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MAGNETIC NANOPARTICLES AND THEIR APPLICATION IN BIOMEDICINE

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ABSTRACT

The magnetic nanoparticles offer some attractive possibilities in biomedicine for the following reasons: First, they have controllable sizes ranging from a few nanometers up to tens of nanometers, which places them at dimensions that are smaller than or comparable to those of a cell (10–100μm), a virus (20–450 nm) or a protein (5–50 nm). Second, the nanoparticles are magnetic, which means that they obey Coulomb's law, and can be manipulated by an external magnetic field gradient. This possibility, combined with the intrinsic penetrability of magnetic fields into human tissue, opens up many applications involving the transport and/or immobilization of magnetic nanoparticles, or of magnetically tagged biological entities. Third, the magnetic nanoparticles can be made to resonantly respond to a time-varying magnetic field, with advantageous results related to the transfer of energy from the exciting field to the nanoparticle. In this paper, we will address the underlying chemical and physics of the biomedical applications of magnetic nanoparticles including radioisotope delivery and a magnetic radiolabeled fluid. We will consider four particular applications: magnetic separation for radio labeled proteins, drug radiolabeled delivery, hyperthermia treatments, and magnetic resonance imaging (MRI) contrast enhancement. There will be included some results obtained in our laboratory in the obtention of these magnetic nanoparticles.

1. INTRODUCTION

Nowadays with nanotechnology and nanoscience advent, that allow us to use more accurate tools of materials characterization in nanometric levels, the magnetic nanoparticles and microparticles have found innumerous applications in the fields of biomedicine, diagnostic, molecular biology, biochemistry, among others. These materials are used as magnetic particles or as magnetic fluids. These magnetic particles show potentiality to arrest metals through complexation reaction of radionuclides from nuclear waste.

2. MAIN APPLICATIONS OF MAGNETIC NANOPARTICLES

2.1 Contrasts for magnetic resonance image

Magnetic resonance image (MRI) is a powerful technique that makes human body maps based on the nuclear magnetic resonance principle. It is the result of difference in the intensity of the signal of each tissue produces in answer to the radiofrequence pulse[1, 2-3]. First, a strong magnetic field is used to polarize partially the proton moments. A pulse of radiofrequence (RF) is applied to modify the proton basic state and during this pulse some of

RF photons are absorbed by the protons causing the "flip" (higher energy state) to the magnetic field. In the end of the pulse the protons relax, coming back to a lower energy state producing a small amount of electromagnetic radiation and its signal is registered in the bobbin and converted in an image. The factors that lead the technique of MRI are basically the proton density and the magnetic relaxation time. Today, polymer encapsulated iron oxide particles are used in biomedical applications. However, the high magnetization of the enhanced ferrite nanoparticles may potentially improve the absorption of the radio frequency, thereby providing better detection of tumor regions and the use of less MRI contrast reagent.
The chromium-EDTA was the first agent of increasing contrast proposed, but its stability so much long hindered its use in clinic application[4]. However, gadolinium diethylenotriaminopentaacetate (Gd-DTPA)[5] had been approved by FDA from USA and it is constantly sold as Magnetvist, another class of contrast agents pertaining to the superparamagnetic family has showed to be equivalent. Since that, the superparamagnetic species don't have their hysteresis above the blockade temperature, they can by used as increasing agents to magnetic resonance therefore they don't have remanescent magnetization when the magnetic field is retired[2]. However their relaxation times are higher when compared with paramagnetic species as Gd-DTPA.
In fact, nowadays, the most used contrast agent is composed by iron oxide superparamagnetic nanoparticles. For example, Feridex I.V, introduced into the market by the Advanced Magnetic Inc., is used to map the liver or vesicular disturbs.

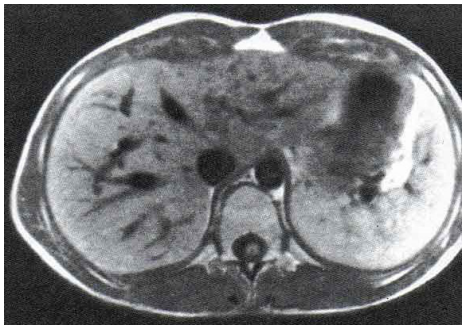

Figure 1 - An MRI scan showing the liver[6].

2.2 Magnetic Hyperthermia

The hyperthermia is basically a termic treatment that induces necrosis or promotes adaptness, with temperature increase of the initial (42-46ºC) by 30 minutes[7]. However, all with exception of the Magnetism Means Hiperterm (MMH) have the problem of necrosis in healthy tissue devided the ability not specify of the target.
The Magnetism Means Hyperthermia was firstly described by Gilchrist, and others in 1957 to treat lymphatic metastasis of the bowel cancer[8]. The concept defines the use of magnetic field to find the ferromagnetic nanoparticle inside the target and keeping the field on a specific duration. It was found that inside of 3 minutes with force field of 200-240 Oe, the heating of the lymphatic nodule tissue is above 14ºC. Two years after, it was realized the total necrosis of lymphatic nodule. Since then, many studies have been published using nanoparticles different of MMH as how methods different of deliver. Actually, the most of the nanoparticles used in hyperthermia are particles superparamagnetic, these can provide more heat in smaller magnetics fields in the ferromagnetics nanoparticles[2, 7].

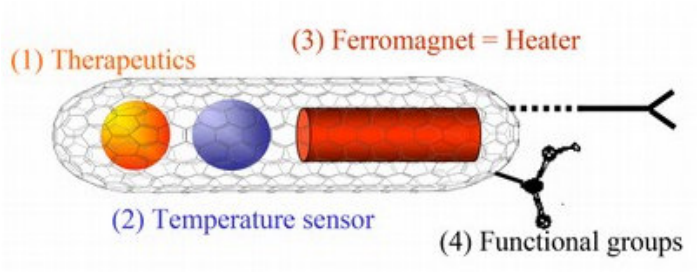

Figure 2 - Functionalized Carbon Nanotube with different filling and biofunctional deviatisation of the outer shell[9].

2.3 Magnetic separation

The magnetic nanoparticles can be connected to the sensors or to the macromolecular. For example, Pel Freez developed a magnetic nanoparticle coated with dextran (magnetite) conjugated with a tetrahedric antibody that recognize the dextran in a extremity and the antigen of surface of cell in other extremity[10]. With a magnetic field weak, and the recognition of cells by coated magnetic with dextran – complex of tetrahedric antibody can be isolated from a cell mixture without complementar antigen.
In additional, the magnetic separation was adapted to the eritrocites separation and quantification. In normal red globules, the organization of fosfatidilserine is oriented in a way that faces the cytoplasm. In damaged red globules, this organization is aleatory and the fosfatidilserine is asymmetric[11]. An intracellular protein, Annexin V, has a specific potentiality of linking to the fosfatidilserine in the presence of Ca^{2+}. Therefore, when connected to the magnetic nanoparticles, provide a path of separating damaged red globules from normal red globules with an additional quantification. This is an important aspect since that the number of damaged red globules has correlation with the erythrocytes evolution in patients with malaria and the Alzheimer disease[12].

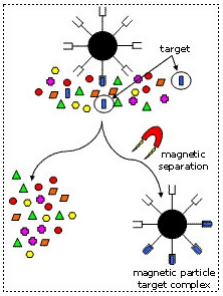

Figure 3 – Magnetic Separation[13].

The damaged red globules quantification is also a mark to the human blood quality stored in blood banks. The connection of Annexin V in the magnetic nanoparticles demonstrated this promising application that were patented and it is being available to the manufactures in the marketing[14]. However, there are several applications that can be associates with the magnetic separation of macromolecules. For example, magnetic nanoparticles connect with sensors that recognize uncommon modification of the membrane can give information like the apoptosis and membrane organization that are important to the cancer research[15].

2.4 Drug

When cirurgic remotion of malign tumors is not an option, chemiotherapy and radiotherapy are usually the chosen treatments to the most of patient. However, many of the side effects associated with the chemiotherapy and elevated dosis of therapeutic drugs introduced complicated questions. The radiation therapy is not specific to the target, consequently, destroying healthy cells join cancer cells.
To reduce the side effects and maximize the drug efficiency, scientists proposed the use of magnetic nanoparticles as carriers of the therapeutic agents. For example, Widder and others, demonstrated that managing magnetic carriers – doxorubicin (citotoxic drug) in the sarcoma tumor in the mouse tail, happen total remission that does not occur when the magnetic carriers are absent[16, 17]. This kind of treatment may be an alternative to the radiation traditional chemiotherapy in human. The magnetic point may guide or find the therapeutic agent in the biologic system with a magnetic field. This blocks or reduces the amount of lost therapeutic agents during the circulation and find the treatment in the specific region.

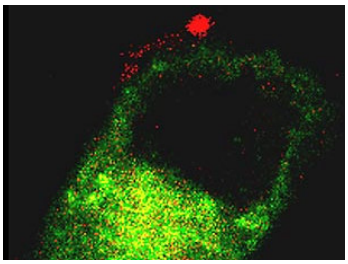

Figure 4 - Delivered via nanoparticle carriers, drug components and lipids enter the membrane of a targeted melanoma cell[18].

2.5 Biohazard Detoxification Using Magnetic Nanoparticles

The system proposed by Argonne lNatyional Laboratory, provides a novel treatment strategy for detoxifying blood-borne radionuclides in humans. Key features of the technology are: a) Biocompatible magnetic nanoparticles that bind the radioactive toxins within the bloodstream and b) A compact, external magnetic separator that sequestrates the toxin-loaded magnetic particles from the body. The magnetic nanoparticles are provided in tiny ampoules, and the process can be self-administered.
Following a radiological event, exposed soldiers can self-administer nanoparticles by injection and then strap on a magnetic filtration unit that attaches to the arm by vascular access to remove the toxin. The nanoparticles are injected directly into the bloodstream. Anti-toxins (e.g., antibodies, radionuclide extractants, receptor mimetics) attach to the nanoparticle surface, selectively capture toxins, and form nanoparticle-toxin complexes. When enough time has passed to allow the formation of the nanoparticletoxin complexes, the soldier or first-response personnel inserts a catheter into an artery or vein and the magnetic filtration system is connected to an artery or vein where the nanoparticles-toxin complexes are magnetically filtered from the blood [19].

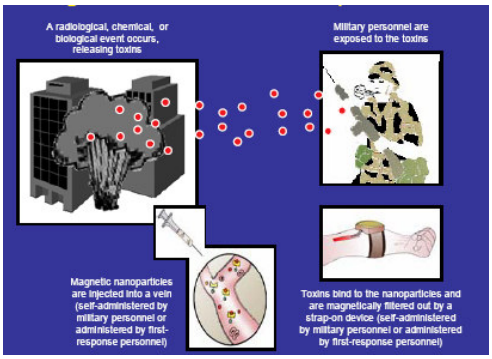

Figure 5 – Magnetic Nanoparticle Designed for Self-Administered, In-Field Use[19]

2.6 "Fluorescence-modified superparamagnetic nanoparticles: intracellular uptake and use in cellular imaging

Investigators at the Université Pierre et Marie Curie in Paris, France, have developed a versatile new method for creating nanoparticles that are both magnetic and fluorescent. They used the nanoparticles created with this method to label and image live cells. The researchers note that these particles could be used to track cell movements within the body and to help separate different cell types in basic research and diagnostic applications. nanoparticles labeled with the fluorescent dye rhodamine to cancer cells growing in culture, they were able to observe that the nanoparticles attached themselves to the outer cell membrane. While viewing the now-labeled cells using a fluorescent microscope, the investigators were able to follow the nanoparticles as the cells transported them through the cell membrane and into internalized compartments known as endosomes. Once the nanoparticles were inside the cells, the researchers applied a magnetic field to the culture dish, turning the nanoparticle-filled endosomes into internal magnets. Like any set of magnets, the endosomes were attracted to one another, forming small chains in the cell cytoplasm.[20]

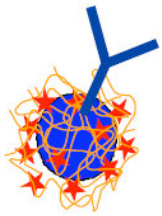

Figure 6.Illustration of a multifunctional magnetic and luminescent NP as biological probes.

3. CONCLUSIONS

There are many subjacent situations that should be solved and optimized. For example, the magnetic carriers that carry therapeutic drugs are frequently administered via intravenous or intraarterial. Therefore factors like the blood flow rate, the magnetic concentration of the nanoparticle, the circulation time and the tissue deep will have importance in the design of

the future magnetic carriers. Other important fact is the aggregation. It is extremely important that the intrinsic attraction of magnetic nanoparticles does not form aggregate, or allows the coagulation. However, there are mathematics models involving hydrodynamic models and as much security models of the specific target treatment, no one solves all the questions. Therefore, there is a great improvement field.
In MRI, recent magnetic nanoparticles with characteristics will increase the temperature that can enhance the contrast during the image formation. In the drug delivery, the different approximation of therapeutic agents of magnetic nanoparticles connect like the development of the systems which allow these conjugated to be administrated with safety *in vivo* will need to be optimized.
With the potentially of synthesis of the magnetic nanoparticles can be coated with a tail for specific functions, and then to take place of the principal paper in therapeutic treatment with a magnetic localization.

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