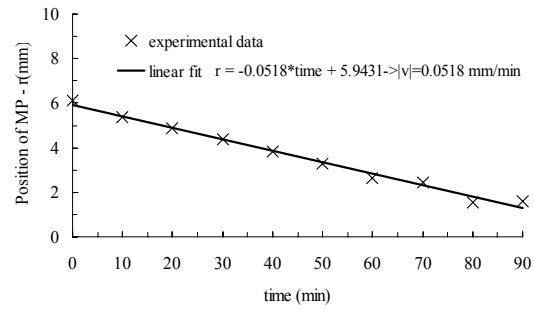


Fig. 6. The position $r(t)$ of fastest MP measured from the ferromagnetic rod surface at various times. The velocity of particles is constant. Parameters used in experiment are: $H_o = 6000$ Oe; concentration of agar $C_{agar} = 0.375$ g/100ml.

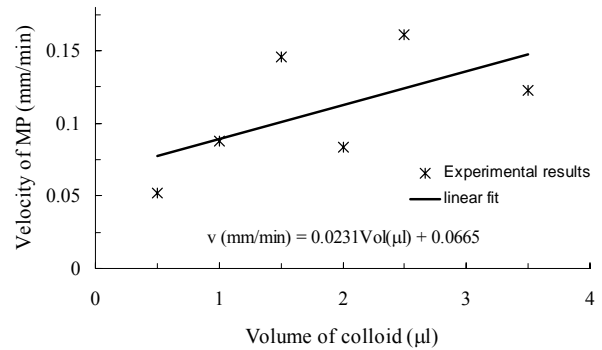


Fig. 7. The dependence of MP velocity on the initial volume of colloid from the “reservoir” (The concentration of agar was 0.35 %, and the magnetization of colloid was $M 115$ Gs).

Fig. 8 presents the variation of MP velocity with the intensity of the background magnetic field. As expected, the velocity of particles has a linear dependence on magnetic field intensity in accordance with eq (2)

$$F_{mz} \sim H_o \quad (3)$$

The dependence of MP velocity on the concentration of agar (porosity of gel) is presented in Fig. 9. The velocity of particles decreases exponentially with increasing agar concentration (the decrease of pore size within the gel), but the gel is not readily permeable for all particles. As seen from Fig. 1 the larger MPs are sieved by the gel and only the smaller ones approach the bottom of the container. Once the particles arrive onto non-permeable surfaces (e.g membranes surrounding various organs) they spread in shapes which follow the geometry of the magnetic poles. Therefore, it is expected as the pattern of MP distribution inside human tissues will depend on several factors: the characteristics of the tissue, the properties of the magnetic particles, the geometry of magnetic poles, and the strength and gradient of the magnetic field. Further investigation needs to be done *ex*

vivo, including experiments using real tissues that take into account the variables mentioned above.

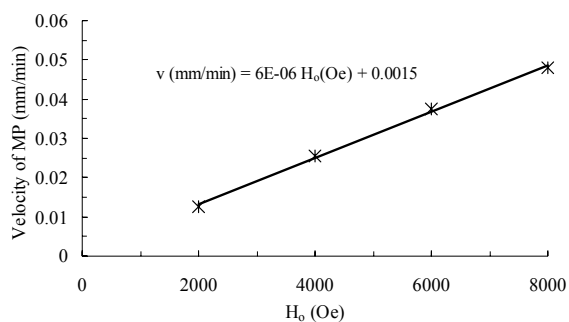


Fig. 8. The dependence of MP velocity on the intensity with the background magnetic field, H_0 . The volume of colloid in the "reservoir" was $0.5 \mu\text{l}$, magnetization of colloid was 115 Gs and the concentration of agar was $0.4 \text{ g}/100 \text{ ml}$.

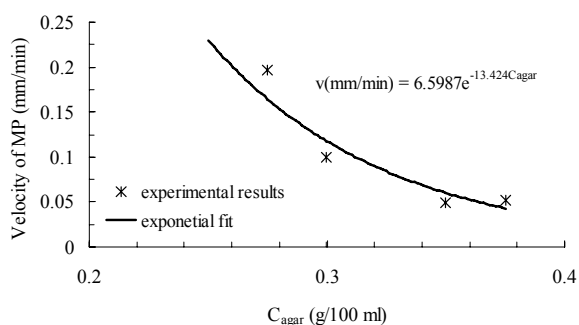


Fig. 9. The dependence of MP velocity on the agar concentration (gel porosity). The volume of colloid in the "reservoir" was $0.5 \mu\text{l}$ and magnetization of colloid was 115 Gs.

4. Conclusions

These results indicate that magnetic techniques using gradient magnetic fields and magnetite colloids have the potential to be practical tools for sub-surface guiding of anti cancerous agents within the human body.

References

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