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Synthesis and stability of functionalized iron oxide nanoparticles using organophosphorus coupling agents

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ABSTRACT

This paper describes syntheses of stable functionalized iron oxide nanoparticles through surface modification of magnetic iron oxide nanoparticles with tailor-made phosphonic acids of type $X(CH_2)_nPO_3H$ (where X = –COOH, $–NH_2$). Iron oxide nanoparticles were synthesized by co-precipitation method and the surface modification process was achieved using ultrasonic probe. XRD analysis shows that the crystalline structure of iron oxide nanoparticle remains unaffected even after surface modification with phosphonic acid-based coupling molecules. FTIR and XPS studies indicate that phosphonic acid binds on iron oxides preferably through tridentate bonding mode. TEM analysis shows narrow size distribution and uniform morphology of phosphonoacetic acid and 2-carboxyethyl phosphonic acid modified particles. BET surface area and phosphorous content analysis show higher coverage by –COOH terminated phosphonic acids than $–NH_2$ terminated phosphonic acids in the particular reaction condition. DLS study shows almost no change in hydrodynamic diameter of phosphonoacetic acid and 2-carboxyethyl phosphonic acid modified particles in a wide pH range.

1. Introduction

Research on functionalized iron oxide nanoparticles is of growing interest now-a-days and has attracted attention of several researchers of various disciplines. Surface-functionalized magnetic nanostructures are especially important because of their potential biomedical applications like in vitro cell separation, in vivo drug delivery, MRI contrast, and hyperthermia treatment of cancer cells [1–6]. For all in vivo and in vitro applications the optimized attachment of biomolecules on magnetic nanoparticle surface plays a crucial role in their applicability. The efficiency of any immobilization process relies on the careful balance of intermolecular forces which promotes the interaction between the solid particle surface and the biomolecule to be grafted [7]. In this context, surface chemistry is a powerful tool to tailor surface properties. As biomolecules exhibit diversities, a flexible generic method of surface modification is required that permits the immobilization of any particular molecular species by a standard approach. In this connection, organophosphorous coupling molecules are interesting candidates for surface modification of iron oxide nanoparticles [8,9]. Though organosilanes are best known and frequently used for preparation of stable colloid of functionalized iron oxide particles till date [10–12], still the process of surface modification is complicated and is not completely understood. Organophosphorous compounds appear complementary to organosilicon coupling molecules as they show an excellent affinity towards metals and transitional metal containing supports such as oxides, hydroxides, carbonates, and phosphates [13]. The ease of formation and stability of M–O–P bond is well illustrated in literature [14]. Surface modification of some transitional metal oxides with bifunctional organophosphorous coupling agents is well studied. In this direction, functionalization of tantalum oxide, titanium dioxide, and zirconium oxides with bifunctional organophosphorous coupling agents of type $X(CH_2)_nPO_3H$ where X = –COOH, –OH, $–NH_2$, have been extensively investigated and it has been concluded that these organophosphorous coupling agents can be used to derivatise these metal oxide surfaces with pendant active functional groups [15]. Surface modification of magnetic iron oxides by alkyl phosphates and/or phosphonates have also been studied by some researchers [8,9,16,17]. However the quantitative adsorption of phosphonic acids and the colloidal stability of modified magnetic nanoparticles in aqueous medium have not been investigated in these works. In the previous work from our laboratory we have shown that phosphate modified poly (vinyl alcohol) imparts excellent stability to aqueous dispersion of magnetite nanoparticles and the colloid is stable for days without any detoriation of particle size [18]. It is quite possible that bifunctional organophosphorous coupling agents would bind onto iron oxide surface selectively through phosphonic acid site, leaving the polar group as free pendant group, which would open up a wide range of possibilities for spe-

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cific binding of biomolecules. In this context, understanding and knowledge of adsorption mechanism, quantitative adsorption and dispersion stability of magnetic nanoparticles in aqueous medium have become essential for optimization of synthesis conditions in order to prepare stable magnetic nanoparticles with uniform and controllable sizes with large number of active functional groups on the surface.

In the present work, we have prepared –COOH and –NH_2 terminated iron oxide nanoparticles using some organophosphorous coupling agents. We have chosen five standard phosphonic acid-based organophosphorous coupling agents as model coupling molecules and investigated the surface modification of magnetite nanoparticles prepared from co-precipitation of Fe^{3+} and Fe^{2+} solutions. The phosphonic acids used in our study are phosphonoacetic acid (PAA), 2-carboxyethyl phosphonic acid (CEPA), 3-aminopropyl phosphonic acid (APPA), 4-aminophenyl phosphonic acid (APA) and 4-carboxyphenyl phosphonic acid (CPPA). The samples were characterized by XRD, TEM, FTIR and XPS. The stability of these surface modified magnetite nanoparticles in aqueous medium was investigated using dynamic light scattering and zeta potential measurements. The extent of surface coverage by different coupling agents was studied by BET surface area analysis.

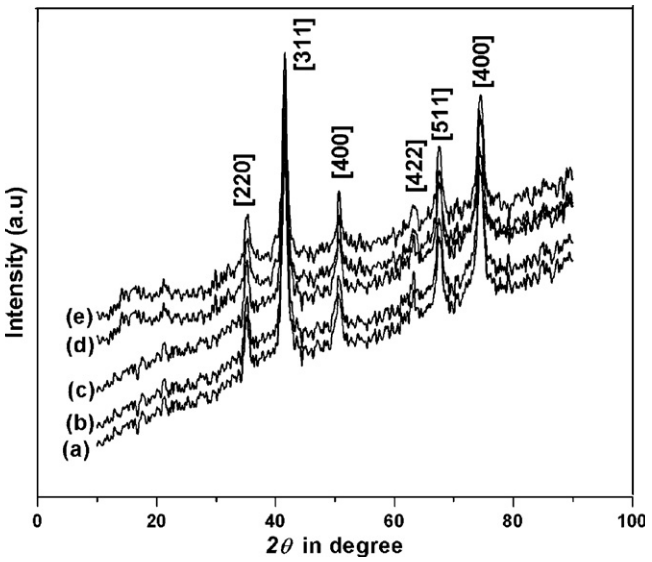

Fig. 1. XRD patterns of (a) PAA, (b) CEPA, (c) CPPA, (d) APPA and (e) APA modified magnetite particles.

2. Experimental details

2.1. Materials

$FeCl_3$ (anhydrous) and $FeSO_4{\cdot}6H_2O$ were procured from Merck, Germany. PAA was taken from Alpha Aesar, UK. 2-Carboxyethyl phosphonic acid and 3-aminopropylphosphonic acid were obtained from Aldrich Chemicals, USA. 4-Aminophenyl phosphonic acid was synthesized according to the procedure previously reported by Silva et al. [19] and also reproduced from our laboratory [20]. 4-Carboxyphenyl phosphonic acid was prepared according to the procedure reported by Gul et al. [21].

2.1.1. Synthesis of 4-aminophenyl phosphonic acid

A mixture of *p*-bromo acetanilide (0.08 mole) and triethyl phosphite (0.05 mole) was heated in the presence of nickel chloride (0.04 mole) at 165 °C for 3 h. The resulting gray solid was dissolved in ethylacetate and the residue was filtered. The crude product was recovered by evaporation of the filtrate. The resulting grey solid was recrystallised from ethyl acetate and hydrolyzed with concentrated HCl at 120 °C for 12 h to obtain *p*-aminophenyl phosphonic acid. m.p. 252 °C (Lit [19], 253–254 °C). MS: 174.03 (M+1100).

2.1.2. Synthesis of 4-carboxyphenyl phosphonic acid

In a 50 ml round bottomed flask 10 mmol (2.5 g) of 4-iodobenzoic acid was taken in 15 ml dry ethanol and 0.5 ml conc. H_2SO_4. Few boiling chips were added to it and the mixture was heated for 4 h. Reaction mixture was extracted with diethyl ether. It was repeatedly washed with water followed by brine. The organic layer was dried over anhydrous sodium sulfate and concentrated to give ethyl-4-iodobenzoate as yellowish oil which was used in subsequent reactions without further purification (1.65 g, 58%). The formation of ethyl-4-iodobenzoate was evident from ^1H NMR ($CDCl_3$, 400 MHz) which shows characteristic signals at δ 1.3–1.35 for the CH_3 group as a triplet, a quartet for CH_2 group at 3.9 and multiplets at 7.6–7.7 for 4 hydrogens in phenyl ring. Ethyl-4-iodobenzoate (1.5 g, 5.41 mmol) was added to triethyl phosphite (1.07 ml, 6.27 mmol) in the presence of anhydrous nickel bromide (64 mg, 0.294 mmol). The mixture was refluxed at 180 °C under N_2 for 30 min. After cooling, dichloromethane (CH_2Cl_2; 20 ml) was added to the solution, which was then washed twice with 5% (v/v) HCl and once with water, and dried with anhydrous Na_2SO_4 and then concentrated in vacuum to give the crude triester. Hydrolysis of this was achieved by heating under reflux with stirring in conc. HCl (8 ml) for 12 h. After cooling on ice, the crude product was isolated by filtration and dried in vacuum over P_2O_5 to give 60 mg of crude 4-carboxyphenylphosphonic acid, 67% yield, m.p. 306–310 °C (Lit [21] m.p. > 300 °C).

2.1.3. Preparation of surface modified magnetite particles

0.324 g $FeCl_3$ and 0.274 g $FeSO_4{\cdot}6H_2O$ were taken in 40 ml millipore water under argon atmosphere. 5 ml 25% NH_3 was injected into it while stirring at 4000 rpm in a mechanical stirrer under continuous argon flow for 1 h. 232 mg (1 mmol) of Fe_3O_4 was dispersed in water thoroughly by using ultrasonic probe (Misonix 3000) with microtip for 20 min. To it 2.5-fold excess of phosphonic acid coupling agent was added and sonicated for 20 min at 37 °C. The pH of the medium was maintained at 5.5 for PAA, CEPA and CPPA and 5 for APA and APPA. The particles were separated magnetically and washed five times with ethanol followed by diethyl ether and dried under vacuum.

2.2. Characterizations

The phase formation and crystallographic state of all phosphonic acid modified samples were carried out by X-diffraction analysis with an Expert Pro (Phillips) X-ray diffractometer using Cu Kα source. The particle size and microstructure were studied by transmission electron microscopy in a JEOL 2010F transmission electron microscope operating at 200 keV. The images were analyzed using image J software. Presence of surface functional groups and mode of surface bonding of phosphonic acids were investigated by FTIR spectroscopy [Thermo Nicolet Nexux FTIR (model 870)] using KBr pellet technique. Thermogravimetric analysis of all the phosphonic acid coated samples was done by Pyris Diamond TG/DTA machine heating the sample at a heating rate 8°/min in an alumina crucible in presence of air. X-ray photoelectron spectra were recorded in an ESCA-2000 Multilab apparatus (VG Microtech) using Al Kα ($h\nu = 1253.6$ eV) excitation source. The data were analyzed using origin 6.1 software. Hydrodynamic size of the particle aggregates was measured in a Brookhaven 90 Plus particle size analyzer using argon laser ($\lambda = 669$ nm) with scattering angle $\theta = 90°$. BET surface area was measured by nitrogen sorption method performed at 77 K on a SA 3100 surface area analyzer (Beckman Coulter) where the samples were degassed at 373 K for 6 h. Zeta potential was mea-