Theoretical Analysis of Transdermal Ferromagnetic Implants for Retention, Retrieval and Guidance of Magnetic Drug Carrier Particles

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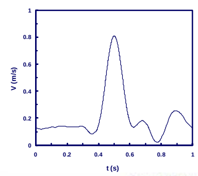
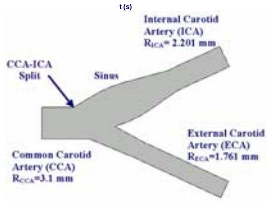
INTRODUCTION

- Drug carriers, such as vesicles and polymeric particles that contain ferromagnetic elements, can be more easily guided to, collected at, and removed from diseased sites in the body, using some kind of magnetic drug targeting (MDT) approach.
- To this end, high gradient magnetic separation (HGMS) principles can offer a wide variety of new possibilities for MDT[1], by using a specially designed ferromagnetic implant to enhance the performance of the MDT system, compared to the conventional approach, which uses only an external magnetic as the magnetic field source.
- One very important application of such a MDT technology is the extravascular use of a transdermal, ferromagnetic wire placed near a diseased and treated carotid bifurcation.
- For example, HGMS-assisted MDT can be used for drug delivery to reduce restenosis, which is the re-narrowing of the artery caused primarily by a healing response of the body to the injured area

OBJECTIVE

- This study examines the use of a ferromagnetic wire that is implanted under the skin next to the carotid artery to assist in the collection of magnetic drug carrier particles (MDCPs) at the common carotid artery – internal carotid artery (CCA-ICA) split using an external magnet.
- A 2-D model[1] developed in the FEMLAB platform is used to determine the trajectory of the MDCPs (χ_P = 1000, $M_{P,S}$ = 480 kA/m) through the CCA-ICA.
- A realistic time dependant, diastolic/systolic velocity profile and a realistic artery geometry are used in this model.
- Three MDT systems are compared: 1) the use of a permanent magnet (M_m=1,200 kA/m, R_m=6.2 cm) combined with a wire (χ_w=1000, $M_{w,s}$=1,650 kA/m, R_w=1.55 mm), 2) the use of a permanent magnet alone, and 3) the use of a homogenous magnetic field (H_0=538 kA/m) combined with a wire.

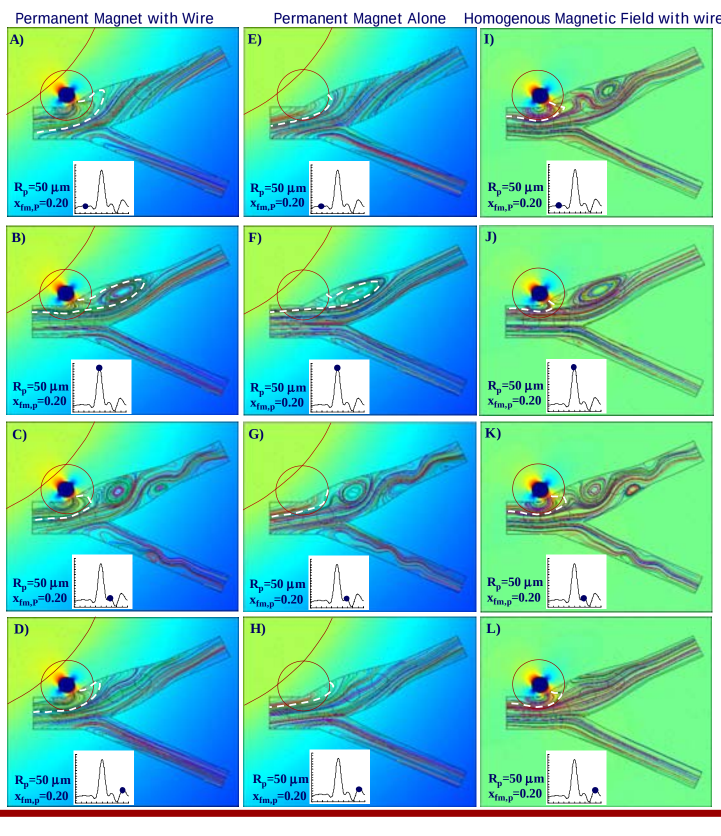




MODEL ASSUMPTIONS

- MDCPs are modeled as clusters of agglomerated particles with interparticle porosity of 0.4 and the external magnet with a field identical to that of a cylinder. A model provided elsewhere is used.[1]
- The model accounts for only magnetic and drag forces acting on the MDCPs. For simplicity, wall, lift and interparticle magnetic forces are not considered, while both the gravitational and inertial forces are assumed to be negligible at the flow conditions investigated in this study.
- Additional assumptions include the blood to be a homogeneous, incompressible Newtonian fluid flowing at a periodic, pulsating velocity (see above).
- Non-slip boundary conditions are applied at every interface in contact with the blood stream.
- The velocity at the inlet of the of the CV is defined by a parabolic profile with average velocity u_o defined as a function of time as indicated by the diastolic/systolic velocity profile above.

TYPICAL SIMULATION RESULTS



PARAMETRIC STUDY

- The study focuses only on the collection of MDCPs at the zone represented by the circle around the wire (i.e., within $R_{RET} = 3R_w$).
- Based on the results shown in Figure 1, the limiting case observed with the highest velocity (i.e., B, F and J) are used for the parametric study.
- This brief parametric study considers only the effect of the 1) MDCP size (R_p) and 2) magnetite content ($x_{fm,p}$) in the MDCP on the collection efficiency (CE)
- The CE of the system is evaluated as the percentage of MDCPs that are diverted and retained at the CCA-ICA split zone.

EFFECT OF PARTICLE SIZE AND MAGNETITE CONTENT ON CE

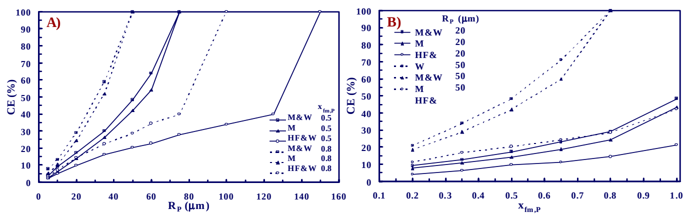


Figure 2: Effect of the MDCP radius (R_p) and its magnetite content (x_{fm}) on the CE at systolic velocity conditions for a permanent magnet and wire (M&W), permanent magnet alone (M), and homogenous field combined with a wire (HF&W). (A) shows the effect of the MDCP radius (R_p) for different magnetite contents ($x_{fm,p}$ = 0.5 and $x_{fm,p}$ = 0.8). (B) shows the effect of the MDCP magnetite content ($x_{fm,p}$) for different MDCP sizes (R_p = 20 µm, R_p = 50 µm). As expected, CE increases with increases in both the MDCP size and its magnetite content. The magnetic force is proportional to the magnetic field and the magnetic field gradient; but it also depends on the MDCP properties. For larger MDCP sizes, the magnetic force increases, thus increasing CE. The same is true for the magnetite content of the MDCP. CEs of 100% are even possible for the very large MDCP sizes and high magnetite contents. However, these larger MDCP sizes are made possible here only through their becoming magnetically agglomeration with each other. Although this is an assumption in this work, it is a very real and interesting phenomenon that is currently being studied. It is also observed that the M&W case exhibits higher CEs compared to the other two cases. This result is expected for the M case; but, it is not so obvious why the M&W case is better than the HM&W case. This is simply due to the small gradient from the permanent magnet playing a role in increasing the force on the MDCP; this gradient does exist at all in the homogeneous field case.

CONCLUSIONS

- The role of a ferromagnetic wire in the collection of MDCPs at a point in the carotid bifurcation, with the wire placed just outside the artery, is found to be quite successful at enhancing the CE.
- In all cases, increasing either the MDCP size or its magnetite content increases the CE of the MDCP. In many cases, under realistic and feasible conditions, CEs of 100% are indeed achievable. These are very encouraging results because they are obtained under systolic (high) velocity conditions. Higher CEs are expected when considering the short recirculation period of the blood circulatory system and under diastolic conditions.
- Magnetic agglomeration of the MDCPs with each other, a commonly observed phenomena, is key to the success of this technique. However, agglomerated MDCPs may harm the bady. This means that de-agglomeration must occur when the magnetic field is removed, or when they are some distance away from the field so the smaller MDCPs can flow through the tiny capillaries without harming the body through necrosis (i.e., blockage). This topic is under investigation.
- An external magnet alone is able to collect some MDCPs; but, without the wire present to create larger magnetic field gradients, the force on the MDCPs is clearly weaker, resulting in low CEs. This diminished collection may be further affected by lift and wall forces (not accounted for here) that tend to bring the MDCPs back to main blood flow. This makes the presence of the wire even more important.
- A homogenous field plus the wire is not as good as the magnet plus the wire, simply due to the magnet imparting an additional contribution to the force due to its small magnetic field gradients that do not exist in the case of the homogenous field.

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REFERENCE

[1]J.A. Ritter, A.D. Ebner, K.D. Daniel, and K.L. Stewart, **"Application of High Gradient Magnetic Separation Principles to Magnetic Drug Targeting,"** ***J. Mag. Mag. Mat.***, **in press on-line (2004).**

Figure 1: FEMLAB simulations showing the retention of MDCP at the CCA-ICA split of the carotid artery at different times. The results shown are for MDCPs (χ_P = 1000, $M_{p,s}$ = 480,000) with radius (R_p) of 50 µm and magnetite content (x_{fm}) of 0.2. (A) to (D) show the area of collection (white dashed line) for the case of a permanent magnet (M_m = 1,200,000 A/m, R_m = 6.2 cm) combined with a wire (χ_w = 1000, $M_{w,s}$ = 1,650,000 A/m, R_w = 1.55 mm). (E) to (H) show the area of collection for the case of a permanent magnet alone (M_m = 1,200,000 A/m, R_m = 6.2 cm). (I) to (L) show the area of collection for the case of a homogenous field (H_0 = 537,780 A/m). Each set of results are taken at a different time during the pulsating velocity cycle as shown in the insert. The results clearly show greater collections of the MDCPs with the permanent magnet and wire combination. They also show a lower limiting case of collection at the high systolic point, where the velocity is greatest.

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