MAGNETIC NANOPARTICLES FOR BIOMEDICAL APPLICATIONS

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Introduction

Biological and medical approaches and applications of nanotechnologies are opening novel, unpredicted and efficient ways of solving health issues. That is why the extraordinary field of bionanotechnology is shaping into one of the leading sciences of the 21st century… Goal of the project is to functionalize Fe_3O_4 magnetic nanoparticles, which according to chemical groups attached at the surface, are able to bind to special pathogens (bacteria or virus) and being easily manipulated by magnetic field, they can be removed from the system taking the pathogens with them as well.

Among them a very specific position belongs to the *carriers* (nanoparticles properly *functionalized* to attach and carry a specific load). Material of the nanoparticles should be biologically compatible, i.e. the nanoparticles can be introduced into the organism (bloodstream) without any damage or side effects. Size of nanoparticles in combination with surface modification favor this condition – it allows for interaction between nanoparticle and molecules of cells and cells surfaces.Nanoparticles are produced by 'wet' chemical way under special conditions. Final product is tens of nanometers in diameter and possesses special superparamagnetic properties, which give it ability to be manipulated while working in complex biological systems such as human body. Surface of the particles is stabilized and treated, so that they maintain their unique properties and remain stable and separated. Certain chemical groups, proteins or residues are attached onto the surface to functionalize it. Particles are then ready to play a key role in recognition of the pathogens binding to the surface of nanoparticles and following applied magnetic field to get out of the system.

Magnetic effects are caused by movements of particles that have both mass and electric charge. These particles are electrons, holes, protons, positive and negative ions. A spinning electric charged particle creates a magnetic dipole, so-called magneton. In ferromagnetic materials, magnetons are associated in groups. A magnetic domain (also called a Weiss domain) refers to a volume of ferromagnetic material in which all magnetons are aligned in the same direction by the exchange forces. This concept of domains distinguishes ferromagnetism from paramagnetism. The domain structure of a ferromagnetic material determines the size dependence of its magnetic behavior. When the size of a ferromagnetic material is reduced below a critical value, it becomes a single domain. Fine particle magnetism comes from size effects, which are based on the magnetic domain structure of ferromagnetic materials. It assumes that the state of lowest free energy of ferromagnetic particles has uniform magnetization for particles smaller than a certain critical size and nonuniform magnetization for larger particles. The former ones are referred to as single-domain particles, while the latter are called multidomain particles. According to the magnetic domain theory, the critical size of the single domain is affected by several factors including the value of the magnetic saturation, the strength of the crystal anisotropy and exchange forces, surface or domain-wall energy, and the shape of the particles. Reaction of ferromagnetic materials on an applied field is well described by hysteresis loop, which is characterized by two main parameters - remanence and coercivity. The latter is related to the 'thickness' of the curve. Dealing with fine particles, the coercivity is the property of prime interest and it is strongly size-dependent. It has been found that as the particle size is reduced, the coercivity increases to a maximum, and then decreases toward zero (*Figure 1*).

When the size of single-domain particles further decreases below a critical diameter, the coercivity becomes zero and such particles become superparamagnetic. Superparamagnetism is caused by thermal effects. In superparamagnetic particles, thermal fluctuations are strong enough to spontaneously demagnetize a previously saturated assembly, therefore these particles have zero coercivity and have no hysteresis. Nanoparticles become magnetic in the presence of an external magnet, but revert to a non magnetic state when the external magnet is removed. This avoids an 'active' behaviour of the particles when there is no applied field. Introduced in the living systems, particles are 'magnetic' only in the presence of external field, what gives them unique advantage in working in biological environments. Since ferrite oxide - magnetite (Fe_3O_4) is the most magnetic of all the naturally occurring minerals on Earth, it is widely used in the form of superparamagnetic nanoparticles for all sorts of biological applications.

Nanoparticles can be used either as support for drugs or as an active medium. Modification of the nanoparticle surface in order to receive a *drug supporter* allows for drugs that can be accumulated at a chosen place by application of a magnetic field. Further, by certain triggering mechanism drug is released locally, not affecting the remaining part of the organism. Jamming the bloodstream with an external magnetic field in a chosen place is also possible. This can be used to *necrotise tumor* (and after switching of the magnetic field letting the blood to circulate again). Another possibility is the use of *thermal cancer ablation.* Functional samples of such nanoparticles were already prepared.

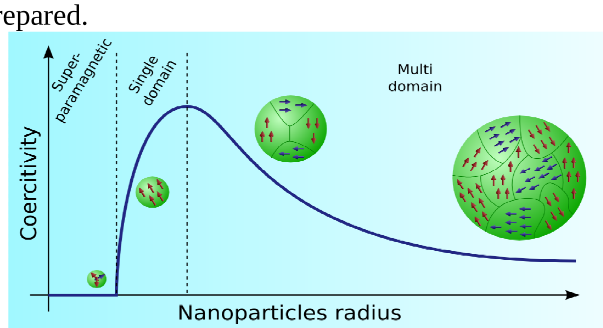

Figure 1 Schematic illustration of the coercivity–size relations of small particles.

Alternatively they could be used in an opposite manner. By surface modification “encapsulation“ (i.e. enclosing the nanoparticle in chemically and biologically impervious shell) and by further surface modifications (another shell of biologically useful molecules) one can use those nanoparticles as *selective seekers of chosen pathogens* (f.e.HIV virus). They are left to *circulate* in the bloodstream for a certain period of time to catch (attract) unwanted species of pathogens and to bind them to the surface of nanoparticles. This is followed by subsequent magnetic *extraction* (as easy as possible) of such nanoparticles from the bloodstream, thus cleaning the organism.

Prospective applications

It is extremely advantageous to extract specific biological entities from their native environment in biomedicine. Magnetic extraction using biocompatible magnetic nanoparticles is performed in this project to 'harvest' pathogens of our interest. Functionalized magnetic carriers working as 'nanoharvesting agents' are mixed with a sample containing target biological entity.

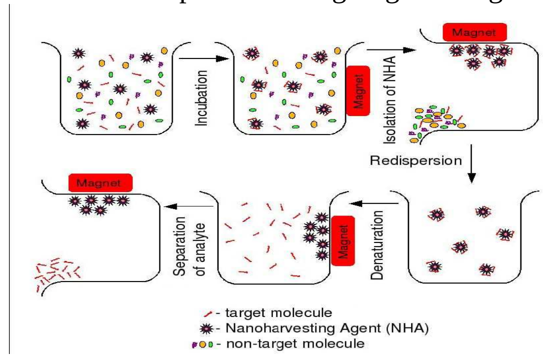

Figure 2 Separating process using functionalized “nanoharvesting” magnetic nanoparticles

After an incubation period when the target entity became bound to the magnetic particles the whole magnetic complex is easily removed from the sample using an external magnetic field gradient. After washing out the non-target compounds, the isolated target entity can be obtained by denaturizing the solution and extracting the nanoparticles (*Figure 2*).

This magnetic separation technique has several advantages. It is very simple, with only a few handling steps and it is the only feasible method for recovery of small magnetic particles at nano-scale in the presence of biological debris and other material of similar size.

Measured properties and characteristics

Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM) allow calculation of particle size and shape. It is well suited for magnetic particles as they are constituted of heavy metals such as iron. Its data may provide a histogram of diameters and log-normal size distribution. Mössbauer Absorption Spectroscopy is perfectly suitable for measuring the phase composition of iron nanoparticles, also providing their magnetic properties, while Superconducting Quantum Interference Device (SQUID) is used to measure extremely small magnetic fields and hysteresis characteristics of weak ferromagnets. Presently, synthesized nanoparticles are being evaluated using AFM and magnetic properties measured by Mössbauer Spectroscopy and SQUID techniques. Data and graphs will be provided during the presentation.

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