MAGNETIC DRIVEN ALGINATE NANOPARTICLES FOR TARGETED DRUG DELIVERY

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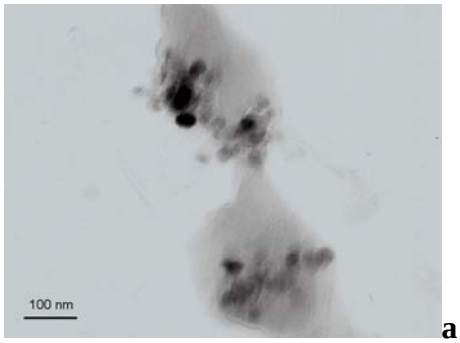
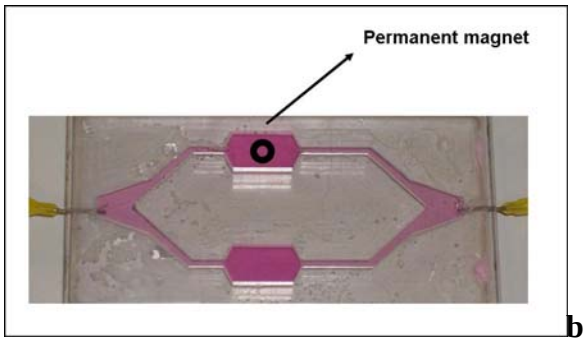
The explosive growth of nanotechnology in the last years has produced dramatic innovations in pharmacology, and it is revolutionizing the delivery of biologically active compounds. The main contribution of today's nanotechnology in pharmacology is that it allows real progresses to achieve temporal and spatial site-specific delivery [1]. Magnetic materials have been proposed for biomedical purposes to a large extent for several years. This has led to various results such as improving the quality of magnetic resonance imaging, hyperthermic treatment for malignant cells, site-specific drug delivery and manipulation of cell membranes [2]. This paper describes the realization, characterization and *in vitro* testing of alginate nanoparticles, embedded with magnetite, which respond to externally applied magnetic fields.
Magnetite powder was obtained as described in literature [3]. Briefly the synthesis is based on reacting iron(II) and iron(III) ions in an aqueous ammonia solution to form magnetite. Magnetite is then isolated from the reaction suspension and completely dissolved in an alginate solution. Alginate magnetic nanoparticles were realized by a homogenization process and reticulation with calcium ions [4].
Such nanoparticles are characterized in terms of external morphology (FIB imaging), microstructure (TEM imaging: as showed by Fig. 1a), size distribution, zeta potential, magnetic properties (SQUID analysis) and drug release behaviour. Magnetization curves show the typical trend of superparamagnetic materials. Important parameters, such as magnetic permeability and magnetic momentum, are derived by employing Langevin theory. Experimental results reveal that a bi-exponential model [5] fully describes the drug release. Finally, *in vitro* experiments on NIH/3T3 cells are carried out and demonstrate that our magnetic alginate nanoparticles can effectively drive the drug delivery towards an external magnetic field source.
Driven drug delivery experiments were carried out by using a low-flow bi-compartmental bioreactor (Fig. 1b). This 2-chambers parallel bioreactor is composed by two cell culture chambers interconnected in parallel configuration and integrated in a polydimethilsiloxane block. The closed loop fluidic system is composed by the bioreactor and a growth medium tank, both connected to a peristaltic micropump through fluidic connectors. The whole system is inserted in an incubator for cell cultures. Culture medium was modified with 50 μg/ml of magnetic alginate nanoparticles loaded with fluorescein sodium salt. Under one chamber of the bioreactor, a permanent magnet was posed, in order to address selectively the nanoparticles only to one compartment, and thus to verify the possibility to "guide" the drug delivery to different sites with the help of an external magnetic field. After 3 h of incubation under dynamic conditions, the glasses into the two chambers were observed with a fluorescent microscope.



a



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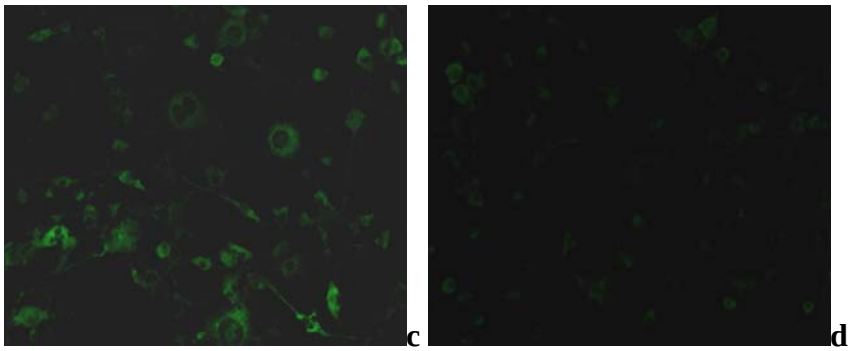

Figure 1 - TEM imaging of magnetic alginate nanoparticles: magnetite inclusions of size about 10-20 nm are visible inside the alginate nanoparticles (a); driven drug delivery: experimental set-up (b); fluorescent image of cells cultured in the chamber above the permanent magnet (c); fluorescent image of cells cultured in the opposite chamber (d). Magnification 20 X. From [6].

Fig. 1c shows a fluorescent image of cells cultured in the chamber over the permanent magnet while Fig. 1d shows the culture in the other chamber. In both chambers fluorescence inside the cells was detected, therefore demonstrating nanoparticles up-take by the cells (fluorescein is a cell impermeable molecule, therefore spontaneous internalization of fluorescein by cells must be excluded). However, the fluorescence intensity of the cells incubated over the permanent magnet is strongly higher. In fact, fluorescent dye – loaded nanoparticles are transported through the whole cell culture device through the imposed flow. Due to their magnetic properties, they tend to accumulate in the chamber over the permanent magnet, where a higher internalization occurs. Thus, this test demonstrates that magnetic alginate nanoparticles can effectively target the drug delivery under the driving of an external magnetic field.

The advantage of the proposed particles lies in a unique combination of magnetic, chemical and drug release properties, which are greatly promising for the development of a new class of nanoparticle-based drugs and therapies. Future work will be devoted to the applicability of magnetic particles to the pre-clinical practice.

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