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A POSSIBILITY FOR LOCAL TARGETING OF MAGNETIC CARRIERS

Gh. Iacob*, O. Rotariu[a], H. Chiriac[a]

University of Medicine and Pharmacy, Faculty of Medical Bioengineering, Iasi, Romania
[a]National Institute of Research & Development for Technical Physics, Iasi, Romania

This work suggests a new procedure for local targeting of magnetic microentities (magnetic oxide particles, ferro-carbon particles, magnetic polymer particles, magnetic amorphous alloys particles, etc.), by placing small sized ferromagnetic wires in the target area or within the area joining the target and applying an external uniform background magnetic field which has to be perpendicular to the magnetizable wires. The possibility to capture the magnetic microparticles and to build deposits is theoretically studied under circumstances similar to the *in vivo* ones.

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1. Introduction

In the process of magnetic separation achieved accordingly to the magnetic susceptibility, on a particle in the magnetic field H acts a magnetic force F_m.

The general expression of F_m is

$$F_m = \mu_0 V_p (\chi_p - \chi_L) H \nabla H , \quad (1)$$

where V_p is the particle volume, χ_p - the particle magnetic susceptibility, χ_L - the fluid susceptibility and ∇H is the magnetic field gradient.

As one can see, F_m depends directly on ∇H so that, in order to obtain a high magnetic force, especially in the case of microsized particles (the magnetic force depends on the cubic radius of the particle), high non-uniform fields must be created.

There are two ways to reach high values of ∇H:

(i) by using an adequate geometry of the magnets and polar pieces: in this case, the ∇H value is often strong enough to capture small particles from a flowing liquid, especially when they pass at a large distance from the magnet or polar piece surface;

(ii) by introducing small sized ferromagnetic elements (wire, balls, etc.) within the space where there is applied the background magnetic field: the role of these elements is to create high local gradients of the magnetic field (of the order ~10^5 kOe/m) [1].

The first way to generate field non-uniformities is not always the best. In most of the cases, the gradient is obtain not mainly due to the shape of the applied permanent magnet surface (open magnetic circuit), but rather due to the different (decreasing) value of the field intensity H when moving away from the magnet surface. Even if a partly closed magnetic circuit would be used (with the polar pieces facing each other), with a gap in which a very strong magnetic field can be generated and the target zone (a deep tumor) can be placed, the obtained field structure would not make possible a field lines concentration upon only the target zone. Moreover, this would become very difficult in the case of a deep target, especially of small dimensions.

* Corresponding author: iacob@phys-iasi.ro

In exchange, the second way permits to reach this aim: an adequate arrangement of ferromagnetic elements (one or more wires) conveniently located within the target zone or near by it will concentrate the magnetic field lines only where is necessary. This procedure would permit to establish with a better accuracy the desired target spot and to ensure an increased efficiency in capturing the magnetic microparticles (magnetic oxide particles, ferro-carbon particles, magnetic polymer particles, magnetic amorphous alloys particles, etc.) from the carrier fluid.

In the case of a ferromagnetic wire placed within a background magnetic field there are three ideal versions of spatial arrangement of the wire: the transversal configuration (T) -the fluid flow, the magnetic field and the wire are mutually perpendicular; the longitudinal configuration (L) -the fluid flow and the magnetic field are parallel to each other and perpendicular to the wire; and the axial configuration (A) -the flow is parallel to the wire, and the magnetic field is transversal.

2. Modeling on the microparticles movement and deposits formation

Let us consider the case of a single cylindrical ferromagnetic wire. The wire can be envisioned as a thin magnetizable acupuncture needle introduced outside a blood vessel near a tumor (Fig. 1).

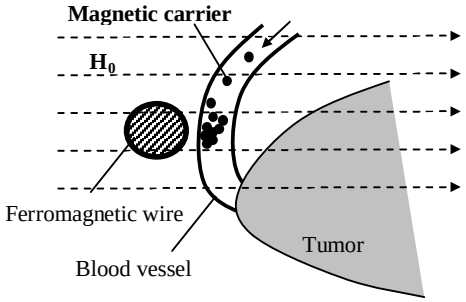

Fig. 1. Ferromagnetic wire placed in the proximity of a blood vessel.

Of the three flow-capture configurations (T, L, A), the most convenient for a practical application is the transversal configuration in which the ferromagnetic wire is introduced near the blood vessel wall perpendicular to it (therefore to the blood flow). The direction of the background magnetic field can be chosen so that it is perpendicular to both the wire and the blood vessel. Yet, a relatively high deviation from the perpendicular alignment between the ferromagnetic wire and the background field direction influences the magnetic carriers capture efficiency [2].

The microparticles trajectories through the liquid are determined by the action of the resultant between the magnetic force (F_m) and the hydrodynamic drag force (F_d); the gravity and the inertia can be neglected due to the very small dimensions of the microparticles. When $F_m \geq F_d$, the magnetic microparticle moves toward the magnetized wire on a certain trajectory, eventually setting down on a surface, for example on the inner surface of a blood vessel.

Most of the times, due to the presence of the magnetic field, the magnetized particles in a fluid will interact (dipolar interaction), agglomerate and then move as small or big clusters.

We have considered an idealized structure of the situation presented in Fig. 1 and we have made a theoretical evaluation of the microparticles movement inside the blood vessel, as well as of the possibility of deposit formation on the blood vessel wall.

The equation for the microparticles motion subjected to the action of the magnetic and hydrodynamic drag forces, for a laminar flow and wire magnetized at saturation is:

$$\frac{dy_a}{dt} = \frac{v_m}{a} f_1(K, y_a, z_a), \qquad \frac{dz_a}{dt} = -\frac{v_0}{a} + \frac{v_m}{a} f_2(K, y_a, z_a) \tag{2}$$

In the equations (2) the position at every moment t for a microparticle/cluster is given by (y_a, z_a) coordinates, that are normalized to the radius of ferromagnetic wire, a. The functions f_1 and f_2 have a nonlinear dependence with the position of microparticle/cluster and are proportionally with the $K=M_s/2H_0$ factor, that depends by the magnetization of ferromagnetic wire (M_s) and the intensity of background magnetic field (H_0). The movement is influenced by the blood flow velocity v_0 and by the "magnetic velocity" of the particle/cluster,

$$v_{mp} = \frac{4}{9}\frac{\mu_0 \chi b^3 K H_0^2}{\eta_f ab} \text{ and respectively } v_{mc} = \frac{4}{9}\frac{\mu_0 \chi b_v^3 K H_0^2}{\eta_f ab_s} \tag{3}$$

The "magnetic velocity" is a parameter including informations about most of the factors that can influence the motion: particle magnetic susceptibility χ , particle radius b, cluster volumetric and surface radii, b_v and b_s respectively (which depend on the component particle radius), ferromagnetic wire radius a, blood viscosity η_f , background magnetic field intensity H_0 , and the specific magnetization factor of the wire, $K = M_s/2H_0$, where M_s is its saturation magnetization [3].

We consider that the initial positions of the particles (clusters) when entering the action zone of the magnetized wire are given by an initial coordinate y^{max} (the initial coordinate normalized to the wire radius is $y_a{}^{max} = y^{max} / a$) which represents the maximum capture distance. It is the maximum possible distance to the wire axis for which a particle can still be attracted and captured on the vessel wall. The value of this maximum capture distance depends on the magnetic field intensity, flow velocity and magnetic properties of both the particle and the ferromagnetic wire. A series of process parameters that influence the microparticles trajectories and deposits formation has been considered: the average velocity and viscosity of the carrier fluid (blood), the wire diameter and saturation magnetization, the microparticles sizes and magnetic properties, the background magnetic field etc.

The numerical solution of the non-linear differential equations (2) was obtained using the Runge – Kutta method and describes the shape of the magnetic microparticle trajectories.

The stability and delimitation of the particles' buildups that accumulate in blood vessels under the presence of a magnetized ferromagnetic wire were analyzed using a model for equilibrium of the forces that act on microparticles. Using the Newton-Raphson method the shape and size of the stable buildups of microparticles are calculated. [4], [5], [6].

3. Results and discussion

Fig. 2 shows the shape of the limit capture trajectories for a single magnetic microparticle, for a cluster consisting of three particles and for another one consisting of five particles.

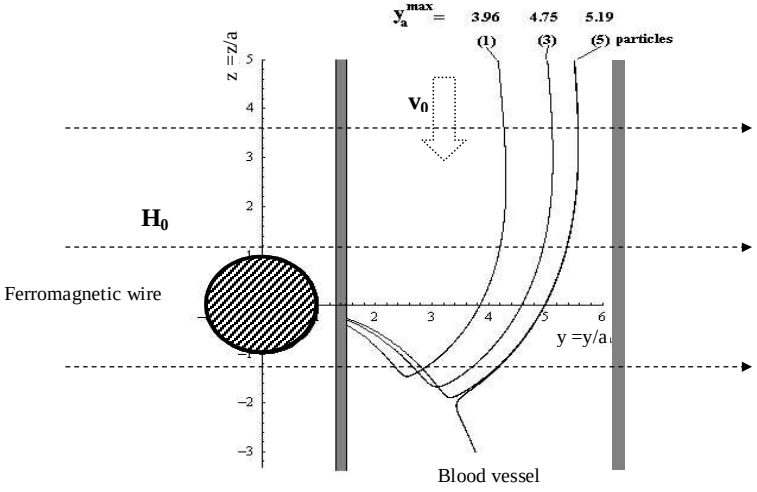

Fig. 2. Limit capture trajectories of 4.5 μm-diameter magnetic microparticles and clusters in the presence of a magnetized ferromagnetic wire.

The process parameters introduced for computing the trajectories have been the same for the three cases, namely: $a = 0.5 \cdot 10^{-3}$ m, $b = 2.25 \cdot 10^{-6}$ m, $K = 0.9$, $H_0 = 64 \cdot 10^4$ A/m, $\eta_f = 0.028$ Kg/ms, $v_0 = 5 \cdot 10^{-2}$ m/s and $\chi = 1.6$. It has been also considered that the magnetic particles are introduced in the carrier fluid (blood) in volume ratios ≤ 0.1 %.

One can notice that after crossing the horizontal wire axis the particle (or the cluster) is slowed down before being attracted by the magnetized wire, the deceleration zone being placed under the horizontal wire axis.

As the same time, one can notice that the limit capture trajectories of the clusters are farther from the magnetized wire as compared to the limit trajectory of a single particle. This means that the active range of the magnetic force is larger for clusters than for single particles.

For the chosen process parameters, one can notice that for a single particle the maximum capture distance y^{max} is almost 4 times the ferromagnetic wire radius, and for the cluster including five particles it exceeds 5 times the wire radius ($y^{max} = 2.5$ mm).

Depending on the values chosen for the variables that influence the particles/clusters motion, one can reach to a situation when the maximum capture distance can exceed the blood vessel diameter, so that all the particles driven through the vessel can be captured on the vessel wall.

Fig. 3 shows the pattern of a cross section through the particle deposit that can be built up on the blood vessel wall, in the proximity of the ferromagnetic wire. The deposit shape corresponds to the saturation threshold (saturated deposit); the particles that keep arriving on the surface of this deposit will no longer be retained since the drag force becomes predominant.

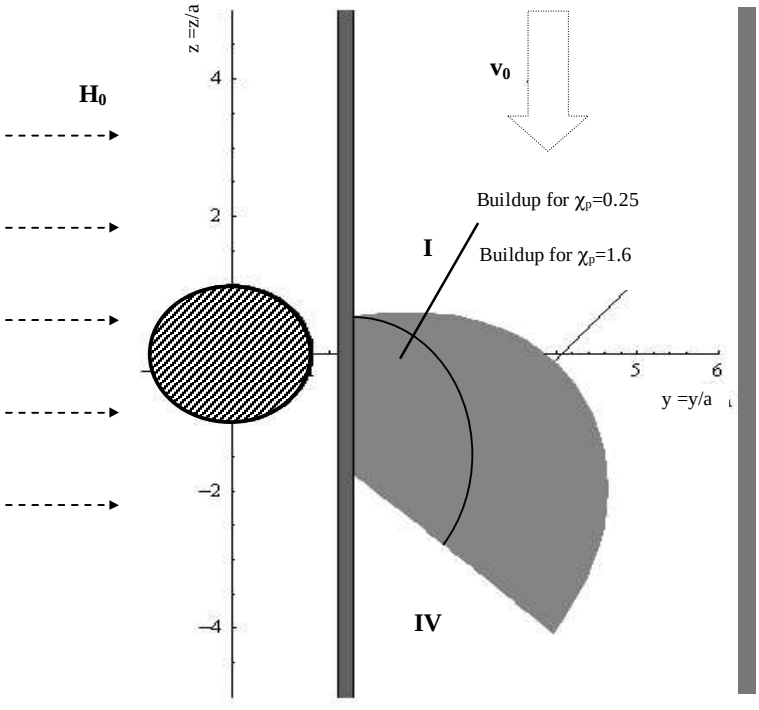

Fig. 3. The pattern of the cross section of a 4.5 μm magnetic microparticles deposited on the blood vessel wall in the proximity of the ferromagnetic wire.

The process parameters used to compute the shape of saturated deposit have been identical with those used to compute the trajectories, only for the magnetic susceptibility of the particles two values have been considered: $\chi_1 = 0.25$ and $\chi_2 = 1.6$.

One can notice that the particle deposit pattern is asymmetrical as related to the symmetry axis of the magnetized wire (Oy_a). This is due to the fact that the magnetic force has a tangential

component acting in the same direction as the hydrodynamic drag force within the first quadrant (favoring the particles rolling toward the Oy_a axis), while in the fourth quadrant it acts against the drag force, preventing the particles rolling upward the wire and favoring in this way the preferential storage in this area. At the same time, one can notice that the cross-area of the deposit consisting of microparticles with a higher magnetic susceptibility is more extended.

From a practical point of view, a complete capture of all the microparticles passing through the blood vessel is desired, either for obtaining a vessel blockage or for retaining them on the vessel wall; this can be done by adequately choosing the process parameters.

The efficiency of the capture process can be optimized by conveniently choosing the groups of parameters and their values. For example, the using of thinner ferromagnetic wires and smaller particles can be compensated by increasing the background magnetic field intensity and/or the particles magnetic susceptibility. At the same time, the use of thinner wires could be convenient for blood vessel in which the velocity of blood flow is lower. Different aspects connected to the way of grouping the parameters, to their values or their influence on the particles trajectories and deposits shapes are still under investigation.

4. Conclusions

A possibility for precisely local targeting of magnetic carriers used in anti-tumor therapies, especially in zones difficult to access, has been pointed out. The method consists of placing magnetizable wires in the target zone and applying a background external magnetic field perpendicular to the wire. Under certain preestablished process conditions for which the maximum capture distance exceeds the blood vessel diameter, all the magnetic microparticles driven by the carrier fluid (blood) will be captured.

This technique could be applied in magnetic drug targeting or local radiotherapy using magnetic carriers labeled by radioisotopes. It could also represent a method of magnetic targeted embolization of blood vessels for therapeutic purposes.

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