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Research review paper

The use of magnetic nanoparticles in cancer theranostics: Toward handheld diagnostic devices

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ABSTRACT

Magnetic nanoparticles are frequently used in a wide range of biomedical applications. In the first part of this review the most commonly used preparation and surface coating approaches of MNPs are briefly summarized including multifunctional hybrid particles. The second part gives a detailed overview of the use of MNPs in "traditional" biomedical applications related to cancer theranostics, like magnetic resonance imaging, drug delivery, hyperthermia and also their applicability in the next generation of point of care devices based on micro nuclear magnetic resonance and surface enhanced Raman spectroscopic detection technology that all can be routinely applied in everyday clinical practice.

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Abbreviations: MNP, magnetic nanoparticle; SPIO, superparamagnetic iron oxide; MRI, magnetic resonance imaging; HR-TEM, high resolution transmission electron microscopy; XRD, X-ray diffraction; DLS, dynamic light scattering; PCS, photon correlation spectroscopy; ξ, zeta potential; ELS, electrophoretic light scattering; FTIR, Fourier transform infrared spectroscopy; NMR, nuclear magnetic resonance; TGA, therogravimetric analysis; DSC, differential scaning calorimetry; ICP-MS, inductively coupled plasma mass spectroscopy; SQUID, superconducting quantum interference device; MPS, magnetic particle spectroscopy; ROS, reactive oxygen species; MWI, microwave imaging; PMF, polarizing magnetic field; μ-NMR, micro nuclear magnetic resonance; DMR, diagnostic magnetic resonance; SERS, surface enhanced Raman spectroscopy; SPR, surface plasmon resonance; CNM, carbon nanomaterial; CNT, carbon nanotube; RF, radiofrequency; TCO, trans-cyclooctene; CTC, circulating tumor cell; μHD, micro-Hall detector; FNA, fine needle aspiration; EpCAM, epithelial cell adhesion molecule; MUC-1, Mucin 1; HER-2, human epidermal growth factor receptor 2; EGFR, epidermal growth factor receptor; BASC, bronchioalveolar stem cell; CD34, hematopoietic progenitor cell antigen CD34; Sca1, spinocerebellar ataxia type 1; BT, benzenethiol; 4-MT, 4-methylbenzenethiol; CEA, carcinoembryonic antigen; HGN, hollow gold nanospheres; LOD, limit of detection; ELISA, enzyme-linked immunosorbent assay.

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1. Introduction

In recent years, magnetic nanoparticles (MNPs) demonstrated their applicability in a wide range of biomedical applications (Beveridge et al., 2011), such as in magnetic resonance imaging (MRI), drug delivery, and hyperthermia, just to list a few (Cole et al., 2011; Colombo et al., 2012; Singh and Sahoo, 2014). Magnetic nanoparticles with sizes less than 100 nm have special properties such as high surface-volume ratios, large surface energy and excellent reactivity compared to their bulk micron-sized counterparts, mainly due to size effects and surface phenomena. They are also comparable in size to some biologically important objects as described in (Kumar, 2006). One of the most widely used magnetic nanoparticle types is iron oxides, and based on size they can be divided into the following three classes: 1) superparamagnetic iron oxide (SPIO) with larger than 50 nm hydrodynamic diameter, 2) ultrasmall (U) SPIO with less than 50 nm hydrodynamic diameter and 3) micron-sized iron oxide particles (MPIO) (Laurent et al., 2010). The physicochemical properties, colloidal stability and biological activity/behavior of MNPs depend on their fabrication conditions and surface functionalization. For biomedical applications, the beads should have very small particle sizes (usually below 100 nm) with narrow size distribution and high magnetic susceptibility for optimum magnetic enrichment. The loss of magnetic characteristics in the absence of magnetic field is also important (superparamagnetism). Biological targeting and biocompatibility are ensured by proper surface coating (Reddy et al., 2012).

In this review the most frequently used preparation and surface coating approaches are summarized for MNPs, including multifunctional hybrid particles and recent developments in "classic" biomedical applications, like magnetic resonance imaging (MRI), drug delivery and hyperthermia. The main focus of this review is the applicability of MNPs in next generation of point of care devices based on micro nuclear magnetic resonance (micro-NMR) and Surface Enhanced Raman Spectroscopic (SERS) detection technology that requires special hybrid gold and iron-oxide MNPs.

2. Preparation, surface functionalization and physical properties of magnetic nanoparticles

There are several excellent reviews focusing on the fabrication techniques of magnetic nanoparticles in detail (Akbarzadeh et al., 2012; Drbohlavova et al., 2009; Hyeon, 2003; Laurent et al., 2010; Lu et al., 2007; Reddy et al., 2012; Wu et al., 2008). Basically, materials like metal oxides (Fe_3O_4, γ-Fe_2O_3, $MnFe_2O_4$, $CoFe_2O_4$, etc.), pure metals (Fe, Co, Ni, etc.), with highly saturated magnetization are usually preferred for the production of MNPs. Although pure metals have favorable magnetic properties, their high toxicity and oxidative sensitivity make them unsuitable for biomedical use without proper and stable surface treatment (Tran and Webster, 2010). The major preparation options to produce MNPs can be divided into the following three categories (Reddy et al., 2012):

(1) *Physical methods* convert the iron particles or molecular precursors like $[Fe(OBut)_3]_2$ to iron oxide nanostructures. However, these methods are unable to control the particle size down to the nanometer scale like gas-phase deposition and electron beam lithography.
(2) *Wet chemical preparation methods* are widely used and feature the most efficient control over particle size. The techniques include sol–gel synthesis, oxidation methods, chemical co-precipitation, hydrothermal reactions, flow injection synthesis, electrochemical methods, aerosol/vaporphase methods, sonochemical decomposition reactions, supercritical fluid methods, and synthesis in nanoreactors.
(3) *Microbial methods* feature high yield, good reproducibility, good scalability and very efficient with appreciable control over the particle size and composition of the resulting material.

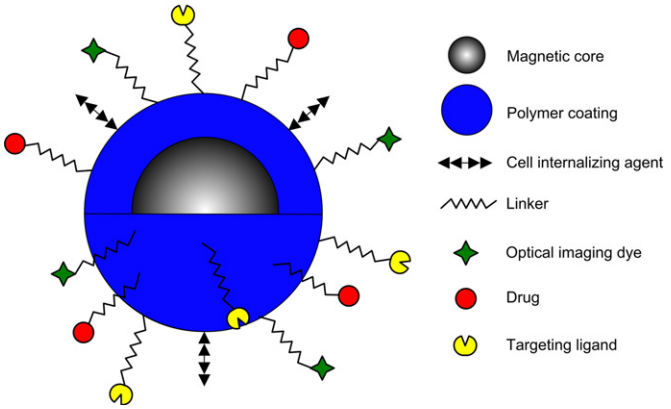

Fig. 1. The core-shell structure of functionalized magnetic nanoparticles.

Once produced, the synthesized MNPs are typically surface-coated to improve their colloidal stability, increase their water-dispersibility, and provide chemical functionality for bioactive molecule additions (Cole et al., 2011). The coated MNP morphology is often referred to as "core-shell" structure (Fig. 1).

Furthermore, with proper surface coating the formation of agglomerates or precipitation can be avoided. It also improves the colloidal stability of MNPs, so their circulation time is prolonged before they are recognized by the body's biological particulate filters, such as the reticulo-endothelial system (RES), which is the primary physiologic mechanism responsible for nanoparticle removal from blood circulation (Tartaj et al., 2003).

Multifunctional hybrid nanostructures represent a new emerging field, where magnetic nanoparticles are combined with other nanocomponents like gold nanoparticles or carbon nanomaterials, resulting in enhanced physicochemical properties (Gao et al., 2009). For example, gold iron-oxide hybrid nanoparticles (AuMNP) exhibit enhanced optical properties, so they are suitable for optical sensing applications because of their strong light absorption and scattering characteristic at the surface plasmon resonance (SPR) wavelength region, which is tunable by changing the size and shape of the nanoparticles. AuMNPs exhibit strong enhancement of Raman scattering from molecules adsorbed on their surface. In surface enhanced Raman spectroscopy (SERS), the scattered light from the Raman active reporter molecules located on the surface of the nanoparticles is enhanced by the gold core (Jans and Huo, 2012; Leung et al., 2012) (discussed later in detail).

The synthesized MNPs exhibit superparamagnetism namely, the particles become magnetized up to their saturation level, but after removal of the magnetic field they lose their magnetization. This phenomenon is size-dependent and generally arises when the size of nanoparticles is around 10–20 nm. At such a small size they act like single magnetic domains and exhibit high magnetic susceptibility (Wahajuddin and Arora, 2012). The key magnetic properties of MNPs are as follows: saturation magnetization (Ms), coercivity (Hc), blocking temperature (T_B), and relaxation time (Neel relaxation — t_N and Brownian relaxation — t_B). These properties can be influenced and optimized by the basic parameters of the MNPs like size, shape, composition, core-shell structure for different type of biomedical applications (Kolhatkar et al., 2013). For biosensing and MRI applications MNPs should have high saturation magnetization values and should enhance the relaxation times of the protons in the surrounding environment (Guardia et al., 2011; Haun et al., 2010; Koh and Josephson, 2009). In hyperthermia applications, the Neel and Brownian relaxations are crucial magnetic properties because the heating effect arises from these relaxations (Deatsch and Evans, 2014). Effects of parameters like shape, size, composition, and structure on the magnetic properties of