Magnetic Nanoparticles in Medicine: A Review of Synthesis Methods and Important Characteristics

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ABSTRACT

Recent technological advances in the synthesis and design of magnetic nanoparticles (MNPs) have opened various avenues for these materials in medical applications. These technology-facilitated features as well as intrinsic features make MNPs as an ideal choice in different medical diagnostic and treatment applications. Some of important attributes of MNPs that make MNPs great choice for medical applications are non-toxicity, biocompatibility, and high-level aggregation in the desired tissue. In addition, these features make MNPs an interesting candidate for drug delivery systems, magnetically assisted transfection of cells and magnetic hyperthermia, and contrast agent for magnetic resonance imaging. These nanoparticles can be synthesized by various methods which can determine their main physical and chemical characteristics. This paper reviews the most common methods for synthesis of MNPs as well as the important features that can be modulated during the synthesis.

Key words: Magnetic Nanoparticles, Synthesis Methods, Physical Characteristics, Chemical Properties, Medical Applications.

INTRODUCTION

Nanoparticles (NPs) are nanoscale inorganic or organic materials with diameters ranging from 1 to 100 nm. Compared with bulk materials, NPs have many unique characteristics making them interesting for different industrial and medical applications[1-4].

Magnetic nanoparticles (MNPs) are one group of NPs which interact with external magnetic fields and exhibit some responses to an applying magnetic field. In this regard, MNPs have various unique magnetic properties including superparamagnetic, high magnetic susceptibility, low Curie temperature, etc. In addition, these materials have been used in various domains such as medical, industrial, and high-tech engineering[5,6]. Magnetic fluids[7], biomedicine[7-9], catalysis[10], magnetic energy storage[11], data storage[12], contrast agents in medical imaging, targeted drug delivery, and cancer treatment are some of these applications. Some of important attributes of MNPs that make MNPs great choice for medical

applications are non-toxicity, biocompatibility, and high-level aggregation in the desired tissue.

In addition, external magnetic field forces MNPs to move into a desire location or to induce heating because of their inducible magnetization attributes. These characteristics make them attractive for different applications including separation techniques and contrast enhancing agents for MRI to drug delivery systems, magnetic hyperthermia, etc[13-15]. However, the most challenging issue in using MNPs is to choose appropriate materials to produce nanostructure materials with adjustable chemical and physical attributes.

To improve chemical and physical characteristics of MNPs and making them appropriate for different applications, different synthesis methods have been developed. Different properties of MNPs such as composition, size, morphology and surface chemistry can be modulated using appropriate synthesis techniques[16, 17].

To use MNPs in biomedical applications, they must be made of a non-toxic and non-immunogenic material. In addition, these particles should be small enough to maintain in the biological circulation and to transit via the capillary systems of tissues. To control the dynamic features of MNPs in the blood vessels with an external magnetic field, the MNPs must have a high magnetization[18, 19]. The synthesis method of NPs can determine the shape, the surface chemistry of the particles, the size distribution, the particle size, and magnetic properties[20-23]. In addition, MNPs can exhibit new phenomena including high saturation field, superparamagnetic, high field irreversibility, extra anisotropy contributions[24].

The present paper focuses on the various synthesis methods of MNPs and the main features of these particles.

Synthesis of Superparamagnetic Nanoparticles Co-precipitation Method

Co-precipitation approach for the first time was introduced by Welo *et al* in 1925 [25]. The convenience, efficiency, and ability to easily prepare the major types of iron oxide nanoparticles are the most important features of this method[26]. Massart *et al* (1981) have developed this technique to synthesize SPIONs in both alkaline and acidic media without addition of any stabilizing molecule[27]. Since then, plenty of studies have been performed to optimize the synthesis parameters such as iron charge (Fe^{2+}/Fe^{3+})[28] and their concentration in the primary media[29], acidity and ionic strength of the final media, reaction temperature, injection flux rates[28], homogenization rates, and bubbling inert gas thorough the solution[30]. These parameters can influence several features of the synthesized particles such as size, shape, morphology of the individual grains, the magnetic saturation, and the composition of particles.

For controlling the surface morphology of SPIONs, surfactants or polymers are introduced in the reaction. For instance, adding oleic acid makes the prepared SPIOs a hydrophobic compound which can well disperse into the organic solvent[31]. Furthermore, dextran, alginate, protein, polyethylene glycol (PEG), polyacrylic acid (PAA), poly (vinyl alcohol) (PVA) and polyethyleneimine (PEI) are used as the stabilizing agents to form stable aqueous solution for SPIONs.

Despite the interesting advantage of co-precipitation synthesis procedure in easily prepare of SPIONs with a high process yield, it suffers some drawbacks. To control the particle size, controlling the pH is vital. Nanoparticles with broad particle size distributions and irregular morphologies are usually synthesized by wet precipitation. Therefore, for successful preparing of SPIONS, it is essential to avoid any oxidation of iron (II) precursor. Since this approach requires a large quantity of water, scaling up is difficult. Finally since controlling the pH is delicate, it is virtually impossible to simultaneously precipitate a protective coating. After preparation, coating of these nanoparticles individually, without aggregation can be difficult[32].

Microemulsion Method

Microemulsion is an alternative method to synthesize the shape- and size-controlled iron oxide NPs. This approach is a thermodynamically stable isotropic dispersion of two immiscible phases (water and oil) under a surfactant present. The surfactant molecules are used to produce a monolayer at the

oil-water interface. In the interface, the hydrophobic tails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase. therefore in this binary systems (water/surfactant or oil/surfactant), self-assembled structures of different types can be prepared, ranging, for example, from (inverted) spherical and cylindrical micelles to lamellar phases and bicontinuous microemulsions, which may coexist with predominantly oil or aqueous phases[33]. Indeed, in a typical procedure to obtain SPIONs, two identical W/O microemulsions containing iron salts and alkaline medium are synthesized. The aqueous droplets in the continuous (oil phase) form perform as nano-reactors to prepare MNPs. After blending of iron salts and alkali medium microemulsions, micro-droplets undergo continuous collision, coalescence, and breaking that result in the precipitation of SPIONs form micelles[17, 34].

The size of particles can be controlled by changing in the droplet size in the reverse micelles and thus by the type and concentration of surfactants. In this method various type of surfactants such as anionic[35, 36], non-anionic[37] and cationic[38] can be employed. In addition, the diameter of the reverse microemulsion droplets can be determined by the water/surfactant molar ratio [36]. This technique has been used by several researchers. Vidal-Vidal *et al* proposed a method for the formation of spherical shaped particles, capped by a monolayer coating of oleylamine (or oleic acid) with a narrow size distribution of 3.5 ± 0.6 nm [39]. In other study by Chin and Yaacob, they developed a technique for the synthesis of magnetic iron oxide NPs (less than 10 nm)[40]. The produced particles were smaller in size and higher in saturation magnetization, compared with the synthesized particles by Massart *et al.,*[41].

High Temperature Method
High temperature method is useful technique to obtain monodispersed nanoparticles with significant size control, and high crystallinity. In this approach, iron complexes such as (hydroxylamineferron [Fe(Cup)$_3$], iron pentacarbonyl [Fe(CO)$_5$], ferric acetylacetonate [Fe(acac)$_3$], iron oleate [Fe(Oleate)$_3$] under high temperature condition, are decomposed inside the

non-polar boiling solvent with a presence of the capping agent. Under such conditions, nucleation and growth mechanisms during decomposition result in narrow size distribution of obtained due to feature of the[42].

The nucleation and growth processes are respectively initiated at approximately 200°C - 230°C and 260°C – 290°C. Fatty acids, hexadecylamine are the materials that can be applied for coating of these nanoparticles[43]. There are three factors to control the size and shape of these hydrophobic nanoparticles: (1) temperature of the decomposition reaction; (2) precursor/capping agent ratio; and (3) duration of the reaction after reaching the boiling point. Between all of these factors, the heating rate and precursor/boiling solvent volumetric ratio have most impact on the morphology of the nanoparticles[44].

Hydrothermal Method
The purpose of applying hydrothermal method is improvement the crystallization of SPIO nanocrystals. This approach has been used by several researchers[45, 46]. For example, Wang *et al* proposed a one step process to prepare well crystallized SPIONs (Fe$_3$O$_4$) using ferrous chloride and diamine hydrate as the starting materials. The synthesized (40 nm) at 140 °C and 100 °C, respectively exhibits a saturation magnetization of 85.8 emu/g and 12.3 emu/g. The high saturation magnetization can be obtained by increasing the temperature[47].

Zheng *et al.,* have used a hydrothermal method for preparing NPs (27 nm) in the presence of sodium bis (2-ethylhexyl) sulfosuccinate (AOT) as a surfactant. The magnetic properties of the NPs exhibited a superparamagnetic behavior at room temperature.

In addition, one of the successful ways of growing crystals for iron oxide NPs is hydrothermal technique[48]. Another hydrothermal technique to form water dispersible SPIO nanocrystals was introduced by Xuan *et al.,* (2007)[49]. Moreover, the solvothermal method based on the reaction between Fe powder and ferric chloride, for creating hydrophobic SPIO nanoparticles have been reported by Si and coworkers[50].

Sonochemical Synthesis

Sonochemical technique is used synthesize particles with unusual characterizations. The chemical effects of ultrasound are based on acoustic cavitation. Acoustic cavitation is defined as the formation, growth, and implosive collapse of bubbles in liquid. In the condition with transient temperatures of 5000 K, pressures of 1800 atm, and cooling rates more than K/s, the implosive collapse of the bubble generates a localized hotspot through adiabatic compression or shock wave creation within the gas phase of the collapsing bubble. These extreme conditions are essential to synthesis the highly monodispersive NPs[51]. Several NPs can be formed by this method. For instance, it is possible to prepare magnetite NPs by sonication of iron(II) acetate in water under an argon atmosphere[52]. A sonochemical approach has been introduced by Kumar *et al* for preparing the pure nanoscale powder with particle size of ca. 10 nm. They have reported that the synthesized NPs have superparamagnetic properties and their magnetization at room temperature is very low (<1.25 emu)[53].

Biocompatibility and Toxicity

For an in vivo application, MNPs should be biocompatible, nontoxic, and stable, These features can be controlled by changing the size and coating of NPs[54, 55]. It has been shown that metallic magnetic substances (iron, nickel, and cobalt) are toxic, due to their oxidation and acid erosion. For these reasons, the coating of magnetic nanoparticles to protect them against degradation is essential[56]. For biomedical application, magnetic nanoparticles should have the ability to escape from reticuloendothelial system (RES) to reach their target. Upon administration of nanoparticles into the blood stream, the opsonization process occurs. In this process, NPs are coated with proteins of plasma and later are deleted by phagocytic cells and they cannot reach target cells[57, 58]. To avoid this event, NPs are coated by organic layer such as surfactants and polymers or inorganic species such as silica and carbon. This additional layer can increase the circulation time and colloidal stability[59, 60].

Several magnetic materials are currently available with a broad spectrum of magnetic attributes. A number of these materials such as cobalt and chromium have high toxicity, thus they cannot be used in biomedical applications without a non- toxic coating which has high mechanical strength[61]. Many studies have been conducted to develop different techniques for using Gadolinium NPs in medical imaging. However, there is serious concern in using this compound for patients with renal failure. Iron oxide NPs are a good alternative for these patients. Relaxivity is problematic when the iron oxide is used as contrast agent, because this factor strongly depends on the size of nanoparticle. However, other types of paramagnetic and superparamagnetic nanoparticles have been developed **t**o overcome these weaknesses.

CONCLUSION

The present study reviewed some current synthesis methods of MNPs. Advances in preparation of MNPs with control of their properties have introduced new generation of particles for diagnostic applications such as utilization of MNPs in hyperthermia, magnetic drug delivery, gene delivery, and magnetic resonance imaging etc. In order to take advantage of these applications, the properties of MNPs must be known and their behavior must be identified under various conditions. The success of MNPs can be affected by physicochemical properties, size, shape, and surface chemistry which can characterize their biodistribution, pharmacokinetic as well as biocompatibility. To characterize and control the physicochemical properties of MNPs, synthesis and coating processes play crucial role. Various structural models for MNPs have been proposed, each of which has its own advantages and drawbacks for medical applications in clinical settings. In order to propose new MNPs and find their behaviors in a living body, high-tech methods are needed. Considering the recent advances in synthesis of NPs as well as biotechnological advances we can expect clinical uses of MNPs in different fields of medicine in near future.

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