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Magnetic particles: From preparation to lab-on-a-chip, biosensors, microsystems and microfluidics applications

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ABSTRACT

Magnetic particles are largely used in various applications and particularly in *in-vitro* biomedical diagnostic and bionanotechnology. In fact, they have been employed for extraction of various biomolecules even from crude samples and as solid support in numerous samples' preparation for *in-vitro* diagnosis. Nowadays, they are also successfully being exploited as a carrier of biomolecules in microsystems, microfluidics, lab-on-a-chip and for detection in specific biosensors. Before any use or any preparation of magnetic hybrid particles, various factors should be considered in order to perfectly target the suitable applications. For instance, in case of nucleic acid, the particles shouldn't induce any inhibition of biological amplification techniques. For microfluidic, these particles should be colloidal stable in order to avoid any jump in the microfluidic canals. Regarding biosensor, these particles need to be chemically well designed generally to enhance specific detection or specific signal.

Contents

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1. Introduction

In the last decade, a great attention has been paid to the unique feature of magnetic nanoparticles (superpara-magnetism), which makes them easily guided by an external magnetic field. This unique property has been exploited in fast separation and particularly for *in vitro* biomedical diagnostic domain [1]. Therefore, the development of reactive magnetic nanoparticles for immobilization and fast magnetic separation of biomolecules (e.g. antibodies, proteins, enzymes, etc.) is of great importance nowadays especially for fast diagnostic applications providing early detection of diseases. This in turn helps us to get optimal results in therapy and consequently management and treatment of diseases at early stages of infection. Moreover, magnetic colloidal particles have also been tried in various *in vivo* diagnostic and therapeutic applications such as in Magnetic Resonance Imaging (MRI) [2] as contrast agents, drug delivery, and hyperthermia.

Among magnetic nanoparticles, iron oxides and in particular magnetite (Fe_3O_4) and its oxidized form maghemite (γ-Fe_2O_3) have attracted much attention due to their biocompatibility, low toxicity, and ease of preparation at low cost [3].

More interestingly, the specific optical (fluorescent) or magnetic feature of magnetic nanoparticles are sometimes exploited and integrated in microsystems in order to elaborate medical devices. This provides fast analysis with high sensitivity for low volume analyte, similar to that existing in large-scale analysis equipments. Such systems are called micro-Total Analysis Systems (μ-TAS) [4] in which all steps are concentrated in one device (e.g. lab-on-a-chip systems(LOC), biosensors, microfluidic systems, etc). These devices and systems (with highly automated operations) are characterized by their small size and robust mechanics. Hence, are important for routine applications and can also be developed as easy-to-use portable devices. In addition, they are not only cost effective but also have low running costs. These are the features that are very much required in biomedical diagnosis, clinical analysis and nanomedicine. Hence, attracting significant attraction from various research groups.

However, in order to be conveniently used in bio-related applications, the control of surface chemistry of superparamgnetic iron oxide nanoparticles (SIONPs) is required. Generally, the pristine SIONPs tend to aggregate into large clusters due to their large surface area-to-volume ratio and dipole-dipole interaction. As a result, this leads to reduction in their intrinsic superparamagnetic properties. Therefore, surface modification of SIONPs is of a paramount importance not only to prevent aggregation of SIONPs, leading to colloidal stability, but also to enhance their water solubility, biocompatibility, bioconjugation, and nonspecific adsorption to cells. Surface modification, therefore, provides them an edge over the other separation techniques (e.g. filtration, centrifugation and sedimentation) that are laborious as well as time consuming. For instance, the coupling of biomolecules (e.g. proteins, enzymes, antibodies, antigens, etc.) to magnetic nanoparticles has been used to achieve simple, fast, inexpensive and highly efficient separation of targeted biomolecules under the effect of an external magnetic field.

Magnetic colloidal particles are commonly used as solid supports (carriers) for the immobilization of biomolecules such as oligonucleotides, peptides, ligands, proteins or antibodies in order to prevent nonspecific adsorption to cell and so enhance the specific capture of the targeted biomolecules (e.g. bacteria, viruses, etc.).

Furthermore, the ideal magnetic nanoparticles should have high magnetic properties, sufficient small size with narrow distribution, high surface functionality and well defined morphology [5]. These characteristics can be achieved by optimizing the synthesis process of SIONPs in order to prepare structured magnetic nanoparticles bearing a reactive shell with well-defined properties [6].

In this regard, several approaches for preparation and modification of SIONPs have been investigated using various materials starting from low molecular weight compounds (e.g. ligands, surfactants, etc) to the use of high molecular weight compounds (e.g. synthetic polymers, synthetic and natural biopolymers like proteins, polysaccharides, polyethylene oxide, dextran, etc.) [7]. The coating or encapsulation of SIONPs with polymers has several advantages in that, they enhance biocompatibility, colloidal stability in aqueous and physiological media, and provide mechanical and chemical stability for SIONPs. More interestingly, they impart functionality to SIONPs to form conjugates with various biomolecules (e.g. enzymes, proteins, antibody, antigen, DNA, RNA, etc), which is highly needed for biomedical applications [8,9]. Recently, there is a great research attempts to use SIONPs in theranostic applications (diagnostic and therapeutic purposes at the same time) [10].

2. Magnetic nanoparticles: from preparation to encapsulation

2.1. Magnetic particles preparation

Main approaches for the preparation of SIONPs include thermal decomposition of iron precursors in organic (or water) media and co-precipitation of iron salts from their aqueous solutions. The latter is attracting much interest due to high yield as well as effectiveness in controlling nanoparticle size and water-in-oil (w/o) microemulsion. Chemical co-precipitation method depends on the type of iron salt as well as pH and ionic strength of precipitating solution. This can be done by either partial oxidation of ferrous hydroxide by different oxidizing agents or by the addition of alkali to an aqueous solution containing mixture of ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions. Iron oxide particles obtained this way are often not stable and hence are stabilized by using low molecular weight legends, surfactants or functionalized polymers. In addition, magnetic nanoparticles are coated with carboxylate surfactants e.g. oleic acid ($C_{18}H_{34}O_2$) during co-precipitation reaction followed by dispersion in organic medium e.g. octane. The obtained magnetic ferrofluids can be used as a template for further encapsulation with various types of polymers.

Surface modification of hydrophilic inorganic nanoparticles has been performed via two main processes namely, physical encapsulation and chemical encapsulation.

Physical encapsulation of SIONPs includes direct modification of magnetic nanoparticles with surfactant adsorption, or via layer-by-layer (LBL) electrostatic adsorption or self-assembly of preformed polymers. LBL assembly method involves controlled synthesis of novel nanocomposites core-shell materials and hollow capsules. By using this strategy, magnetic colloidal particles have been coated with alternating layers of polyelectrolyte, nanoparticles, and proteins that can be utilized for various biomedical applications.

Chemical encapsulation of SIONPs includes surface functionalization or modification of magnetic nanoparticles via specific grafting, surface initiated controlled polymerization, inorganic silica/polymer hybridization, or by heterogeneous polymerization in dispersion media. Inorganic silica/polymer hybridization involves the encapsulation of SIONPs by a cross linked silica shell through hydrolysis/condensation reactions with the hydroxyl groups on the surface of iron oxide nanoparticles. Heterogeneous polymerization is used to prepare well-defined SIONPs-embedded magnetic spheres as well as cross-linked microgels and nanogels. For *in vitro* diagnostic applications, seeded emulsion polymerization technique has been extensively used [11].

3. Magnetic particles as a solid support and as a carrier

Although, polymer and hybrid particles have been used for numerous biomedical applications but magnetic colloidal particles [12]