Magnetic capturing and guiding of magnetite-polyvinyl alcohol ferrofluids for targeted drug delivery

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Abstract. We presented some results concerning the targeting/capture and guidance of the colloidal magnetic particles (MP) in/through simulated blood vessels/tissues. A bipolar magnetic device was used to investigate the capture of MP in capillary tubes at flow velocities similar to those encountered in the capillary beds of tumors. The capture was influenced by the gradient of the magnetic field, the flow velocity, the concentration and surface properties of the MP. The physical guidance of the MP through simulated tissues was also investigated and it depends on the magnetic field, the MP properties and the interstitial space between the cells.

1. Introduction
The magnetic targeting of MP carrying anticancer agents is efficient for drug delivery, reducing the systemic side effects [1]. Despite real progress obtained with this method [2, 3] some technical and physiological problems hinder the application of the method in practice, so understanding of the physical conditions for the magnetic capture of carrier particles is required. The aim of our study was to evaluate the optimal physical and physiological conditions for the magnetic manipulation of the MP inside the human body, in order to increase the efficiency of the magnetic targeting techniques for tumour treatments. We present an experimental device for studying MP’s capture within fluidic systems simulating the flow regime in small blood vessels [4]. It was studied the possibility of MP retention and entrapment inside plastic tubes, within regions that have similar sizes with the cancer tumours. We also present an experimental model for studying the guidance of MP through agar gels (structure and porosity resembles the interstitial space from real tissues) which simulates the magnetic targeting of carrier particles in human tissues [5]. The movement MP through the gels is studied as function of gel porosity, the properties of the magnetic field and the volume of MP colloid.

2. Materials and methods

2.1. Preparation and characterization of ferrofluid
The ferrofluid was prepared by co-precipitation in aqueous media of the iron salts with a concentrated NaOH solution, at 70°C, followed by stabilization with 1% aqueous polyvinyl alcohol solution (MP-PAV). The size of the MP was measured by dynamic light scattering (Nano/Microtrac, Inc.US). The magnetization of the MP was measured using a magnetometer with vibrating probe.

2.2. Capture of magnetic particles
The experimental setup used for the deviation/capturing of MP is presented in Fig. 1. The ferrofluid was pumped through the plastic tube into the bipolar magnetic capture system; the MP were magnetically attracted from the flow field and captured onto the tube’s wall. Time necessary for the vessel to be blocked and the length of MP deposit were estimated as a function of the initial fluid velocity, the MP concentration and the position of “blood vessels” within the magnetically active zone.
2.3. The guidance of MP through gels

Agar gels with a range of solid concentrations (0.275 to 0.375 %) were prepared by heating agar-deionised water solution at 90°C, followed by cooling at 4°C for 24 hrs. Before cooling, the agar solutions were poured in “Plexigals” rectangular containers (20x20x23 mm) and a 2.5 mm diameter vertical well (13 mm long) was formed by inserting a cylindrical plastic pin in the solution. The obtained well simulates a “reservoir” (e.g. diseased blood vessel) which can accommodate various amounts of MP (0.5 to 3.5 µl). A non-uniform magnetic field generated by a magnetized ferromagnetic rod 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 and their velocity through the gel was determined by image analysis.

3. Results and discussion

3.1 The characterization of magnetic particles

The DLS dimensional analysis showed a log-normal distribution, the MP-PAV had sizes between 0.05 to 1.15 µm (mean size = 0.36 µm). We chose such a distribution of the MP because large particles can create a magnetic gradient responsible for the capture of the small particles that otherwise are not captured. The MP-PAV magnetization was 4250 G.

3.2. The capture of MP – PVA

The time interval necessary to block the capillary vessels with MP (blocking time) is an important parameter necessary to establish the time scale for an in vivo treatment procedure, giving the approximate time of injecting MPs into the blood stream. Also, the extension of the MP deposits onto the tube’s walls (length of the deposit) is important to estimate the volume of tissue which can be treated by the magnetic targeting procedure. The blocking time and the length of particle deposits vary with the process parameters.
(tube position in the magnetic field, x, the strength and gradient of the magnetic field, the initial fluid velocity/flow rate, the MPs concentration and their magnetization). The blockage appears earlier in the proximity of the rectangular magnetic poles ($t = 677 \text{ s}$ at $x = 7.7 \text{ cm}$ and $t = 723 \text{ s}$ at $x = 7.2 \text{ cm}$), later in the proximity of conical magnetic poles ($t = 1103 \text{ s}$ at $x = 0.5 \text{ cm}$ and $t = 1224 \text{ s}$ at $x = 1.0 \text{ cm}$) and does not appear at $x = 1.5$ and $6.7 \text{ cm}$. (Fig. 3a). The length of the deposits varies, being higher in the proximity of the rectangular poles, where the gradient of the magnetic field/magnetic force is intermediate (Fig. 3b). However the capture takes place even at larger distances from the poles ($x = 1.5$), where the gradient is smaller. A maximum deposit length of 7.7 cm was observed, but the deposit was not stable. Moreover, when the tube is placed at $x = 6.7 \text{ cm}$ the appearance of avalanches is evidenced and the length of deposit fluctuates. The variation of MPs-PAV concentration and the fluid velocity affects the time of blockage and the length of deposit (Fig. 4). At low velocities ($v = 0.43 \text{ cm/s}$) that is are similar to that found in diseased capillaries the blockage takes place even at very low concentrations. But, the time necessary to block-up the tube increases and the length of deposit decreases ($t = 1074 \text{ s}$, $L = 2.79 \text{ cm}$ for $c = 0.02 \text{ g/ml}$ and $t = 1954 \text{ s}$, $L = 2.23 \text{ cm}$ for $c = 0.01 \text{ g/ml}$). When the fluid flows at a rate representative of normal arterioles ($v = 0.86 \text{ cm/s}$) the deposits of particles are longer ($L = 7.7 \text{ cm}$) but unstable and the tubes are not blocked. Using the MPs-PVA and the results for their deposit lengths, and taking into account that the magnetic field has an axial symmetry within the active space of the magnetic circuit, it is possible to appreciate that the maximum volume of diseased tissue hypothetically blocked at the capillary level is ~100 cm$^3$.

![Figure 3](image1.png)

**Figure 3.** (a) The mass of fluid collected as a function of time. (b) Length of deposit versus time ($v = 0.29 \text{ cm/s}; c = 0.02 \text{ g/ml}$)

![Figure 4](image2.png)

**Figure 4.** (a) The mass of fluid collected as a function of time. (b) Length of deposit versus time

### 3.3 The guiding studies
The velocity of the fastest particles measured by imaging techniques is constant along the MP path through the gel (Fig. 5). Moreover, the MP velocity further depends on the initial amount of
colloid from the “reservoir” (Fig. 6), the intensity of the background magnetic field (Fig. 7), with agar concentration (Fig. 8). The gel is not permeable for all particles, the larger MP being sieved by the gel and only the smaller ones approaching 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.

\[ r = -0.0518 \times \text{time} + 5.9431 \rightarrow |v| = 0.0518 \, \text{mm/min} \]

![Figure 5. The position of fastest MP](image)

![Figure 6. MP velocity / volume of colloid](image)

![Figure 7. MP velocity function of the intensity of magnetic field, \(H_0\).](image)

![Figure 8. MP velocity versus the agar concentration (gel porosity)](image)

4. Conclusions
The obtained results indicate that the magnetic drug targeting technique using gradient magnetic fields (particularly a “C form” magnetic circuit) is suitable for the treatment of cancers in regions that can be fit to the active space of 8.7 cm (head, neck, breast, hands and legs) and situated at sub-surface of the body because of the values of the magnetic field/gradient, by either concentrating drugs within the tumour or embolization to block the blood supply to the tumour. 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
[1] Marcucci F and Lefoulon F 2004 Drug Disc. Today 9 219
[2] Alexiou C, Arnold W, Klein R J, Parak F G, Hulin P, Bergemann C, Erhardt W, Wagenpfeil S and Lubbe A S 2000 Cancer Res. 60 6641
[3] Lubbe A S, Bergemann C, Riess H, Schriever F, Reichardt P, Possinger K, Matthias M, Dorken B, Herrmann F, Gurtler R, Hohenberger P, Haas N, Sohr R, Sander B, Lemnke A J, Ohlendorf D, Huhnt W and Huhn D 1996 Cancer Res. 56 4686
[4] Udrea L E, Badescu V, Strachan N J C and Rotariu O 2007 J. Optoelectr. Adv. Mat. 9(8) 2593
[5] Rotariu O, Udrea L E, Strachan N J C and Badescu V 2007 J. Optoelectr. Adv. Mat. 9(4) 942