# MAGNETIC SUPPORT NANOPARTICLES FOR THE TARGETING OF DRUGS: PHYSICAL CHARACTERIZATION AND MANIPULATION IN MAGNETIC FIELD♦

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**Abstract:** The magnetic capture of colloidal magnetic particles (MPs) flowing in capillary tubes is studied. This models magnetic the embolization of "blood vessels" as a treatment for cancer. The study investigates the evolution of MPs deposition using video imaging and flow recording techniques. The parameters of practical importance (length of MPs deposits, time of capillary blocking) are estimated, and they are dependent on the initial fluid velocity, the MPs concentration and the position of capillary tubes within the magnetically active zone.

The study reveals that stable deposits of colloidal MPs block - up the capillary tubes on lengths of few centimeters when the tubes are positioned in the proximity of the magnetic poles and the colloid velocity is low (< 0.5 cm/s). Depending on the particle concentration and the flow velocity, the blocking time varies between 10 to 30 minutes. A dynamic deposition regime appears when the capillary tubes are positioned far away (1.5 to 6.0 cm) from the magnetic poles. In this case the length of the MPs deposits increases up to 7.7 cm, but the deposits are unstable and avalanches take place. These results indicate that magnetic embolization is suitable for treating sub-surface cancers within the human body.

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## INTRODUCTION

The active targeting of particulate drug carriers, bearing anticancer agents, can achieve more efficient drug delivery, so that the drug predominantly affects only the cancer cells, hence reducing the systemic side effects [1]. The magnetic delivery of anticancer drugs/agents (MDD) is an alternative to current systemic treatments. However, the challenge is to target the drugs precisely for the local treatment of solid cancer tumours [2]. The method uses the ability of the magnetic particles (MPs) to bear/entrap anticancer drugs that can be fixed and slowly released at the diseased site, by using an external gradient magnetic field. Despite real progress obtained with this new method (permanent remission of squamous cell carcinoma [3] and encouraging results in clinical trials [4]) a series of technical and physiological problems hinder the application of the method in clinical practice.

Therefore, a better understanding of the physical conditions for the magnetic capture of carrier particles is required. Moreover, the use of MPs capacity to block blood vessels and stop the nutrients supply to tumours can be an alternative or adjuvant method to treat cancer. The physical aspects of the MPs concentration into microvasculature have been experimentally investigated for MPs at high concentrations (up to 54%), magnetic fields with high strengths (0.5 – 1.0 T) and medium field gradients (0.2 T/cm) [5]. These results showed the possibility that embolization of blood vessels could be achieved within minutes, for an active magnetic space of maximum 4 cm. However, the conditions for high magnetic fields focused at any region of the human body are difficult to realize.

This paper presents and tests an experimental device for the MPs capture within fluidic systems simulating the flow regime in small blood vessels, by using a magnetic circuit having a large active space (the width of air gap - 8.7 cm), with a medium field of 0.3 T and medium field gradient of 0.15 T/cm). The aim of the study is to prove the possibility of MPs retention and entrapment inside plastic tubes (“blood vessels”), within regions that have similar sizes with the cancer tumours.

## EXPERIMENTAL

The experimental setup simulates the deviation/capturing of MPs from the aqueous suspensions and the building of particle deposits onto the capillary tubes walls (Figure 1). About 5 mL of magnetic colloid (magnetite – size - 10 to 100 nm, magnetization of saturation – 340000 A/m, obtained in our laboratory) suspended in deionised water (1% w/v polyvinyl alcohol content) is pumped by the injection pump (house maid, flow rate – 0.05 to 1.0 mL/min) (1), through the vertical plastic tube (5), into the magnetic system (7). The MPs are deviated by the magnetic forces from the flow field and captured onto

the tube's wall into the region that is supposed to be affected by the tumour. The evolution of the particle buildup is monitored by the camcorder (11). The clean fluid passes to the collector (8), is weighed by a balance (10) and the data are stored on the PC (12). Alternatively, the colloid passes in a systemic way to the collector (9) through the ramification (2) and the plastic tube (6) that is not placed in the magnetic filed. The valves (3) and (4) are used for the variation of the fluid flow rate.

The mass of the fluid that passes through the magnetic system is measured at one second time intervals. The evolution of the collected mass permits the evaluation of the flow conditions through a hypothetical region targeted by MPs. Also, it gives the time necessary for the tube to be blocked. The evolution of the particle buildup is acquired at 30 frames/second. The length of MPs deposit is evaluated at time intervals of 30 seconds. This gives an indication of the affected area which can be targeted by the magnetic system. The above parameters are estimated as function of the initial fluid velocity, the MPs concentration and the position of capillary tube within the magnetically active zone.

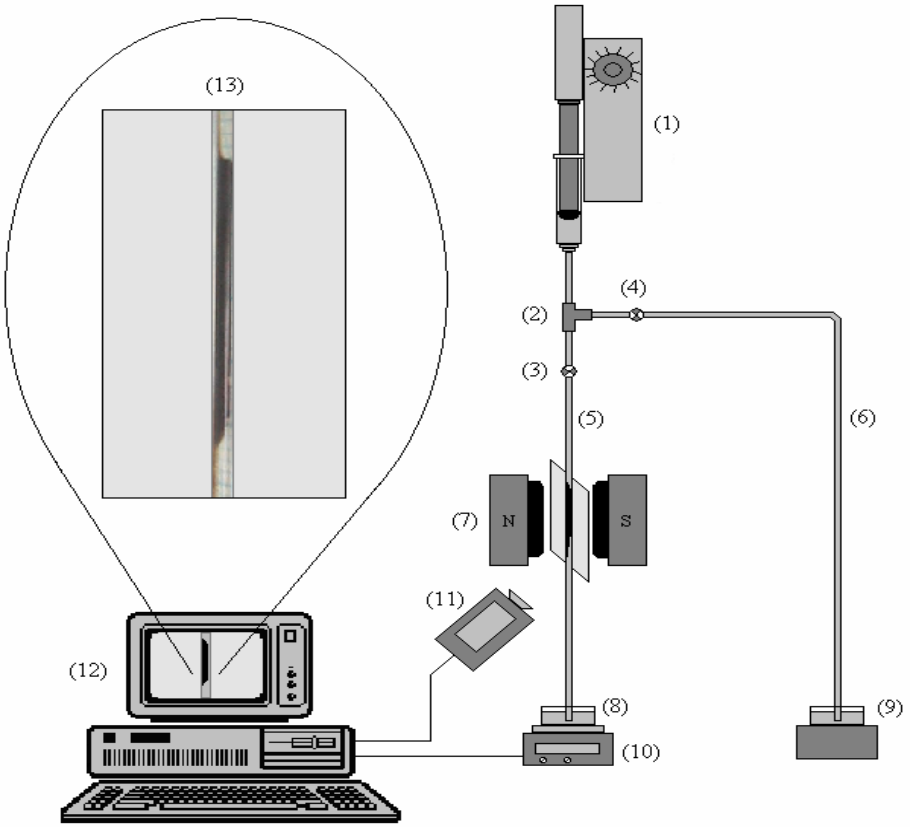


***Figure 1.*** *Experimental device to prove the principle of magnetic particle targeting inside of capillary tubes*

*(1) injection pump, made in our laboratories; (2) – ramification; (3 – 4) – valves; (5 – 6) – capillary plastic tubes with 0.75 mm inner diameter; (7) – magnetic system – "C form" magnetic circuit with 8.7 cm air gap, made in our laboratories; (8 - 9) – collectors; (10) – Acculab LA-200 electronic balance with PC interface; (11) – Sony DCR-HC85E Handycam camcorder; (12) – PC with video acquisition program; (13) – detail of an acquired image.*

## RESULTS AND DISCUSSIONS

The magnetic system (7) (Figure 1) consists of a "C form" magnetic circuit with conical (the diameter – 13 mm, the cone angle – 60°) and rectangular polar pieces (50 x 50 x 12 mm). Using the 2D "Finite Element Method Magnetics" program (FEMM 3.4) from Foster–Miller (http://femm.foster.miller.com) the values of the magnetic field are calculated for the symmetry axis of the air gap (Ox) and this varies between 0.11 to 0.54 T (Figure 2). The experimental values, measured using a portable Hall effect Gaussmeter (MG-5DP, Walker Scientific Inc., Worcester, USA) agrees well with the numerical results. These field values are high enough to magnetize the MPs at the saturation value. The gradient of the magnetic field is maximum at the surface of the polar pieces (0.31 T/cm on the conical polar piece and 0.2 T/cm on the rectangular polar piece) and is null at $x$ = 3.5 cm. This means that the magnetic force exerted by the external magnetic field on the MPs should be higher towards the conical pole, lower at the middle of the air gap and moderate towards the rectangular pole. Accordingly, the capture of MPs must follow the same behavior.

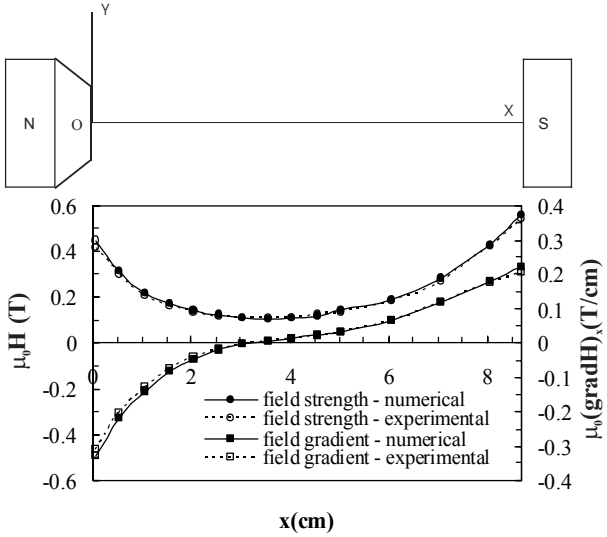


***Figure 2**. The magnetic field and field gradient in the air gap of the magnetic system*

Figure 3a presents the mass of the fluid depleted by MPs after it passes through the magnetic system (7) and is collected in the collector (8) as a function of time. The distance $x$ between the plastic tube (5) and the conical magnetic pole is a variable parameter. The saturation of the mass values indicates embolization being achieved within the tube as previously was found for high concentrations of MPs [5]. This means that once the MPs build-up a strong "embolus" then all of the suspension is diverted through the by-pass tube (6). However, the tube (5) is not always embolized. The embolization appears earlier in the proximity of the rectangular magnetic poles ($t$ = 677 s at $x$ = 7.7 cm and $t$ = 723s at $x$ = 7.2 cm), later in the proximity of conical magnetic poles ($t$ = 1103 s at $x$ = 0.5 cm and $t$ = 1224 s at $x$ = 1.0 cm) and does not appear in the middle of the air gap ($x$ = 1.5 and 6.7 cm). The length of the deposits varies between $l$ = 12.6 mm and $l$ = 27.8 mm, being higher in the proximity of the rectangular poles, where the gradient of the magnetic field/magnetic force is intermediate (Figure 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 77 mm was observed, but the deposit was not stable. Moreover, when the tube is placed at $x$ = 6.7 cm the appearance of avalanches is evidenced and the length of MPs deposit fluctuates (figure 3b).

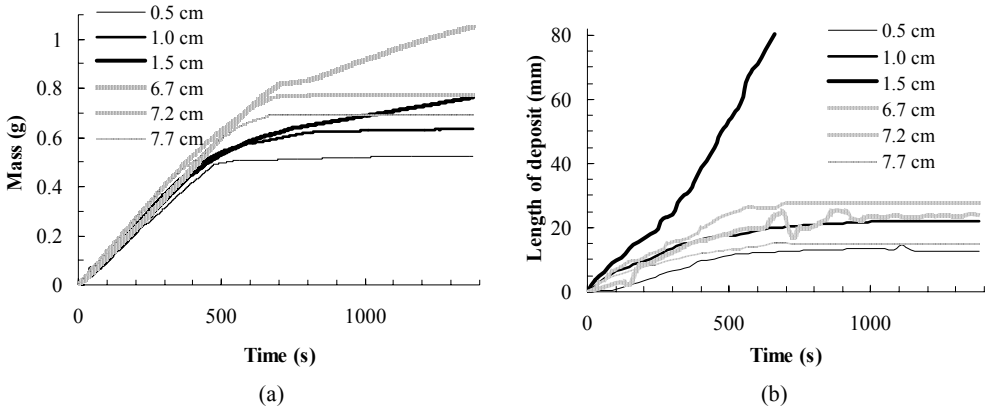


***Figure 3.*** *(a) The mass of fluid collected in the collector (8) after the suspension passes through the magnetic system (7) as a function of time. (b) The variation of the length of deposit as a function of time. Parameters used in the experiments were: the initial velocity (calculated at the beginning of the capture process) of the fluid – v = 0.29 cm/s; the concentration of MPs – c = 0.023 g/mL; the tube was positioned at various distances in the air gap of the magnetic system.*

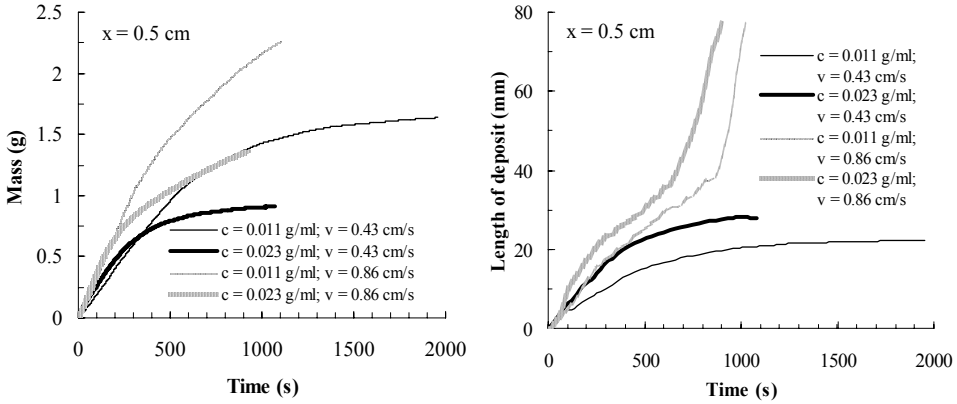


***Figure 4.*** *(a) The mass of fluid collected in the collector (8) after the suspension passes through the magnetic system (7) as a function of time. (b) The variation of the length of deposit as a function of time. Parameters used in the experiments were: the initial velocity of the fluid – v = 0.43 and 0.86 cm/s; the concentration of MPs – c =0.011 and 0.023 g/mL; the tube was positioned at x = 0.5 cm from the conical magnetic pole.*

The variation of MPs concentration and the fluid velocity affects the time of embolization and the length of deposit (Figure 4). At low velocities ($v$ = 0.43 cm/s) that is are similar to that found in capillaries and small arterioles the embolization 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 s, $l$ = 27.9 mm for $c$ = 0.023

g/mL and $t$ = 1954 s, $l$ = 22.3 mm for $c$ = 0.011 g/mL). When the fluid flows at a rate representative of normal arterioles ($v$ = 0.86 cm/s) the deposits of particles are longer ($l$ = 7.7 cm) but unstable and the tubes are not blocked.

Although the aqueous suspension of MPs used in this experiment has a viscosity 3-4 times smaller than that of the normal blood, its rheology drastically increases in the presence of the magnetic field, where the suspension turns from fluid-like to solid-like system [5]. This makes the viscosity of the suspension media (e.g. blood) a less important parameter when studies the embolization of blood vessels by using MPs.

Using the results for the 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 $cm^3$. This suggests that using the "C form" magnetic circuit and colloidal magnetic particles it is possible to embolize the capillary vessels from medium size tumours, which will be starved from blood supply and will become necrotic.

## CONCLUSIONS

The magnetic capture of magnetite MPs was obtained in a small capillary tube placed in the air gap of a "C form" magnetic circuit. Stable "emboli" were obtained in fairly rapidly (~10 minutes) at small MPs concentration and low fluid velocities (<0.5 cm/s) that are specific to the tumour microcirculation. The range of stable capture was up to 1.5 cm from the magnetic poles and the length of MPs deposits extended up to 28 mm. These results suggests that the magnetic targeting technique using gradient magnetic fields (particularly a "C form" magnetic circuit) is suitable for embolization of small blood vessels to treat sub-surface cancers within the human body.

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