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Coating Nanomagnetic Particles for Biomedical Applications

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1. Introduction

Magnetic particles with dimensions ranging from the nanometer to the micrometer scales are being used in an increasing number of medical applications, since the mid-1970s. The most important properties of magnetic particles for clinical diagnostics and medical therapies are clearly nontoxicity, biocompatibility, injectability, and high-level accumulation in the target tissue or specific organ, being strictly and spatially confined to the planned region of the internal body (Ito et al., 2005). The unique feature of NMPs to be guided by an external magnetic field has been used in magnetic resonance imaging (MRI), tissue repair, hyperthermia, drug delivery, and in cell separation (Duguet et al., 2006; Gupta & Gupta, 2005; Gupta et al., 2007; McCarthy et al., 2007). For these biomedical applications, magnetic particles exhibiting superparamagnetic behavior at room temperature are preferred because they do not retain any magnetism after removal of the magnetic field. For NMPs, this behavior can be explained by their extraordinarily reduced sizes (Mørup et al., 1976; Pfannes, 1997). The magnetization relaxation depends on KV/kT (Gupta & Gupta, 2005; Gupta et al., 2007) in which K is the particle anisotropy constant, V is particle volume, k is Boltzmann's constant and T is temperature. At a certain reduced size (volume), KV becomes comparable to the thermal energy kT . As a result, the magnetization of the particle fluctuates rapidly from one direction to another due to the thermal agitation, leaving no net magnetic moment. At this magnetic stage, the particle is said to be superparamagnetic (Xu & Sun, 2007). Fig. 1 shows a magnetization curve obtained by Andrade *et al.* for a NMPs with particle size of 7 nm (Andrade et al., 2009). This shows that a particle can be magnetized under an external magnetic field (H), reaching a maximum moment (M) when the field is strong enough. However, there is no remnant magnetic moment, i.e. without an external magnetic field, the net moment of the particle is randomized to zero. Therefore, these superparamagnetic nanoparticles are very useful for biomedical applications as they are not subject to strong magnetic interactions in the dispersion and are readily stabilized in physiological conditions (Gupta & Gupta, 2005; Neuberger et al., 2005; Sonvico et al., 2005).

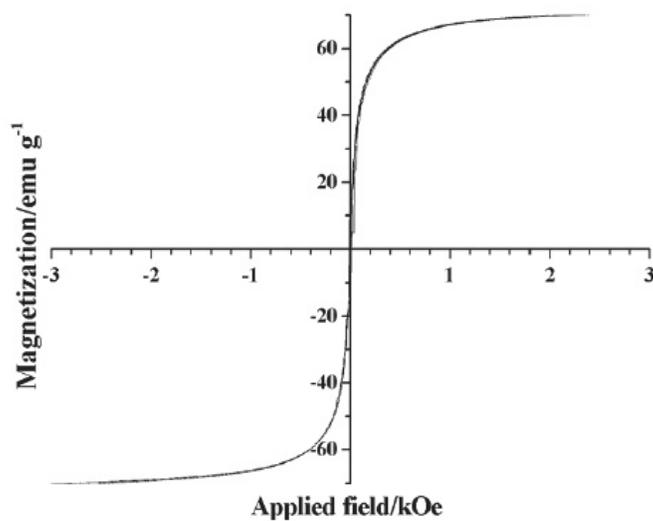


Fig. 1. Magnetization curve for NMPs with the applied magnetic field. This hysteresis loop indicates nearly zero value for coercivity and magnetic remanence.

Among superparamagnetic nanoparticles, iron oxide nanoparticles such as magnetite (Fe_3O_4) or its oxidized form maghemite ($\gamma\text{-Fe}_2\text{O}_3$) are by far the most commonly employed in biomedical applications, as their biocompatibility has already been proven (Schwertmann & Cornell, 2000; Souza et al., 2008). Highly magnetic materials such as cobalt and nickel are toxic, susceptible to oxidation and hence are of little interest. Nanoparticles of magnetic iron oxides, are usually modified through the formation of few atomic layers of polymer/surfactant or inorganic metallic (such as gold) or oxide surfaces (such as silica or alumina), which prevents agglomeration and also allows further functionalization by attaching various biomolecules (Berry & Curtis, 2003; Ferreira et al., 2009).

NMPs with suitable surface characteristics have potential applications both *in vitro* and *in vivo*. Information about the way the magnetic particle system is prepared and its surface is modified must be accompanied by its full characterization, by determining particles size distribution and morphology, their surface chemistry and, obviously, magnetic properties. All these features are critically important, if the material is planned and destined for application in medical practices (Andrade et al., 2009). This review covers most of these essential topics with illustrative examples of applications of monodisperse NMPs in clinical diagnostics, magnetic separation and human medical therapy.

2. Application of magnetic nanoparticles

Uses of NMPs in biotechnology and biomedicine have dramatically increased over the last few of years. They can be grouped into two broader categories, depending on the methodology: *in vitro* and *in vivo* procedures. For *in vitro* applications, the main use is in diagnostic and separation/labeling of biomolecules, such as protein, cell, DNA/RNA, microorganism, for *in vivo*, applications can be further split into (i) diagnoses (magnetic resonance imaging (MRI)) and (ii) therapies (drug delivery and hyperthermia).

The applications of superparamagnetic nanoparticles in biomedicine can be rationalized as follows: firstly, the superparamagnetic nanoparticles are a class of intrinsically ordered magnetic materials. As their magnetic signal is generated by application of external strong magnetic field it far exceeds that signal from any of the known biomolecules. This makes

them readily identified by a magnet or magnetic sensor from an ocean of biomolecules. Secondly, at diameters less than 20 nm, these particles are smaller than or comparable to a cell (10–100 μm), a virus (20–450 nm), a protein (5–50 nm) or a gene (2 nm wide and 10–100 nm long). These, plus their capability of being manipulated under an external magnetic field, provide controllable means of magnetically tagging biomolecules, leading to potentially highly efficient bioseparation, highly sensitive biosensing and magnetic resonance imaging (MRI) contrast enhancement, as well as site-specific drug delivery (Dobson, 2006; Gupta & Gupta, 2005; Neuberger et al., 2005; Sunderland et al., 2006). Such particles also respond resonantly to an alternating magnetic field, allowing the transfer of magnetic energy to the particles as a form of heat. This has been proposed to be one of the key approaches to successful cancer therapy in the future (Hilger et al., 2005; Ito et al., 2005).

These potential biomedical applications of NMPs require that the nanoparticles be monodisperse, meaning that each individual nanoparticle has identical physical and chemical properties allowing controlled biodistribution, bioelimination and contrast effects (Andrade *et al.*, 2011).

In the absence of any surface coating, NMPs have hydrophobic surfaces with a large surface area to volume ratio. Due to hydrophobic interactions between the particles, they tend to agglomerate forming large clusters. Coating favors the effective stabilization and dispersion ability of NMPs. Besides this, coatings making them better water- or oil-soluble, thus providing better conditions for functionalization to form conjugate biomolecules. A variety of experimental approaches have been proposed and used to coat NMPs, including *in situ* and post-synthesis coating (Laconte et al., 2005). In the *in situ* approach, the NMPs are coated with some stabilizer such as surfactants or polymers during the synthesis process. Various surfactants, e.g., oleic acid, sodium oleate, dodecylamine, sodium dodecylbenzene sulphonate have been used in the synthesis of NMPs. These surfactants always form a double layer on the surfaces of magnetic particles turning them more stable (Shen et al., 1999; Shen et al., 2001; Wooding et al., 1991). Surfactants such as polymers, cyclodextrins and large capping ligands stabilize nanoparticles through steric repulsion of interparticle interaction. However, small-molecules like carboxylates and phosphates engage the electrostatic mechanism in aqueous medium. Magnetic nanoparticles stabilized by electrostatic layer and steric layer are showed in Fig. 2.

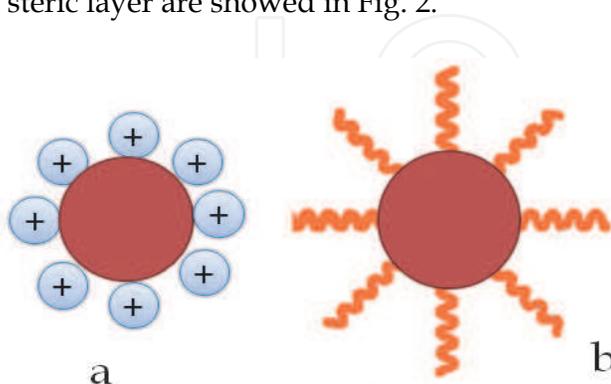


Fig. 2. Nanoparticles stabilized by: a) electrostatic layer and b) steric layer.

Polymeric coating materials may be either synthetic or natural. Examples of synthetic polymers are: poly (ethyleneglycol) (PEG) (Suzuki et al., 1995), poly (vinyl alcohol) (PVA) (Lee et al., 1996), poly (lactic acid) (PLA) (Gomez-Lopera et al., 2001), polyethylene

(Chatterjee et al., 2002) and block copolymer (Harris et al., 2003). Natural polymers include dextran (Paul et al., 2004), chitosan (Hassan et al., 1992) and starch (Veiga et al., 2000).

The post-synthesis coating methods for NMPs make use of a variety of materials, including monolayer ligands, polymers, combinations of polymers and biomolecules such as phospholipids and carbohydrates, and inorganic materials, such as silica (Kobayashi et al., 2003) and gold (Kinoshita et al., 2003). These coatings not only provide stability to nanoparticles in solution but also help in binding the several biological ligands on the nanoparticle surface, as needed for medical applications. The aim of surface functionalization of magnetic composite particles, such as polymer-coated NMPs and silica coated NMPs, is to introduce some functional groups on the surface intending to immobilize biomolecules and biological ligands, such as antibodies, proteins, transferrin (Berry et al., 2004), folic acid (Zhang et al., 2002). These can be attached onto the polymer surfaces coating the magnetic nanoparticles, by chemical coupling, to make the particles target-specific.

Surface functional groups are usually introduced into magnetic particles-polymer systems by two main methods: copolymerization and chemical modification of the preformed polymer. In copolymerization, a large amount of functional groups are usually buried in the polymer and only a low surface density of functional groups is obtained. Chemical modification has been reported to be an efficient way to obtain abundant functional groups on the surface of magnetic particles (Liu et al., 2005; 2004a, 2004b; Ma et al., 2005a, 2005b). However, in some reactions, due to high acid or strong oxidation effect, the magnetic iron oxide inside the composite particles gets deteriorated, thus resulting in the loss of magnetic properties.

For silica coated magnetic particles, the functional groups are usually introduced by silanation using silane coupling agents (Levy et al., 2002; Liu et al., 2004c, 2004d). A typical silane coupling agent has the structure of $Y-(CH_2)_n-Si-X_3$, where X represents the alkoxy or halide groups and Y, the organic functional groups, including amine, thiol, carboxylic, phosphate, vinyl, cyanide, and methacrylate. The Si-X₃ group hydrolyzes readily in the presence of water and catalyst to form silanol groups which couple with surface silanol groups, forming Si-O-M bonds upon dehydration. As a result, the organic functional groups (Y) remain reactive on the surface. This unique feature of silane coupling agents has made silanation a widely used method in modifying surface properties and introducing functional groups on particles. A large volume of literature is available for the surface functionalization of magnetic silica particles by silanation (Berry & Curtis, 2003; Dong et al., 2008; Koneracka et al., 1999; Sulek et al.).

2.1 Magnetic separation

The processes of isolation and separation of specific molecules are used in almost all areas of biosciences and biotechnology, and are the most documented and currently the most useful application of NMPs (Lucena et al., 2011 ; Smith et al., 2006).

The basic principle of magnetic separation is relatively simple. NMPs with an immobilized affinity or hydrophobic ligand or ion-exchange groups are mixed with a sample containing the target compound. Following an incubation period, when the target compound binds to the NMPs, the magnetic complex is easily and rapidly separated from the sample using an appropriate magnetic separator Fig 3. The system can be reused several times. After washing out contaminants, the eluted magnetic material will be ready for new usage.

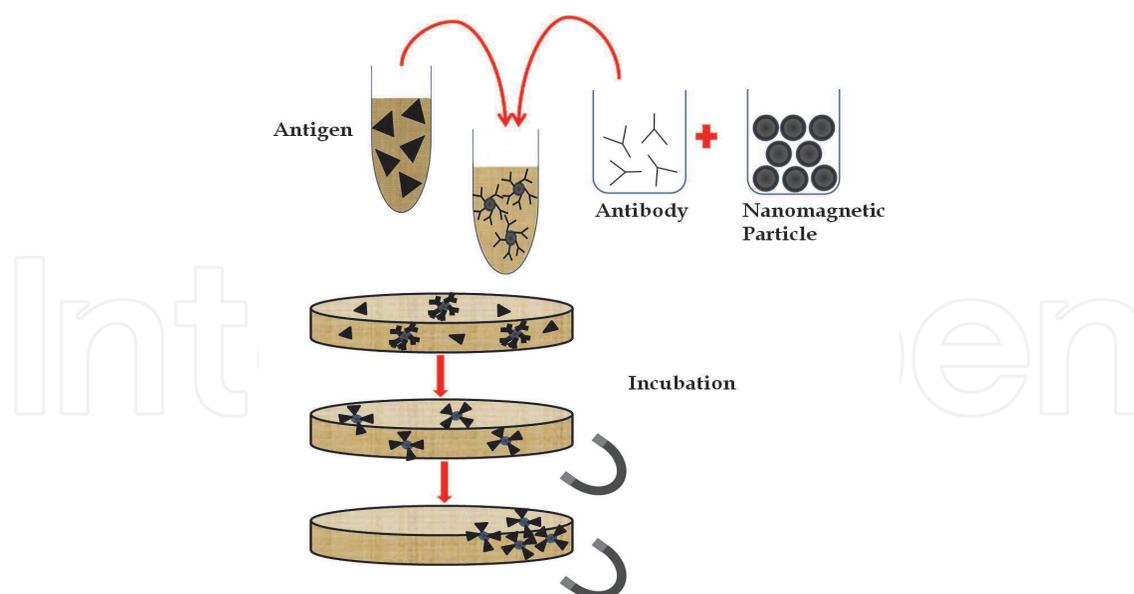


Fig. 3. Magnetic separation of antigens with antibody-functionalized NMPs

Compared to other standard separation procedures, such as chromatography and centrifuges, magnetic separation has several advantages: it is usually very simple and can be performed directly in crude samples containing suspended solid materials. In fact, magnetic separation is the only feasible method for recovery of small magnetic particles in the presence of biological debris and other fouling materials of similar size (Safarik & Safarikova, 2004). Magnetic separation has wide application in biotechnology and biomedicine. The protein separation with organosilane, such as carboxyl, aldehyde, amine, and thiol groups, and also assembled silica coated NMPs was achieved for model proteins such as bovine serum albumin (BSA) and lysozyme (LSZ) at different pH conditions. A work on using these amino functionalized silica coated NMPs for protein purification indicates that they have many advantages such as easy preparation, low cost, easy handling and rapid purification. These particles have extensive potential for serving as a very useful tool for facilitating biotechnology applications (Chang et al., 2008). Ma et al. had developed magnetic poly (methacrylate-divinylbenzene) (mPMA-DVB) microspheres with copper ions capable of binding proteins that display metal affinity. It was showed a high adsorption capacity of the microspheres with rather low non-specific adsorption when the model protein, bovine hemoglobin (BHb), was adopted to investigate (Ma et al., 2005a). A simple and efficient method for protein separation using hydrophobic pocket-modified Si-NMPs was demonstrated by Chang et al. Silica-coated NMPs (Si-NMPs) with alkyl as the hydrophobic pockets of target proteins such as BSA was prepared. It was demonstrated the efficient adsorption or desorption depends on the hydrophobic pockets size adsorption. The study showed an appropriate surface modification technique to prepare system can be used in clinical diagnoses and protein/enzyme recognition processes (Chang et al., 2010).

Array-based bioassay is a promising approach for DNA, protein, and microbe analyses (Macbeath & Schreiber, 2000; Mark Schena, 1995; Wilson & Nock, 2003). Currently, fluorescence and chemiluminescence technologies are used as a standard for the detection on microarrays owing to their high sensitivity, dynamic range, and multiplexing capabilities. However, this approach has the disadvantage in that the signal from the labels is often reduced in intensity because of photo-degradation. To improve the performance of

the array-based assay, the development of molecular labels for bioassay is an important issue for improving detection sensitivity. As one of the attractive materials for the assay system, nanoparticles conjugated with biological molecules have been proposed for use as a label (Amemiya et al., 2005; Baselt et al., 1998; Goldman et al., 2004; Park et al., 2002; Reichert et al., 2000). NMPs are detectable by measuring their magnetism. They are unaffected by the measurement process, and the samples may be stored indefinitely (Richardson et al., 2001). Detection techniques based on magnetic labels are simple to perform and inexpensive in terms of instrumentation compared with the fluorescence detection method, and therefore they are suitable for miniaturization of the detection system (Edelstein et al., 2000; Richardson et al., 2001). NMPs are also much less costly than fluorescent dyes including quantum dots.

NMPs also have been coated with amorphous silica shells for enhanced surface reactivity and RNA and DNA purification (Park & Chang, 2007)**Error! Reference source not found..** DNA is a polyanionic molecule due to the presence of phosphate groups on the nucleic acid backbone and is conveniently captured on a polymeric resin or other metal/inorganic supports with positively charged functional groups. However, current DNA purification methods suffer from several drawbacks that make them unsuitable for the manufacture of pharmaceutical grade. They often involve the use of solvents, toxic chemicals such as cesium chloride, ethidium bromide, phenol, and chloroform, or animal-derived enzymes such as ribonuclease A and lysozyme that are either not approved or not recommended by regulatory agencies. Finally, many techniques were designed to produce small quantities of DNA for laboratory use and are not suitable for the production of therapeutic materials at larger scale (Park & Chang, 2007). Surface modifications of NMPs with suitable intermediates are commonly used to extract the desired target. The driving forces for adsorption processes are hydrophobic, electrostatic, and ligand binding interactions (Donselaar et al., 1997; Massart & Cabuil, 1987). Desorptions of the biomolecules from the magnetic particles could be achieved by using high concentration salts, changing pH, and temperature, for undergoing conformational changes. An example is a sensitive and selective method for DNA detection related to HIV gene using nanoparticle-based Raman tags and magnetic nanoparticles as immobilization and separation tool have developed by Liang et al (Liang et al., 2007). The method based on DNA hybridization uses biocompatible Ag/SiO₂ nanoparticle-based Raman tags functionalized with oligonucleotides applied as detection tool and the amino group functionalized silica-coated magnetic nanoparticles with captures strands as immobilization and separation tool. In addition to facilitate separation, the magnetic nanoparticles led to enhances the Raman signal. However, despite the potential benefits of this technology, it still remains limited to analytical or laboratory scales rather than preparative scale, largely due to low binding capacity of magnetic particles. In magnetic separation, classical proteinaceous ligands, such as streptavidin, antibodies, protein A, protein G, trypsin, inhibitors and cofactors are used most often throughout protein separation. In recent years, some other pseudo affinity ligands, such as triazine dyes (Ma et al., 2006b; Odabaš & Denizli, 2004), metal ions (Akgöl et al., 2004; Ma et al., 2006a; O'brien et al., 1996) have gained much interest. Classical proteinaceous ligands suffer from the disadvantage of high cost, low binding capacity on immobilization, and liability to sanitizing agents used to regenerate the supports. In comparison, pseudo affinity ligands (e.g., metal ions) offer the advantage of low cost, high stability, and easy coupling to the supports with high density, resulting in high-capacity supports. Thus, pseudo affinity ligands are more suitable for large-scale protein separation (O'brien et al., 1996, 1997;

Odabaš et al., 2004). NMPs have been used in separation of target cells from a heterogeneous cell mixture. A novel MHC/peptide complex-conjugated bacterial magnetic particle was developed for separation of melanoma-specific cytotoxic T lymphocytes (CTLs). CTLs are essential in anticancer and antiviral immunity and purification of CTLs from heterogeneous immune cells is desired for an efficient immunotherapy and fundamental research. In the work proposed by Takahashi et al. CTLs were successfully separated from stimulated peripheral blood mononuclear cells derived from a vaccinated melanoma patient (Takahashi et al., 2009).

2.2 Magnetic target drug delivery and magnetic guided gene transfection

The major disadvantage of most drugs for tumour chemotherapy is their relative non-specificity. The drugs are administered intravenously for general system distribution, resulting in deleterious side effects as they attack normal, healthy cells in addition to the target tumour cells. Preferably, the drugs should be localized to the tumourous site. In the late 1970s researchers proposed the use of magnetic carriers to target drugs to specific sites within the body (Widder et al., 1978; Senyei et al., 2009). The attachment of drugs to magnetic particles can be used to reduce drug doses and potential side effects on healthy tissues and the costs associated with drug treatment. The size, charge and surface chemistry of the magnetic particles are particularly important in affecting both blood circulation time as well as bioavailability of the particles within the body (Berry & Curtis, 2003). In addition, magnetic properties and internalization of particles depend strongly on the size of the NMPs and the surrounding magnetic field strength. Also, some hydrodynamic parameters, such as blood flow rate, particle concentration, infusion route play significant roles. Since the 1970s, a variety of NMPs and microparticle carriers have been developed to deliver drugs to specific target sites *in vivo*. The optimization of these carriers has continued to this day. Generally, the magnetic particle core is coated with biocompatible polymers to be used for the intravenous applications. Recently, inorganic coatings such as silica and gold have been developed. The coating acts to shield the magnetic particle from the surrounding environment and can also be functionalized by attaching functional groups, e.g., biotin, avidin and other molecules.

A treatment of hepatocellular carcinoma (HCC) via trans-arterial chemoembolization in the hepatic-artery applying therapeutic magnetic microcarriers (TMMC) was proposed by Pouponneau et al. TMMC is constituted of biodegradable poly (D,L-lactic-co-glycolicacid) microparticles loaded with doxorubicin as antitumour drug and iron-cobalt nanoparticles. *In vitro* and *in vivo* studies showed that the magnetic resonance navigation was successfully carried out using endovascular steering of the TMMC. This work had showed the capability of MRN to enhance drug targeting in deep tissue (Pouponneau et al., 2009).

Several researchers have studied NMPs as drug carriers for paclitaxel. In one interesting study, poly-D,L-lactide-co-glycolide nanospheres loaded with biocompatible magnetic fluid and anticancer drug taxol were prepared with efficiency encapsulation and sufficient magnetization to be used as magnetic carrier (Koneracká et al., 2008). A new group of candidates as anticancer drugs were proposed by Hwu et al. Paclitaxel-conjugated nanoparticles were synthesized by using Fe_3O_4 and Au as nanoparticles and functioned as drug carriers of paclitaxel which was liberated in the presence of phosphodiesterase. Hydrophilic and hydrophobic paclitaxel conjugates were produced by synthesizing Au-NPs through different methods (Hwu et al., 2008).

Magnetically guided gene transfection (magnetofection) is another way to enhance the performance of nucleic acid and gene delivery for both, *in vivo* or *in vitro* essays (Schillinger et al., 2005). The fundamental principle of magnetofection is simple and comprises the steps of: a) formulating a magnetic vector composed of a therapeutic gene and surface modified NMPs; b) adding it to the medium covering cultured cells; c) injecting it systemically via the blood stream or applying it locally to a target tissue, and d) applying a magnetic field in order to direct the vector towards the target cells or retain it in the target tissue. It has been proved that magnetofection can greatly improve the efficacy of nucleic acid delivery and it is a powerful tool in cancer therapy.

Until now, only a small number of clinical trials with magnetic drug targeting has been performing. The first clinical trial using magnetically targeted drug was conducted Lubbe et al. in 1996 (Lübbe et al., 1996). This phase I clinical trial was performed using nanomagnetic particles loaded epirubicin in patients with advanced cancers or sarcomas. They demonstrated that the infusion of ferrofluids was well tolerated in most of the 14 patients studied and successfully directed to the tumour site in 6 patients. In 2002, Koda et al. applied doxorubicin coupled to a magnetic particle (MTC-DOX) carrier in patients with hepatocellular carcinoma. In this study, 22 patients were studied and the tumours were targeted successfully in 20 of them (Koda et al., 2002). Another clinical trial was performed by Wilson et al. in 2004 using MTC-DOX. The particles were directed to the tumour sites by magnets and monitored by MRI image. The results showed the drug had treated between 64 and 91% of tumour volume (Wilson et al., 2004).

2.3 Magnetic resonance imaging and cancer diagnosis

Magnetic resonance imaging (MRI) is a very common noninvasive method for diagnosing soft tissue and early cartilage pathologies. The method principle is based on the fact that the relaxation times of hydrogen atoms are influenced by the medium and, in particular, the disease medium. The disease processes alters molecular shapes and/or cell behavior which can be identified from molecular imaging. This insight allows the early detection of disease, so the prognoses, the effective treatment, and, personalized drugs and treatment times can be prescribed. Hence, molecular imaging is one promising tool to promote laboratory and clinical progress (Gamarra et al., 2010). The demand for innovative contrast agents encouraged the studies in the synthesis and coating of NMPs. NMPs probes for biomedical applications are comprised of nanoscale superparamagnetic iron oxide cores of magnetite and/or maghemite which are encapsulated in natural or synthetic polymers, silica and Au coatings. Cobalt ferrite (Morais et al., 2004) and gallium chelates were also used (Flacke et al., 2001; Louie et al., 2000).

The performance of the magnetic iron oxide contrast agents can be evaluated by their clearance, cell response, and toxicity. Particles sizes over 200 nm undergo mechanical filtration by the spleen and liver. Particles below 10 nm are rapidly removed during extravasations and renal clearance (Gupta & Wells, 2004). Amphiphilic coatings increase the circulation time of NMPs from minutes to hours which enhances the targeting potential of the contrast agent. One important problem related to the NMPs is finding the dose necessary to MRI detection. Some techniques which involves intracellular trapping (Kelly et al., 2005) have being of particular worth. In this approach, receptor-mediated uptake of NMPs is exploited to accrue elevated levels of the contrast agent within the desired cells.

2.4 Magnetic nanoparticle induced hyperthermia

Hyperthermia is a cancer therapy which consists in heating selectively tumour zones. Those zones have less blood vessels and are less oxygenated than health ones. Consequently, they are more sensible and died when the local temperature increases above 43 °C. Among the methods used for this therapy are induction heating, capacitive heating and hot water. The great advantage of this therapy is the fact that, in principle, all kinds of tumour cells can be treated. However, it is needed to control the temperature rising to prevent the death of health cells. Magnetic hyperthermia is another method to induce hyperthermia using NMPs. In this approach, NMPs are firstly introduced into the desired tissues and then guided by an external magnetic field. An externally applied oscillating magnetic field induces the hyperthermia as illustrated in Fig 4. (Ferreira et al., 2011; Jordan et al., 2009; Mitsumori et al., 1994; Wada et al., 2001).

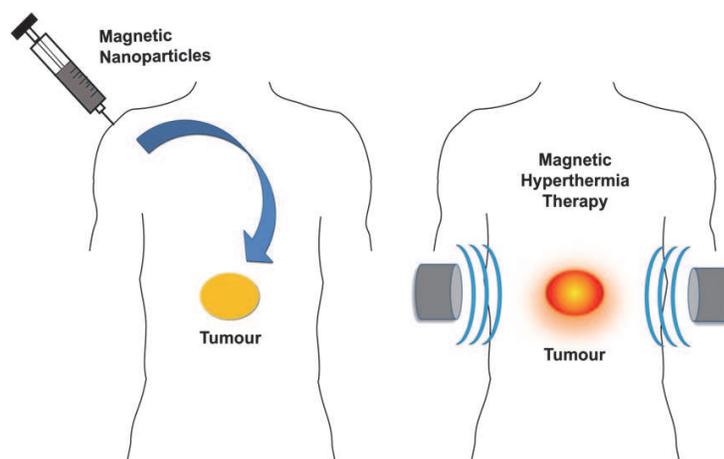


Fig. 4. Sketch showing the general procedure for the endovenous injection of the NMPs suspension into the human body: (a) the particles are first injected in a tumour and, then, (b) an externally applied alternating magnetic field induces the hyperthermia.

In 1979, Gordon *et al.* first proposed the concept of inducing intracellular hyperthermia it means, the magnetic field heating effects in a scale smaller than that of biological cell diameters (Gordon et al., 1979). They believed that intracellular hyperthermia should be more efficacy than the extracellular one since the cell membranes are not good thermal conductors and could act as thermal barriers. In this process, the cells can be selectively killed by the heat generated by nanomediators located inside the cell. Gordon *et al.* also showed that NMPs colloidal suspension injected intravenously can be phagocytized by cancer cells and after application of alternating magnetic field the cancer cells were selectively destroyed. In a more recent study, Wilhelm et al. showed that maghemite anionic nanoparticles are efficiently captured by human prostatic tumour cells (PC3) and concentrate within intracellular vesicles (Wilhelm et al., 2007). After these works, some researchers have proposed modifications on superparamagnetic particle surfaces to obtain magnetic colloidal ferrofluids to provide hyperthermia treatments. Magnetite nanoparticles (Fe_3O_4) coated with sodium oleate and poly(ethylene glycol) partially inhibited the growth of cancerous B16 cell sat the highest tested dose (2.1 mg/ml of Fe_3O_4 in MFPEG (Zavisova et al., 2011). In the presence of external alternating magnetic field bimagnetic Fe/ Fe_3O_4 core/shell nanoparticles encapsulated by dopamine-oligoethylene glycol ligands showed considerable anti-tumour effect on murine B16-F10 melanoma.

Decrease in tumour size was observed 24hrs after intravenous administration of the NMPs followed by three days of alternating magnetic field. This study showed attenuation of the tumour without the undesirable side effects associated with traditional cancer therapy (Balivada et al., 2010).

Kim et al. developed promising materials to be applied in magnetic targeted hyperthermia based on chitosan-coated nanomagnetic particles. The hyperthermic thermoseed generated a temperature rise of 23°C under an alternating magnetic field and the capturing rate of the nanomagnetic particles was 96% under an external magnetic field of 0.4 T. The study showed that chitosan-coated nanomagnetic particles were biocompatible and exhibited higher affinity of KB carcinoma cells than L929 normal cells magnetic (Kim et al., 2009).

The potential hyperthermia application of magnetic fluids based on magnetite coated by biocompatible starch layer was studied by Linh et al. (Linh et al., 2009). The investigation of the heating ability was performed on magnetic fluid samples with particles concentration varying from 3 to 15 mg/ml under an alternating magnetic field with frequency of 184 kHz and field strength of 12 kA/m. The results obtained for sample with minimal iron oxide concentration are particularly of interest for applications in the heating therapy because this sample combined the high specific loss power value (129 W/g) with the saturation temperature of 45°C, which is appropriate for cancer treatment application.

Several works have studied magnetoliposomes in hyperthermia cancer treatment. An example is the study using magnetite cationic liposomes (MCLs) as a mediator of local hyperthermia to treatment of rat mammary cancer under alternating magnetic field with frequency 360 kHz. MCLs were infused into the rat tumour by using an infusion pump to obtain approximately 2 mg MCL per mL tumour volume. The rats were exposed to 3 series of hyperthermia treatments for 30 min each. The treated tumours were well controlled over a 30-day observation period showing an induction of immunological antitumour activity mediated by the MCLs (Motoyama et al., 2008).

The use of anti-HER2 immunoliposomes containing nanomagnetic particles (HMLs) for anti-HER2 antibody therapy and tumour-specific hyperthermia has been exploited for many research groups. The first time that the combination of anti-HER2 antibody therapy and tumour-specific hyperthermia displaying a strong cytotoxic effect was in the study published by Ito et al. (Ito et al., 2004b). In this study, anti-HER2 immunoliposomes magnetite nanoparticles were synthesized. Analysis of combined effect of anti-HER2 antibody and hyperthermic treatment was performed on SKBr3 breast cancer cells *in vitro* showing strong cytotoxic effects after the cells heated at 42.5°C and incorporation of more than 60% of magnetite nanoparticles into SKBr3. Kikumory et al. investigated the retention ability of HML and the hyperthermic effects of HMLs on the subcutaneous tumours of breast cancer in nude mice. HMLs were injected into subcutaneous cancer nodules of BT474 (high HER2 expression) or SKOV3 (low HER2 expression) cells in nude mice and exposed to an alternating magnetic field, but HMLs accumulation was observed only in BT474 tumours. After hyperthermic treatment, tumour temperature increased to 45 °C, while the body temperature stayed around 38 °C. Tumour regression was observed and sustained for 10 weeks after hyperthermia (Kikumori et al., 2009).

The ability to conduct magnetic hyperthermia upon exposure to low-frequency alternating magnetic field and the biocompatibility were evaluated in maghemite nanoparticles embedded in a ordered mesoporous silica-matrix MMS. Cell culture experiments showed that MMS particles were efficiently internalized by human A549, Saos-2 and HepG2 cells and presented good biocompatibility. Magnetic hyperthermia tests performed under

alternating magnetic field at a frequency of 100 kHz and a magnetic field intensity of 200 Oe. It was observed that in low concentration of MMS ($48\text{mg}\cdot\text{mL}^{-1}$) the temperature in the culture medium increased to $44\text{ }^{\circ}\text{C}$ in 30 min and the cell viability index dropped to about 0.5. When the tests were performed in high concentration ($80\text{ mg}\cdot\text{mL}^{-1}$) cells increased the temperature of culture medium to $50\text{ }^{\circ}\text{C}$ in 25 min and the cell viability index decreased to 0.8 (Martín-Saavedra et al., 2010).

The influence of the oleic acid surface coating on Fe_3O_4 and NiFe_2O_4 nanoparticles on their magnetic and calorimetric characterization was investigated. Fe_3O_4 (particle sizes of 15–20 and 20–30 nm) and NiFe_2O_4 (particle sizes of 20–30 nm) were dispersed in oleic acid. The temperature rising in the oleic-acid-coated nanoparticles was greater than that of the uncoated ones. The viscosity dependence on the self-heating temperature of Fe_3O_4 under an alternating magnetic field was measured. The temperature rise for both Fe_3O_4 particle sizes exhibited a strong dependence on viscosity and magnetic field frequency. Moreover, *in vitro* cytotoxicity test of Fe_3O_4 and NiFe_2O_4 was performed using human cervical carcinoma cells (HeLa), and the cytotoxicity of NiFe_2O_4 was compared to that of Fe_3O_4 .

2.5 Tissue engineering using nanomagnetic particles

The application of nanomagnetic particles in tissue engineering has increased in the last years. These materials can allow develop new tissues *in vitro* with function and anatomical structure similar to original. The method consists in develop degradable tissue scaffolds to grow new tissues (Langer, 1993). It is possible to culture the principal cell (the keratinocyte) of the epidermis and use these cells to reconstitute human tissue (Bell et al., 1981; Yannas et al., 1982). Ito et al. proposed the use of magnetite cationic liposomes (MCLs) in a novel methodology (Mag-TE) to construct multilayered keratinocyte sheets and collect the sheets without enzymatic treatment in presence of magnetic field. It was possible obtain keratinocytes further stratified and, subsequently, 10-layered epidermal sheets (Ito et al., 2004a). The technique Mag-TE was applied to construct heterotypic layered coculture system of rat hepatocytes and human aortic endothelial cells (HAECs). In this study, HAECs accumulated onto hepatocyte monolayers at sites where a magnet was positioned, and then adhered to form heterotypic, layered construct with tight and close contact. Albumin secretion was enhanced in the homotypic hepatocyte culture in presence of a magnetic force compared with the culture without magnets (Ito et al., 2004c).

3. Conclusion

Recent progress in nanomaterials syntheses has proved that solution-phase syntheses are capable of producing monodisperse NMPs with controlled chemical and magnetic properties. Surface modification and functionalization allows the NMPs to attach to various biomolecules, making them promising magnetic labels for bioseparation, biodetection and contrast enhancement of magnetic resonance imaging. Moreover, they can act as contrast agent and drug delivery system simultaneously which enhances the probability of success of many therapy diseases. Once the issues in toxicity, biodistribution and bioelimination of these nanoparticles in a biological system are solved, the functionalized monodisperse nanoparticles will serve as powerful magnetic labels or delivery vehicles for highly sensitive/efficient biosensing, drug delivery and magnetic fluid hyperthermia applications.

4. Acknowledgment

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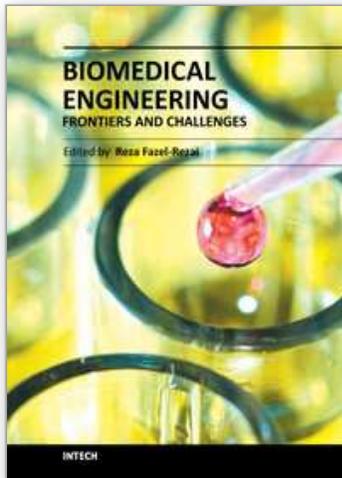
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In all different areas in biomedical engineering, the ultimate objectives in research and education are to improve the quality life, reduce the impact of disease on the everyday life of individuals, and provide an appropriate infrastructure to promote and enhance the interaction of biomedical engineering researchers. This book is prepared in two volumes to introduce recent advances in different areas of biomedical engineering such as biomaterials, cellular engineering, biomedical devices, nanotechnology, and biomechanics. It is hoped that both of the volumes will bring more awareness about the biomedical engineering field and help in completing or establishing new research areas in biomedical engineering.

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