Biodecorated Magnetic Nanoparticles Preparation, Modification and Properties

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Abstract. *For the discussed biomedical applications, the vast number of known magnetic materials is strongly reduced by the demands of biocompatibility including: (i) non-toxicity; (ii) a sufficient chemical stability in bio-environment; (iii) an appropriate circulation time in the blood; and (iv) a harmless biodegradability. As a consequence investigations mainly concentrate on magnetic iron oxides Fe_3O_4 (magnetite) and γ-Fe_2O_3 (maghemite). The quality of the magnetic nanoparticles (MNPs) required for a specific biomedical application is strongly related to their structural and magnetic properties. For most biomedical applications, the particles should have intrinsically a large saturation magnetization allowing for large magnetic moments despite the small particle volumes. Due to the biocompatibility constraint, the choice of magnetic substances is, at least at the moment, concentrated on the strong magnetic iron oxides: magnetite and maghemite.*

Keywords*: Magnetic Nanoparticles, Fe_3O_4, γ-Fe_2O_3, Biotherapeutics, Magnetic Drug Targeting, Hyperthermia*

Subject and Methods

Various synthesis methods were developed and adjusted to meet the requirements for biomedical applications MNPs. The reaction mechanism of microemulsion and the size of metal particles prepared by the microemulsion (the particle diameter varies with the ratio $w = [H_2O]/[\text{surfactant}]$) are summarized in Figs. 1 and 2. At w values below ca. 10, water mobility is greatly reduced (bound water) and particles below 5 nm can be prepared. Above $w = 10$, the linear increase in the water pool diameter, d_w, with w (from 6 to 18 nm) is explained by a geometrical model that assumes a constant area per surfactant molecule and that all surfactant molecules participate in the reverse micelle interface. The volume of water added to the solution is the main parameter controlling the droplet diameter or final particle size [1].

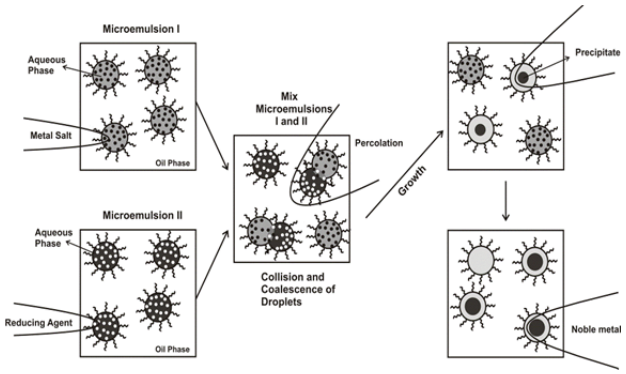

Fig. 1. Proposed mechanism for the formation of magnetic (Fe_3O_4) nanoparticles in the microemulsion.

MNPs with diameter of 8 nm were prepared using a coprecipitation method using NaOH - $FeCl_2$ - $FeCl_3$. An oxidation precipitation method in a $FeCl_2$–$NaNO_3$–NaOH aqueous system appeared

larger 24 - 400 nm MNPs. Core-shell nanoparticles with different coatings (from 10 wt% to 30 wt%) were prepared with various stabilizers such as oleic acid (OA,), sodium bis(2-ethylhexyl)sulphosuccinic acid (AOT), sodium dodecylsulfate (SDS), 2,3-dimercaptosuccinic acid (DMSA), phosphonoacetic acid (PA), dextran (Dx), aminodextran (ADx), carboxydextran (CDx) and citric acid (CA) (Fig. 3). The colloidal stability and particle size is also function of costabilizers (or solvents, such as acetone, acetonitrile,..) which passivate the particle size [1-3].

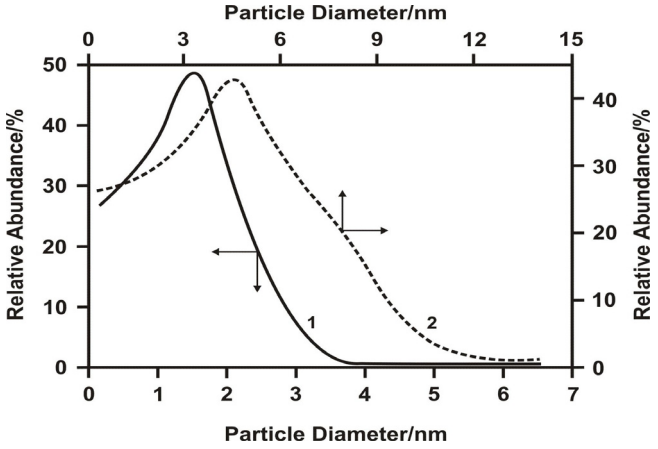

Fig. 2. Variation of particle diameter with $w = [H_2O]/[Na(AOT)]$, (1) $w = 2.5$, $d = 1.5$ nm, (2) $w = 15$, $d = 5$ nm, w determines the reverse micelle size where surfactant is adsorbed on the particle surface.

The volume of water added to the solution is the main parameter controlling the droplet diameter.

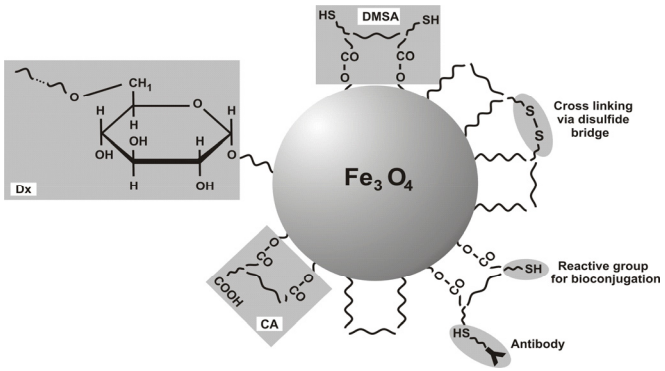

Fig. 3. Schematic picture of 2,3-dimercaptosuccinic acid (DMSA), dextran (Dx) and citric acid (CA) - coated water-soluble Fe_3O_4 where surfactants and chemisorbed on the particle surface which is passivated by solvent molecules.

Nanoparticle dispersion stability depends on charge and surface chemistry, which give rise to both steric and electrostatic repulsion. Conventionally, a zeta potential higher than ±30 mV would be considered stable, i.e., the dispersion will resist aggregation. In the case of DMSA-, PA-, Dx- and CA-coated samples, the ionizable carboxylate groups on their surfaces govern the pH dependent evolution of the Z-potential, whose high values indicate the formation of stable systems. A pure polymer-coated sample, such as dextran sample, shows lower electrostatic stabilization (lower Z-potential), due to the lack of ionizable surface groups; the steric effect helps to maintain a stable dispersion, independently of the pH. The uncoated particles show the typical Z-potential values reported for bare iron oxide nanoparticles (unstable) nanoparticles, which is ~ 0 at pH 7. All negatively charged samples had similar hydrodynamic sizes (~ 80 - 100 nm) and the highest coating (Fig. 4). On the contrary, aminodextran (ADx) has the smallest coating [2].

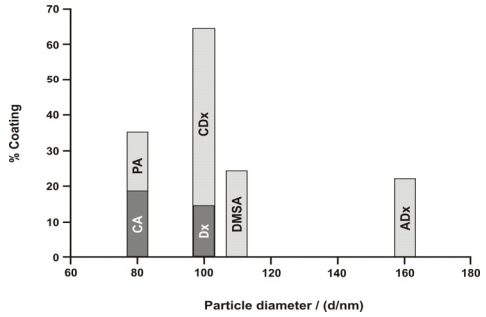

Fig. 4. Variation of % coating with the particle diameter for each surfactant.

MNPs modified with dextran or oleic acid, and functionalized with a polymer or liposome, and/or further conjugated with an anticancer therapeutic drug can also improve the colloidal stability of the magnetic fluid, affinity for the carcinoma cell, or confer a tumor-specific targeting ability. These modified magnetic particles show an improved adsorption and accumulation in the area of a tumor, and also have an improved heating efficiency on exposure to an AC magnetic field (Fig. 5). Particles modified with DMSA showed the most efficient adsorption/release capacity. Changes in synthesis method and particle coating not only altered the crystalline nature of the particles, but also modified their capacity to adsorb and release biomolecules (ligands) [3, 4].

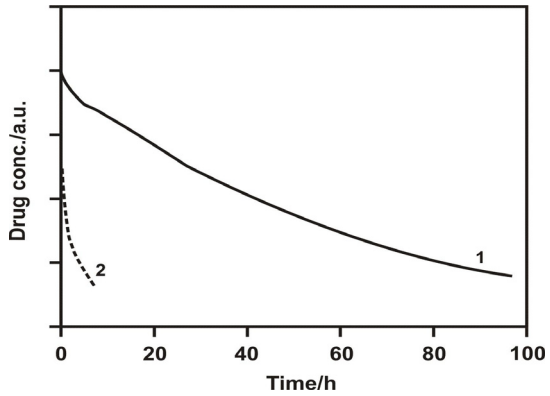

Fig. 5. Nanoparticles can have extended pharmacokinetics over the therapeutic entity alone. The data are from a nanoparticle containing drug (dox) (1) and a small-molecule drug (2) in rats.

Magnetic nanoparticles have been used, for example, for magnetic cell separation or magnetic resonance imaging (MRI). The development of biocompatible nanosized drug delivery systems for specific targeting of therapeutics is the focus of medical research, especially for the treatment of cancer and diseases of the vascular system. An important advantage of these carriers is the possibility for detecting these nanoparticles after treatment with common imaging techniques (i.e. x-ray-tomography, magnetorelaxometry, magnetic resonance imaging), which can be correlated to histology. Magnetic hyperthermia has recently attracted significant attention as a safe method for cancer therapy. It can increase the temperature in tumors to 41 - 46 °C, thereby killing the tumor cells with minimum damage to normal tissue. This method involves the introduction of ferromagnetic or superparamagnetic particles into the tumor tissue, followed by irradiation using an alternating current (AC) magnetic field. In general, magnetic particles generate heat in an external AC magnetic field from several physical mechanisms. These include relaxation loss or hysteresis loss, which strongly depends on the frequency of the external field, as well as the nature of the particles, such as the particle size and surface modifications. The dependence of the magnetization M_s and the coercivity H_c on the particle size d is in the Fig. 6 [5].

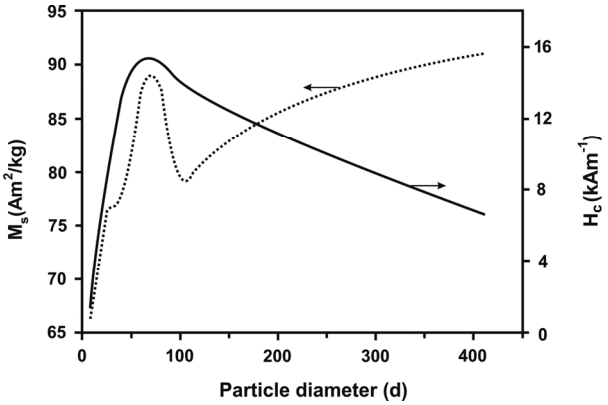

Fig. 6. Variation of the magnetization M_s and the coercivity H_c with the particle diameter d [nm].

Results

There are a variety of nanoparticle systems currently being explored for cancer therapeutics. The material properties of each nanoparticle system have been developed to enhance delivery to the tumor. For example, hydrophilic surfaces can be used to provide the nanoparticles with stealth properties for longer circulation times and positively charged surfaces can enhance endocytosis. Functionalization of nanoparticles with proteins, for example, is necessary to increase circulation times through avoidance of removal by the reticuloendothelial systems (RES). Short circulation times decrease the efficiency of the delivery of the nanoparticle to the tumor site. Incorporation of a hydrophilic groups or segments to the surface of the nanoparticle allows for a reduction in opsonization, which reduces removal by the RES. Active targeting involves the use of peripherally conjugated targeting moieties for enhanced delivery of nanoparticle systems. Although antibody targeting is regarded as a promising strategy, some groups have reported that antibody targeting might not increase tumor localization. The targeting moieties are important to the mechanism of cellular uptake. Long circulation times will allow for effective transport of the nanoparticles to the tumor site through the enhanced permeation and retention (EPR) effect, and the targeting molecule can increase endocytosis of the nanoparticles. The internalization of nanoparticle drug delivery systems has shown an increased therapeutic effect. If the nanoparticle attaches to vascular endothelial cells via a noninternalizing epitope, high local concentrations of the drug will be available on the outer surface of the target cell. Although this has a higher efficiency than free drug released into circulation, only a fraction of the released drug will be delivered to the target cell. In most cases, internalization of the nanoparticle is important for effective delivery of some anticancer drugs, especially in gene delivery, gene silencing, and other biotherapeutics [6].

Acknowledgements

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