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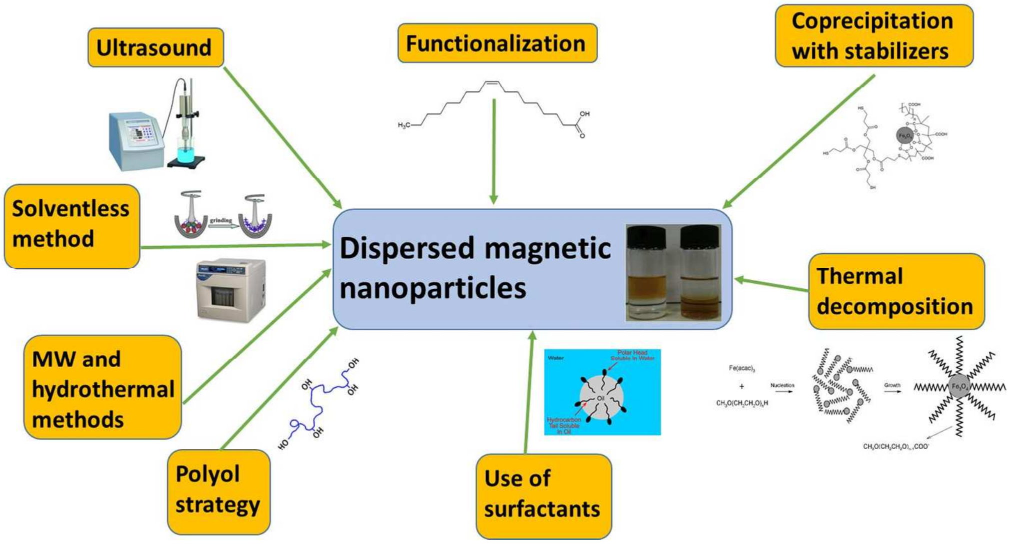

(available as a ppt file "Graphical abstract")

Solubilization and stabilization techniques for magnetic nanoparticles in water and non-aqueous solvents are reviewed.

Solubilization, dispersion and stabilization of magnetic nanoparticles in water and non-aqueous solvents: recent trends.

Boris I. Kharisov,[1] H.V. Rasika Dias,[2] Oxana V. Kharissova,[1*] Alejandro Vázquez,[1]
Yolanda Peña,[1] Idalia Gómez[1]

1. Universidad Autónoma de Nuevo León, Monterrey, Mexico. E-mail bkhariss@hotmail.com.
2. Department of Chemistry and Biochemistry, The University of Texas at Arlington, USA. E-mail dias@uta.edu.

**Author to whom all correspondence should be addressed.*

Abstract

Recent achievements in the solubilization and stabilization of magnetic nanoparticles (MNPs) are reviewed. The predominant number of reported MNPs correspond to iron-based {nZVI, superparamagnetic iron oxides (SPIONs), core-shell Fe/Au or Fe_xO_y/Au nanoparticles and ferrites} nanoparticles, lesser MnO and cobalt nanoparticles. Magnetic nanoparticles could be solubilized in water or non-aqueous solvents for short or long time periods. Main approaches for MNPs solubilization are discussed: suitable choice of precursors, pH, surfactants/coting agents and solvents, as well functionalizing agents. MNPs are generally solubilized by functionalization with water-soluble compounds/moieties (in particular, sulfonic acid disodium salts, soluble polymers, porphyrins and calixarenes), in the conditions of thermal decomposition of low-stable metal complexes, coprecipitation, by microwave heating, and ultrasonication. Polyol strategy is frequently applied for increasing MNPs solubility. Stabilization of MNPs in solutions could be achieved with aid of inorganic, monomeric and polymeric compounds.

Keywords: solubilization; dispersion; magnetic nanoparticles; polyol strategy; functionalization; coprecipitation.

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Introduction

In the area of nanotechnology, one of hottest topics corresponds to the magnetic nanoparticles (MNPs) due to their extensive applications in such areas as biomedicine[1] (in particular as MRI agents),[2] drug delivery,[3] and for remediation of pollutants[4] {generally Cr(VI), As(V), Ni(II)}. A series of recent books,[5 6 7] book chapters,[8 9] reviews[10 11 12 13 14 15 16 17 18] and a host of experimental articles have been published in this century, describing synthesis and characterization methods, functionalization, peculiarities, and applications of MNPs. Among them, predominant number of recent reports are dedicated to the nanoparticles of the elemental iron {"nano zero-valent iron" (nZVI)}, iron oxides {"superparamagnetic iron oxide nanoparticles" (SPIONs)}, core-shell iron (or iron oxide)-gold nanoparticles,[19] more rarely for MnO, cobalt nanoparticles[20] and ferrites, for instance functionalized $Zn_xMn_{1-x}Fe_2O_4$ (x=0, 0.2, 0.4, 0.6, 0.8, 1) nanoparticles.[21] To date, most interest in the clinical use of magnetic nanoparticles has focused on iron oxide because of the chemical stability, biological compatibility, and relative ease of manufacture of magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) nanoparticles.[22]

Magnetic nanoparticles possess distinct "solubilities" in aqueous and non-aqueous solvents, depending on their size and type of functionalizing molecules. The capacity to be solubilized or dispersed for short or long period and the stability of MNPs in liquid phases is very important for the applications above, so considerable efforts have been made to reach a higher solubility of MNPs first of all in aqueous media. Highly soluble MNPs have much more applications in biomedicine; soluble iron oxide MNPs result stronger remediation effects in comparison with insoluble ones. Studying changes in solubility of MNPs, magnetic interactions[23] between them, in particular, should be taken into account, as well as strategies of nanoseparations[24] and magnetic separations.[25] In this review, we generalize recent achievements on the solubilization of MNPs and give an overview on their stabilization in solutions. In advance, we note that special investigations on the transformations "insoluble (already prepared) → water- or organic-soluble MNPs" are rare: generally, researchers synthesize directly soluble NPs.

Definitions of solubilization and dispersion terms in relation with nanoparticles

According to non-nanochemical classic definitions, reported in *Wikipedia* and elsewhere, *solubilization* (an IUPAC definition[26]) is a short form for micellar solubilization, a term used in colloidal and surface chemistry. Solubilization may occur in a system consisting of a solvent, an association colloid (*i.e.*, a colloid that forms micelles), and at least one other component called the solubilizate (*i.e.*, the component that undergoes solubilization).

Solubilization is distinct from dissolution (the process by which a solute forms a solution in a solvent) because the resulting fluid is a colloidal dispersion involving an association colloid. This suspension is distinct from a true solution, and the amount of the solubilizate in the micellar system can be different (often higher) than the regular solubility of the solubilizate in the solvent. *Dispersion* is a process by which (in the case of solids' becoming dispersed in a liquid) agglomerated particles are separated from each other and a new interface, between an inner surface of the liquid dispersion medium and the surface of the particles to be dispersed, is generated.[27] Dispersion is a much more complicated (and less-understood) process than most people believe.

Nanoparticles in solutions present typical colloidal systems consisting of a continuous phase which is a dispersed medium (solvent) and a dispersed phase (nanoparticle).[28] Such systems having a solid dispersed phase and a liquid dispersed medium are called sols. Colloidal systems in organic solvents are frequently called organosols, while analogous dispersions in water are called hydrosols. A distinctive feature of colloidal solutions is their relatively low stability attributed to large particle size with perceptible free surface energy. Each nanoparticle appears to be an aggregate of atoms or more or less simple molecules. Any change in conditions might result in aggregate size variation and precipitate fallout. The stability of colloidal solutions is considered to be one of the key problems of colloidal chemistry. A system turns out to be stable when its dispersed phase can exist as separate individual particles for a long time (a few months and even years).[28]

Applying both terms above (solubilization and dispersion) to nanoparticles and analyzing the published scientific research articles, it is evident that there is an important issue or misunderstanding between the terms "*dispersion*" and "*solubilization*" (in particular, a discussion of these terms for the carbon nanotubes is presented in[29]). Many researchers use the terms interchangeably, particularly when stating the interaction of CNTs with liquids, which causes confusion. The fundamental question when dealing with carbon nanotubes in liquids, particularly in water, is: are they dissolved or dispersed? It has been suggested that it is most appropriate to use the term "dispersion" rather than "solution". For other nanoparticles, in particular magnetic NPs, similar discussions might also appear later.

Nanoparticles have a particular tendency to lower their very high surface energy, which is the origin of their thermodynamic instability. Bare nanoparticles tend to stabilize themselves either by sorption of molecules from the surroundings or by lowering the surface area through coagulation and agglomeration. In order to avoid this, nanoparticles have to be stabilized; the *stabilization* of NPs[30] is a very important aspect in nanochemistry. There are two types of stability of colloidal solutions.[28] The *kinetic* one is stability of the systems relative to gravity forces. Crucial factors that determine kinetic stability of colloids are Brownian motion, dispersion, viscosity of the medium, etc. *Aggregation stability* is the ability of the system to preserve the degree of particle dispersity.[28] This type of stability is attributed to the ability of nanoparticles to create large aggregates to adsorb low-molecular ions on their surface from the solution leading to formation of an adsorption layer.

Overview of main synthesis techniques for magnetic nanoparticles

A plethora of techniques are nowadays used for MNPs fabrication (Fig. 1). However, not all they are suitable for obtaining soluble MNPs. Among them, we consider the surface functionalization of MNPs with organic materials[31] [32] {relatively small molecules (amino acids,[33] citric acid salts,[34] vitamins,[35] cyclodextrin,[36] etc.) and surfactants,[37] polymers,[38] [39] biological molecules,[40] [41] etc.} or with inorganic materials (silica,[42] [43] metals,[44] metal oxides or sulfides[45]) as the most common in order to obtain soluble MNPs. Other techniques for the preparation of soluble or insoluble MNPs include coprecipitation,[46] synthesis in reverse micelles,[47] sonolysis,[48] electrochemical deposition,[49] mechanochemical dispersion,[50] solution plasma[51] and sol-gel processes,[52] arc discharge,[53] spray[54] and laser[55] pyrolysis, flow injection synthesis,[56] thermal decomposition,[57] hydrothermal,[58] [59] microwave[60] and microwave solvothermal,[61] combustion synthesis,[62] high-temperature annealing[63] and other high temperature syntheses,[64] micro-[65] and nanoreactors such as protein cages,[66] vesicles,[67] and microemulsions.[68] Talking about advantages and disadvantages for preparing iron oxide nanoparticles (IONPs), in terms of size and morphology control, thermal decomposition and hydrothermal synthetic route seems the optimal method. For obtaining the water-soluble and biocompatible IONPs, co-precipitation often was employed, but this method presents low control of the particle shape, broad distributions of sizes and aggregation of particles. As a time-competitive alternative, sonochemical route can also be used to synthesis iron oxide NPs with unusual magnetic properties. Among more rare methods, we can mention “greener” synthesis of α-Fe_2O_3 NPs using potato as starch template,[69] plant extracts[70] or use of microorganisms for obtaining Fe_3O_4 and Fe_3S_4.[71]

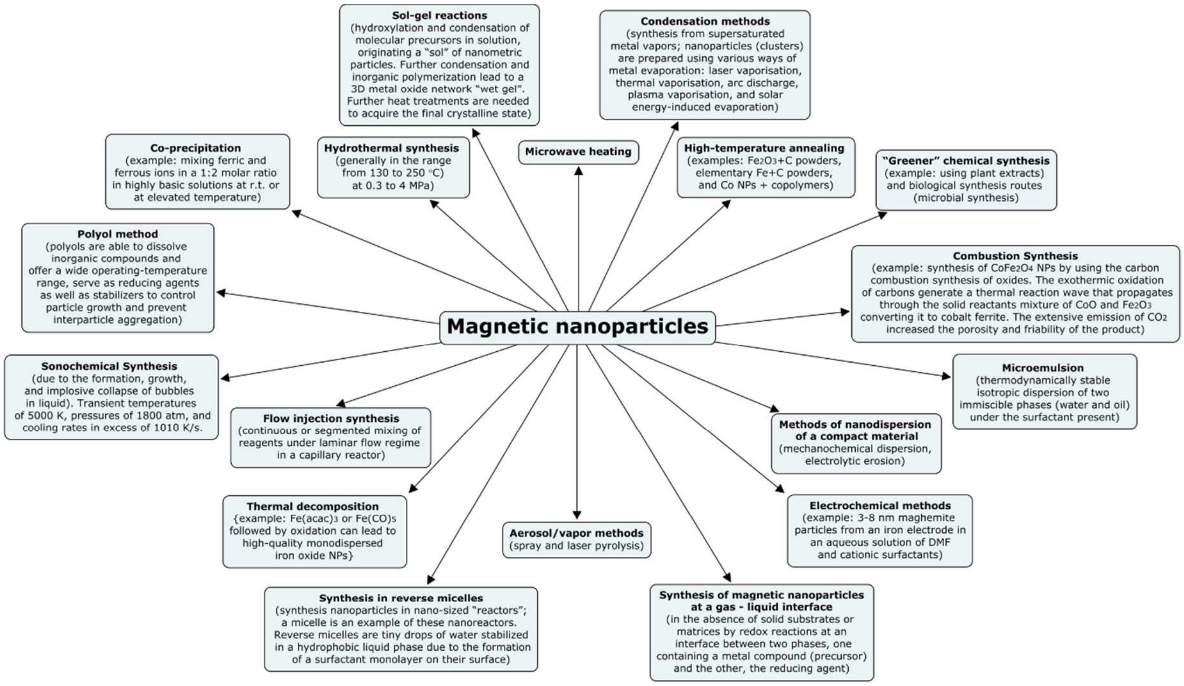


Fig. 1. Synthesis methods for magnetic nanoparticles.

Iron-based nanoparticles and fluids: definitions and solubility

For IONPs as the mostly frequent MNPs, small molecules or surfactants functionalized IONPs can be simply divided into three types: oil-soluble, water-soluble, and amphiphilic.[72] *Oil-soluble* type refers to the surface of functionalized IONPs containing the molecular which have a *weak* attraction for the solvent environment, it is generally hydrophobic group {for instance the fatty acid, alkyl phenol (n = 6–10, linear or branched}. *Water-soluble* type refers to the surface of functionalized IONPs with chemical groups having a *strong* attraction for the solvent environment (generally hydrophilic groups, such as the ammonium salt, polyol, lycine). *Amphiphilic* type refers to the surface of functionalized iron oxide NPs containing *both hydrophilic and hydrophobic* chemical groups, the main chain of these functionalized small molecules or surfactants showed concurrence of hydrophobic and hydrophilic structural regions, which also will make the functionalized NPs possess both oil-solubility and water-solubility (such as sulfuric lycine).

A special form of soluble MNPs is called as “magnetic fluids”: stable colloidal systems of fine single-domain magnetic particles (for example Fe_3O_4, γ-Fe_2O_3, Co, $MnFe_2O_4$, etc.) coated with surfactants, suspended in liquid carrier such as water, mineral oil, damping oil, paraffin, kerosene and so on. The properties of magnetic fluids are well controlled by external magnetic field that gives broad possibilities for technical and biomedical applications.[73] [74] The most commonly used ferrofluid contains spherical magnetic particles with typical size of 10 nm, dispersed in an apolar solvent. Sedimentation of these particles is sufficiently counteracted by Brownian motion to keep them dispersed for years. To prevent aggregation, the colloids can be covered with a thin layer of surfactant, commonly a monolayer of oleic acid (steric repulsion), or the particles are prevented from sticking to each other by electrostatic bilayer (electrostatic repulsion), which makes the particles stable in many liquid carriers. They have found many applications in a variety of fields such as electronic packing, mechanical engineering, aerospace or bioengineering. One of many unique properties of ferrofluids is their tuneable viscosity by the external magnetic field (called the magnetoviscous effect).

Iron oxide nanoparticles, due to the favorable features they exhibit, are the only type of MNPs approved for clinical use by *Food and Drug Administration*.[75] These attributes are as follows: facile single step synthesis by alkaline co-precipitation of Fe^{2+} and Fe^{3+}, chemical stability in physiological conditions and possibility of chemical modification by coating the iron oxide cores with various shells, *i.e.*, golden, polymeric, silane, or dendrimeric (Fig. 2). In addition, their extremely low toxicity allows remediation uses on the basis of reactions shown in Fig. 3. In this respect, that’s why the nZVI, IONPs and others (about 15 compounds) are the most frequent MNPs, attracting so much attention of researchers.

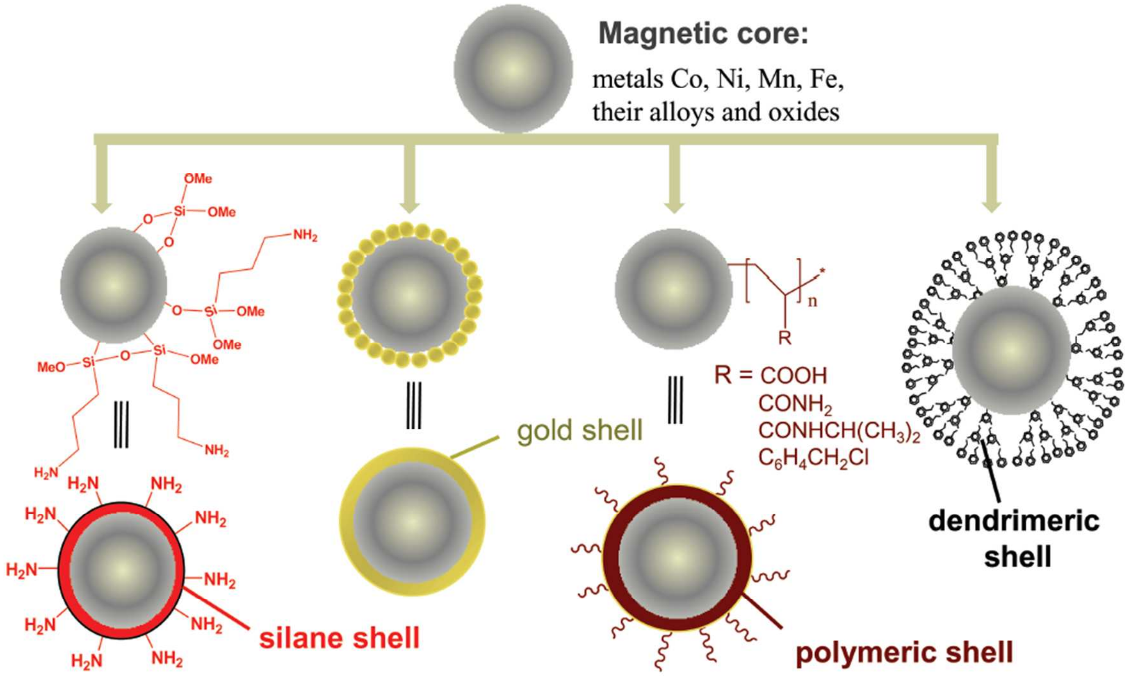


Fig. 2. Magnetic nanoparticles with various shells. Reproduced with permission of *Institute of Pharmacology, Polish Academy of Sciences* {Wilczewska, A.Z.; Niemirowicz, K.; Markiewicz, K.H.; Car, H. Nanoparticles as drug delivery systems. *Pharmacological Reports*, **2012**, *64*, 1020-1037.}.

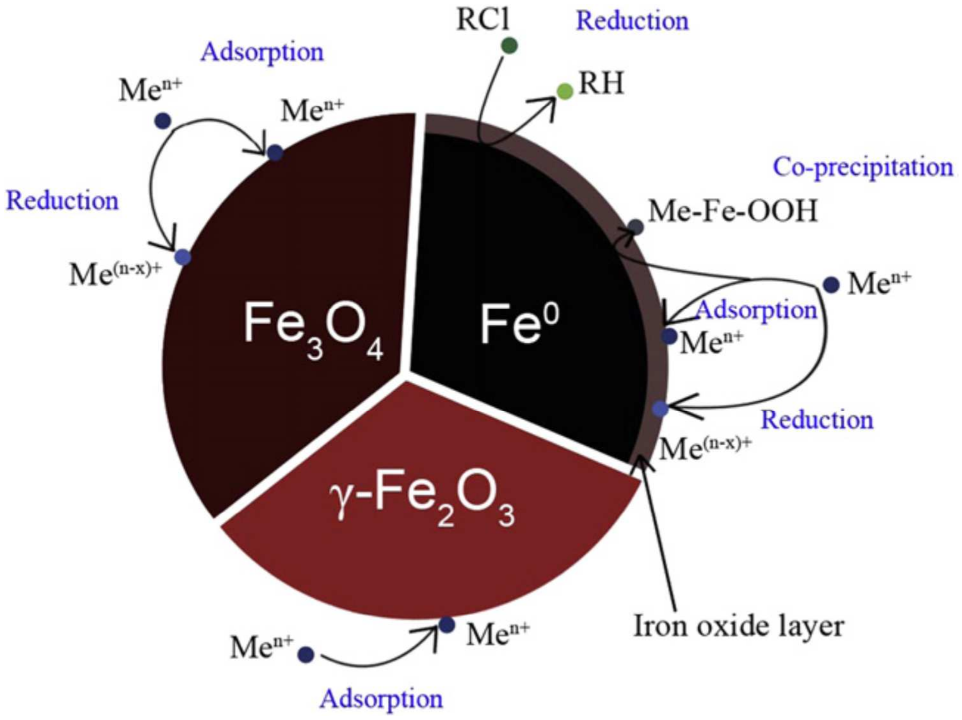


Fig. 3. Schematic model of magnetic nanoparticles (nZVI, Fe_3O_4 and γ-Fe_2O_3). Zero-valent iron in the core mainly provides the reducing power for reactions with contaminants. The oxide shell provides sites for sorption. Adsorption is also occurred on the iron oxides (Fe_3O_4 and γ-Fe_2O_3) surface, while Fe_3O_4 possess reducing power.[76] Reproduced with permission of *Elsevier Science* {Tang, S.C.N.; Lo, I.M.C. Magnetic nanoparticles: Essential factors for sustainable environmental applications. *Water Res*., **2013**, *47* (8), 2613-2632.}.

Solubilization of MNPs by functionalization

The functionalization of MNPs by a variety of distinct organic compounds is the standard route to increase their solubility. The MNPs, formed by reduction reactions from metal salts, could be functionalized directly or step-by-step by substitution of primary coating organic layer by final compound. Among the compounds, most widely used in the first step of MNPs functionalization, we note oleic acid[77] (Fig. 4), sodium oleate[78] and oleyamine.[79] [80] [81] [82] Oleic acid is frequently used in ferrite nanoparticle synthesis because it can form a dense protective monolayer, thereby producing highly uniform and monodisperse particles. Generally, the MNPs composites, functionalized with oleic acid, are prepared and then the oleic acid moiety is substituted by other compounds. Due to its long hydrophobic tail, colloidal Fe_3O_4 NPs prepared using oleic acid, are highly soluble in organic solvents such as toluene, hexane, chloroform etc.[83]

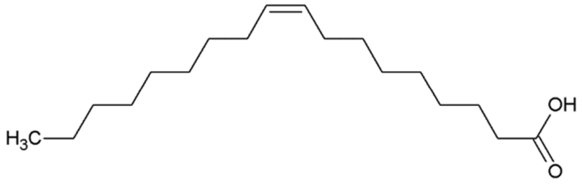


Fig. 4. Oleic acid (*left*) and its linkage with iron oxide nanoparticle (*right*).

Among a host MNPs with functionalizing agents, <u>*dopamine*</u> (DA)-coated superparamagnetic iron oxide nanoparticles (SPIONs, Fe_3O_4@DA) were synthesized using a one-step process by modified coprecipitation method and then 2-3 nm gold nanoparticles were easily conjugated to Fe_3O_4@DA nanoparticles by the electrostatic force between gold nanoparticles and amino groups of dopamine to afford water-soluble Au-Fe_3O_4 hybrid nanoparticles (Fig. 5).[84] These formed hybrid nanoparticles presented good water-soluble ability and were easily functionalized with a targeted small peptide A54 and fluorescence probe fluorescein isothiocyanate (FITC) for liver cancer cell BEL-7402 imaging. In a related report,[85] monodisperse, ultrasmall, water dispersible superparamagnetic IONPs were initially synthesized in organic solvents using oleic acid as a dispersant and then the subsequent *ligand exchange* of oleic acid for dopamine and Tiron (4,5-dihydroxy-1,3-benzenedisulfonic acid disodium salt) (Figs. 6 and 7) allowed for superior colloidal stability in aqueous media. Zeta potential measurements confirmed the stability of the nanoparticles upon redispersal in water or biologically relevant buffers. The synthesized particles also preserve their general shape, size, and crystallinity after ligand exchange. This exchange method is quick, consumes minimal reagents, and is conducted at room temperature making it an efficient synthetic procedure. Earlier, this ligand exchange process of oleic acid for dopamine was studied in detail.[86] Both oleic acid and dopamine are covalently bound to the surface *via* a chelating bidentate interaction to the iron species. Iron oxide NPs upon this new functionalization become more hydrophilic. The origin of the improvement in the magnetic properties of the Fe_3O_4 nanoparticles upon functionalization was hypothesized to lie in the steric interaction between the surfactant molecules, oleic acid and dopamine, arising from their strongly covalent interaction with the Fe atoms on the oxide NP surface to form a chelating bidentate bond.

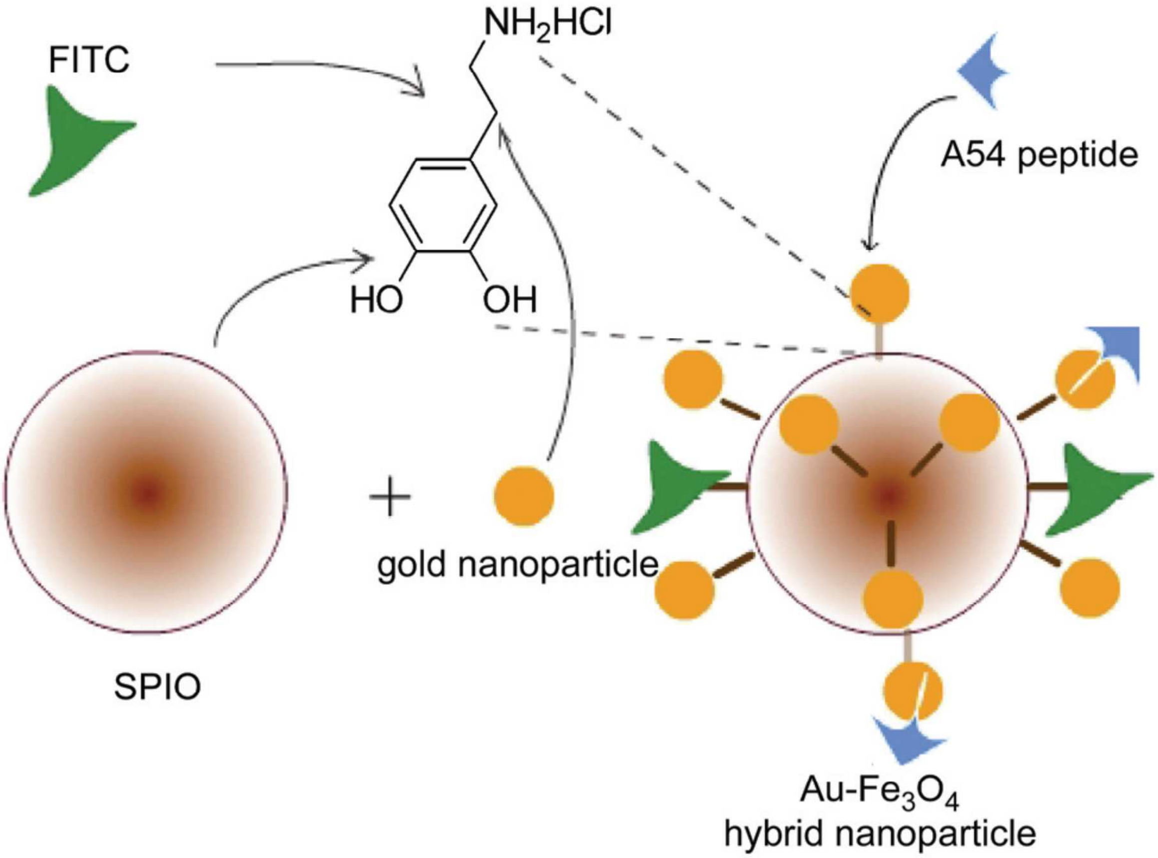


Fig. 5. Schematic diagram for synthesis of fluorescent Au-Fe_3O_4 hybrid nanoparticles (FITC = fluorescence probe fluorescein isothiocyanate). Reproduced with permission of *Wiley* {Liang, Z.; Wu, X. A Facile Approach to Fabricate Water-soluble Au-Fe_3O_4 Nanoparticle for Liver Cancer Cells Imaging. *Chin. J. Chem.* **2012**, *30*, 1387-1392.}.

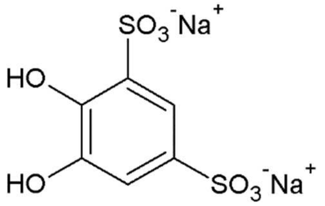


Fig. 6. Structural formula for Tiron at neutral pH.

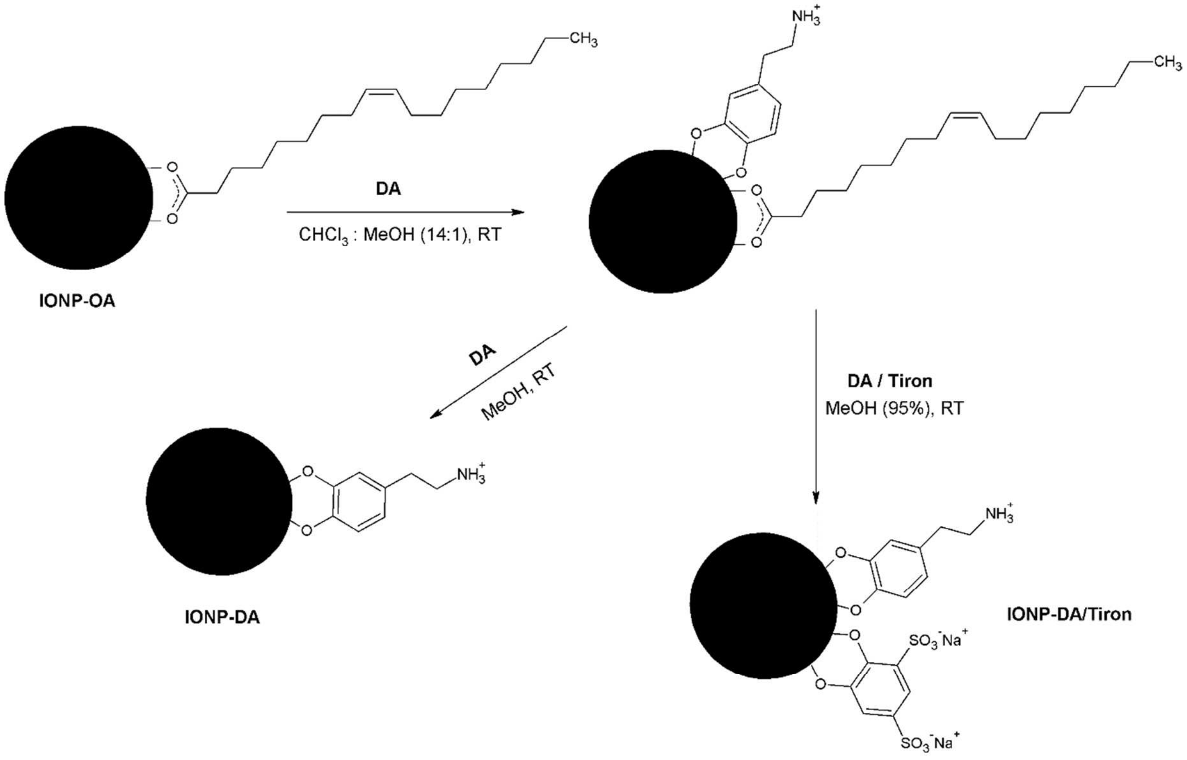


Fig. 7. Summary of ligand exchange of oleic acid (OA) for dopamine (DA) or DA and Tiron on the iron oxide nanoparticle surface. Either shaking or sonication was used to facilitate ligand exchange at each step. IONP-DA was only stable in water, whereas IONP-DA/Tiron was stable in water and a variety of buffers.

1,3-Dialkylimidazolium-based *ionic liquids* were chemically synthesized and bonded on the surface of magnetic Fe_3O_4 nanoparticles with easy reactions (Fig. 8).[87] The solubility of these NPs in organic solvents depend on the alkyl chain length and the anions of the ionic liquids. Moreover, the obtained NPs showed the specific extraction efficiency to organic pollutant, polycyclic aromatic hydrocarbons, while superparamagnetic property of the NPs facilitated the convenient separation of MNPs from the bulks water samples. The modified NPs were *not* soluble in water regardless of the alkyl chain and anions, although they *could be dispersed* ultrasonically. However, they were soluble and stable in polar organic solvents (e.g., MeOH, EtOH, and CH_2Cl_2); their solubility and stability depend on the solvent. In strong polar solvents like MeOH and EtOH, the modified NPs with chloride as anion were more soluble than those with PF_6^- as anion. The solubility decreased with increasing alkyl chain length: hexyl > octyl > decyl. On the other hand, in CH_2Cl_2, a weak polar solvent, the modified NPs with PF_6^- as anion were more soluble, with solubility increasing with increasing chain length: decyl > octyl > hexyl. Strangely, NP-OTIMPF$_6$ (1-octyl-3-TIM hexafluorophosphate) had highest solubility in both strong and weak polar solvents (Fig. 9). Neither naked NP nor modified NPs were soluble in nonpolar organic solvents, such as hexane.

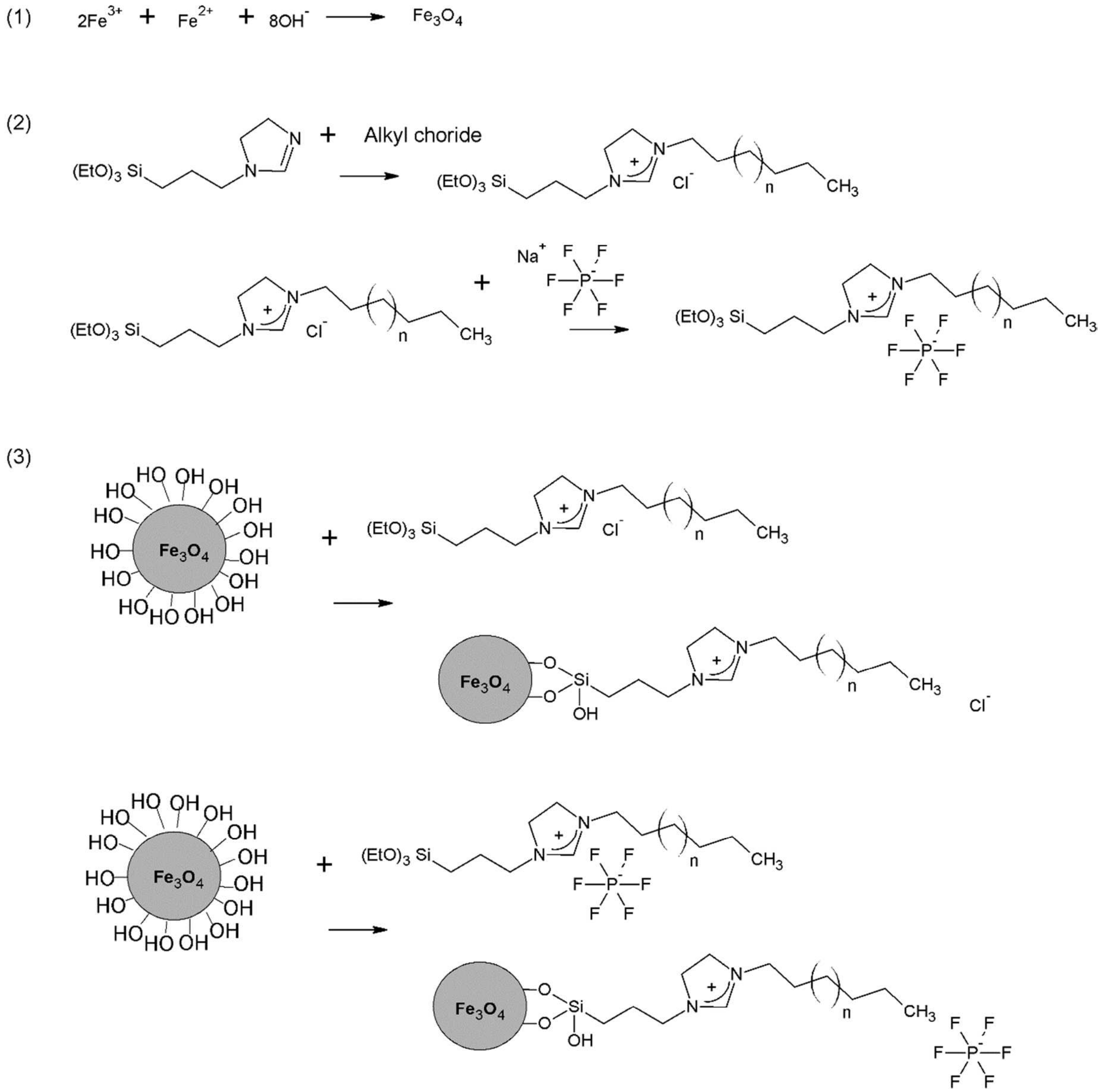


Fig. 8. Synthesis of ionic liquid-modified Fe_3O_4 NPs (alkyl = hexyl, octyl, and decyl).

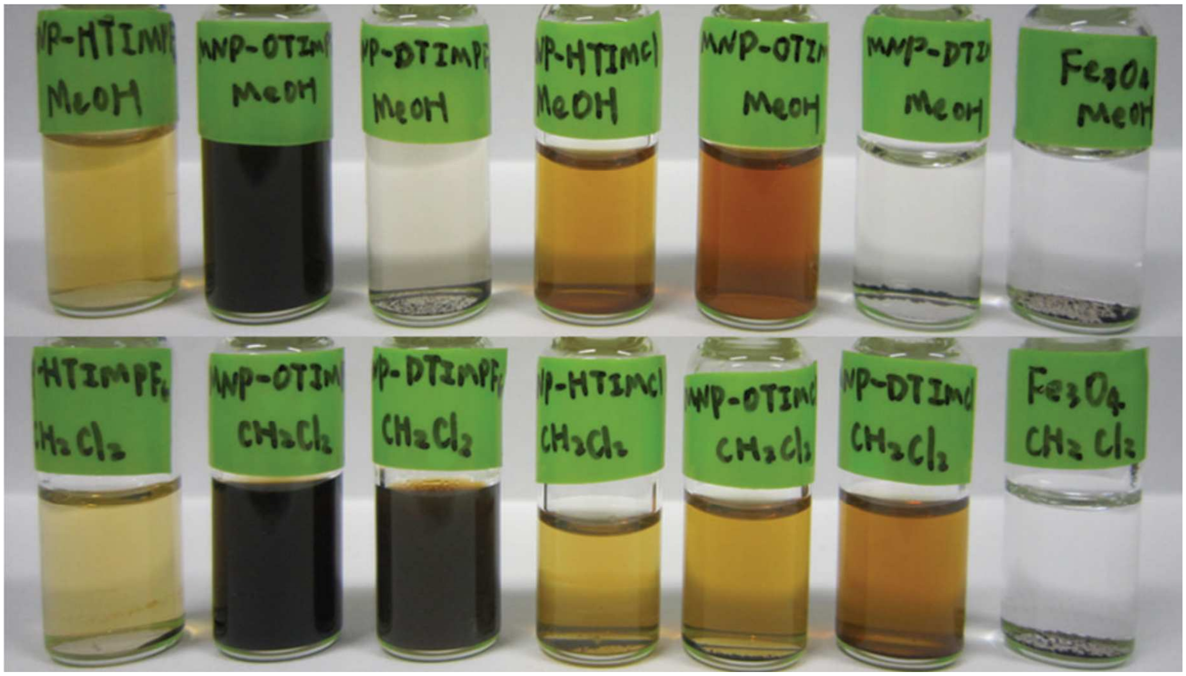


Fig. 9. Solubility of the naked and modified NPs in methanol and CH_2Cl_2.

Certain attention is being paid to *citrates*[88] and mechanisms for their interactions with MNPs. Thus, molecular functionalization of the promising manganite nanoparticles $La_{0.67}Sr_{0.33}MnO_3$ (LSMO) in citrate media for their solubilization in aqueous environments was studied.[89] It was revealed that citrates are covalently attached to the surface of the NPs (Fig. 10). The calculated donor–acceptor distance is 2.24 nm, which indicates a very high efficiency of energy transfer and clearly supports the idea that 2AP was in close proximity to the solubilized LSMO NP surface. The prepared LSMO nanoparticles were rendered water-soluble using the reactivity of carboxylate group of citrate with the Mn centre in LSMO, by two hours of extensive mixing using the cyclo-mixer. These functionalized manganite NPs may find applications in the field of nanobiotechnology, as the solubilizing layer (citrate) provides multiple functional groups (hydroxyl and carboxylic acids) for covalent conjugation with other biological macromolecules such as small peptides, DNA, RNA and biocompatible polymers. In a related report,[90] large-scale hydrophilic superparamagnetic Fe_3O_4 nanoparticles (Fig. 11; 20-40 nm in size) were prepared in the presence of citrate and sodium nitrate from ferrous ion alone. The Fe_3O_4 NPs were found to be quite stable and can be freely dispersed in water; the 20-nm particles have the best stability in water. A possible formation mechanism is proposed by authors to explain why the magnetic nanoparticles are very well soluble in water. Thus, since the NPs are soluble in water but cannot be dissolved in alcohol, the charge of the citrate ions as surfactant plays a key role. There are three carboxyl groups in every citrate ion, and the repulsive forces between the electric charges of the radical ions make the NPs more dispersed in water. At the same time, if mass of $NaNO_3$ was added into the reactive solution, the ionic strength was highly increased. This increase of ionic strength makes the charges of the NPs surround with citric acid radical equally distributed. The presence of a large amount of salt changes the solubility of organic molecules. The presence of anion with bigger hydrated ion radius will steady the water-oil interface and then increase the solubility between water and surfactant. It was also concluded that in the synthesis with ferrous ions alone (reactions *1-3*), Fe_3O_4 is formed as a result of the dehydration reaction of ferrous hydroxide and ferric hydroxide, in which the latter compound is produced by the partial oxidation of ferrous hydroxide by O_2 dissolved in water. The formation of $Fe(OH)_2$ would be the first process of the synthesis. The transition temperature of $Fe(OH)_2$ to Fe_3O_4 was found to be 60°C.

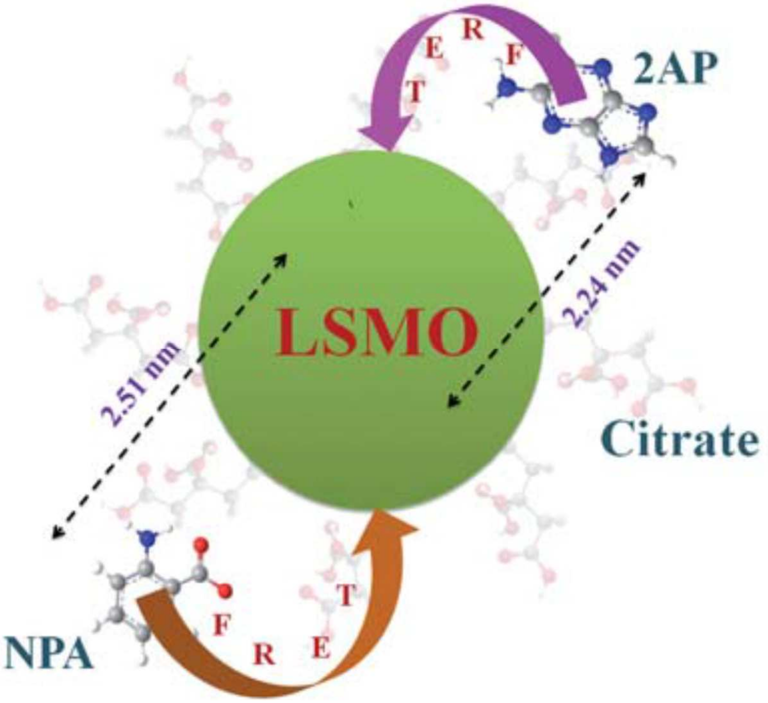


Fig. 10. Functionalization of the manganite nanoparticles (NPs) with citrate ligands. Covalent attachment of the fluorescent probe NPA (4-nitrophenylanthranilate) and non-covalent adduction of one of DNA base mimics 2AP (2-aminopurine) are also shown. The efficient energy transfer (FRET) from the fluorescent ligands to the NPs and corresponding donor–acceptor distances is also indicated.

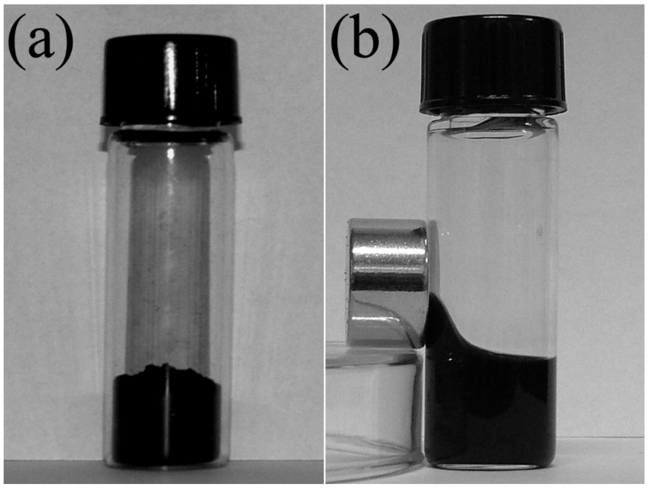


Fig. 11. Gram-scale well-soluble hydrophilic Fe_3O_4 NPs were prepared by using a facile one-step method. (a) Samples of solid state hydrophilic Fe_3O_4 NPs powder. (b) Dispersion in water, which can be moved by a magnet. Reproduced with permission of *The American Chemical Society* {Hui, C.; Shen, C.; Yang, T.; Bao, L.; Tian, J.; Ding, H.; Li, C.; Gao,H.-J. Large-Scale Fe_3O_4 Nanoparticles Soluble in Water Synthesized by a Facile Method. *J. Phys. Chem. C* **2008**, *112,* 11336–11339.}.

$$Fe^{2+} + 2OH^{-} = Fe(OH)_2 \quad (1)$$
$$3Fe(OH)_2 + 1/2O_2 = Fe(OH)_2 + 2FeOOH + H_2O \quad (2)$$
$$Fe(OH)_2 + 2FeOOH = Fe_3O_4 + 2H_2O \quad (3)$$

It was also found that the concentration of the Fe^{2+} ions is a key factor for controlling Fe_3O_4 NPs' sizes. A decrease of ferrous precursor concentration from 0.1 to 0.02 M allows an increase of the average size from 20 to 40 nm; a mean diameter of about 20 nm NPs were prepared by using 0.10 M Fe^{2+} solution. If the concentration of the Fe^{2+} ions was decreased to 0.05 and 0.02 M, 25- and 40-nm Fe_3O_4 NPs would be obtained. In addition, citrates can be used for MNPs functionalization <u>*without any solvent*</u> for further solubilization. Thus, amorphous citrate-coated iron oxide nanoparticles (NPs) with excellent water-solubility were synthesized from $FeCl_3{\cdot}2H_2O$ and $FeSO_4{\cdot}7H_2O$ as precursors at r.t. without the presence of any solvents (Fig. 12).[91] Advantages of this method rely not only on the simplicity and nontoxicity but also on the low cost, highly suitable for further applications. The authors proposed that the citrate formed complex compound with Fe atoms in the first stage, which facilitated the binding of carboxylate groups to surface of iron oxides NPs in the second step. The citrate in this reaction plays a dual role as complexing agent and stabilizer to prevent interparticle aggregation. The unique hydrophilic surface structure of the particles leads to the particles being stable in aqueous solution with different pH values from 5 to 7 (Fig. 13).

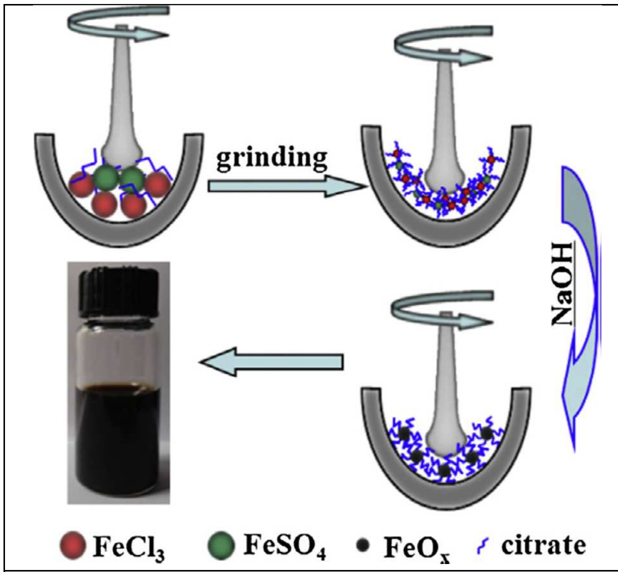


Fig. 12. Schematic illustration of the solventless synthesis process. Reproduced with permission of *Elsevier Science* {Wang,

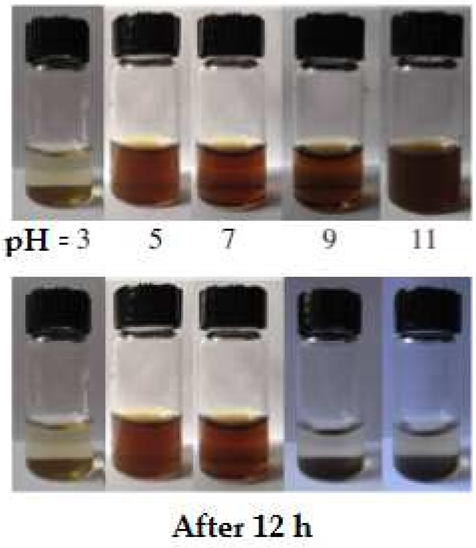


Fig. 13. Photographs of iron oxide NPs dispersed in aqueous solution with different pH values of 3, 5, 7, 9, and 11

Z.; Zhao, L.; Yang, P.; Lv, Z.; Sun, H.; Jiang, Q. Water-soluble amorphous iron oxide nanoparticles synthesized by a quickly pestling and nontoxic method at room temperature as MRI contrast agents. *Chem. Engin. J.*, **2014**, *235*, 231–235.}.	(from left to right). Reproduced with permission of *Elsevier Science* {Wang, Z.; Zhao, L.; Yang, P.; Lv, Z.; Sun, H.; Jiang, Q. Water-soluble amorphous iron oxide nanoparticles synthesized by a quickly pestling and nontoxic method at room temperature as MRI contrast agents. *Chem. Engin. J.*, **2014**, *235*, 231–235.}.

Derivatives of *porphyrin*-type macrocycles have been also observed as functionalizing units for MNPs dissolution. Thus, photofunctional magnetic nanoparticle, where photofunctionality is provided by the photosensitizer (PS) of [5,15-bis(phenyl)-10,20-bis(4-methoxycarbonylphenyl)-porphyrin]-platinum (Fig. 14), generating singlet oxygen in high quantum yield, was strategically designed and prepared by a modification process.[92] Fe_3O_4 nanoparticles covered with oleylamine, prepared from $Fe(acac)_3$, 1,2-hexadecanediol, oleylamine, and phenyl ether, were used as precursors. It was shown that the immobilized PS molecules retain their optical and functional properties including the high efficiency of singlet oxygen generation. The photofunctional magnetic nanoparticles have good solubility and stability in water which are induced by the surface modification process. In a related report,[93] PS-conjugated magnetic nanoparticles with ~20 nm in diameter were strategically designed (Fig. 15) and prepared for gastric cancer imaging and therapy. The second generation PS chlorin e6 (Ce6) was covalently anchored on the surface of magnetic nanoparticles with silane coupling agent. The prepared Ce6-MNPs own high water-solubility, non-cytotoxicity, good biocompatibility, and remarkable photodynamic efficacy upon irradiation. Compared with MNPs-NH_2, the zeta potentials of Ce6-MNPs all bear negative charge (-23.72, -27.09, -24.94, -23.92, -21.91), which may be responsible for the prepared Ce6-MNPs' highly water dispersibility and solubility. At last, highly soluble superparamagnetic manganese oxide nanoparticles (Fig. 16) were synthesized by thermal decomposition of manganese(II) oleate in 1-octadecene at elevated temperatures and then functionalized using a hydrophilic ligand containing protoporphyrin IX as PS (Fig. 17).[94] The optical properties of protoporphyrin IX were found to be not significantly changed by binding to the MnO surface. These hydrophilic functionalized MnO nanoparticles showed potential for application not only as imaging agents for MRI and fluorescence microscopy but also as target systems for photodynamic therapy. In addition to porphyrins, we note *calixarenes*, for example water-soluble calix[4,6]arene appended magnetic nanoparticles (p-C[4]-MN and p-C[6]-MN, Fig. 18) were used for removal of some carcinogenic aromatic amines.[95] It was shown that sulfonic acid groups play a major role for the formation of hydrogen bonds and electrostatic interactions, similarly to the Tiron-functionalized MNPs observed above.

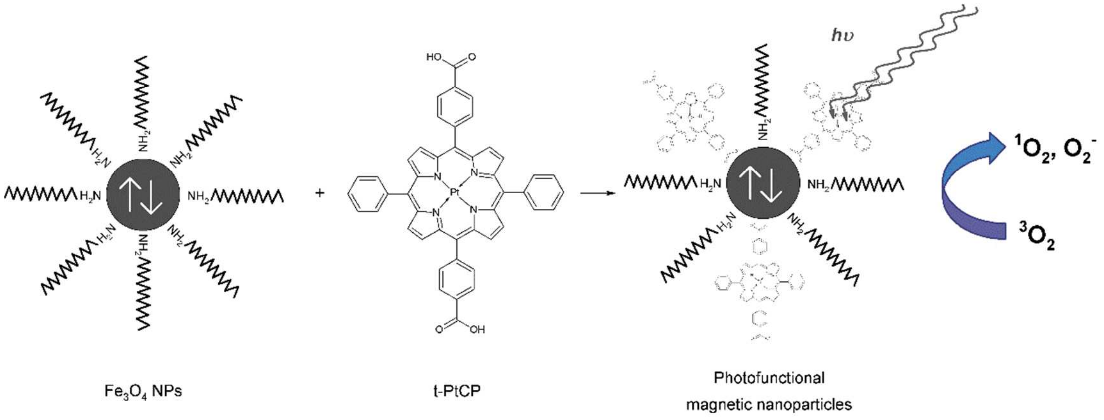


Fig. 14. Fabrication procedure of the photofunctional magnetic nanoparticles.

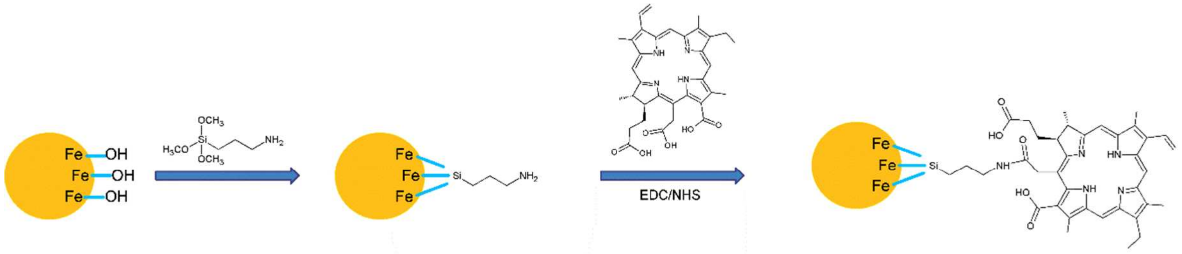


Fig. 15. Synthetic procedure of Ce6-MNPs.

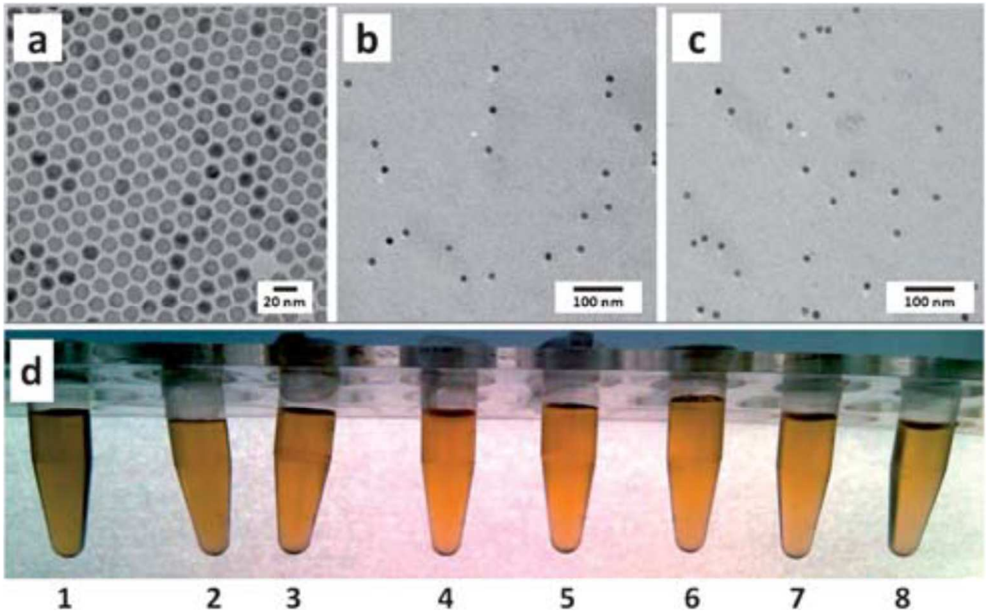


Fig. 16. Transmission electron microscopic (TEM) images of spherical manganese oxide nanoparticles: (a) as-prepared, (b) functionalized with DA-PEG-NH_2 (DA = 3,4-dihydroxyhydrocinnamic acid), and (c) functionalized with DA-PEG-PP (b and c in water; PP = protoporphyrin). (d) Aqueous solutions of DA-PEG-NH_2 (odd numbers) and DA-PEG-PP functionalized MnO nanoparticles after more than two weeks: 1 and 2 in human

blood serum (stored at 4°C), 3 and 4 in human blood serum (at 37°C), 5 and 6 in deionized water (at 4°C), and 7 and 8 in deionized water (at 37°C).

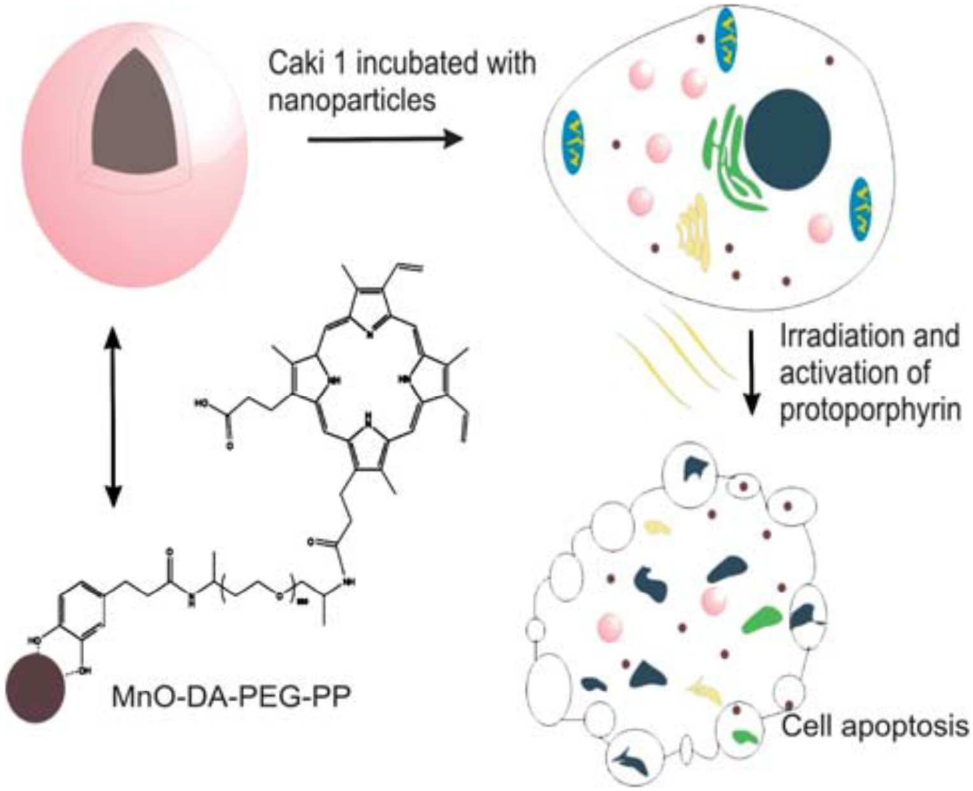
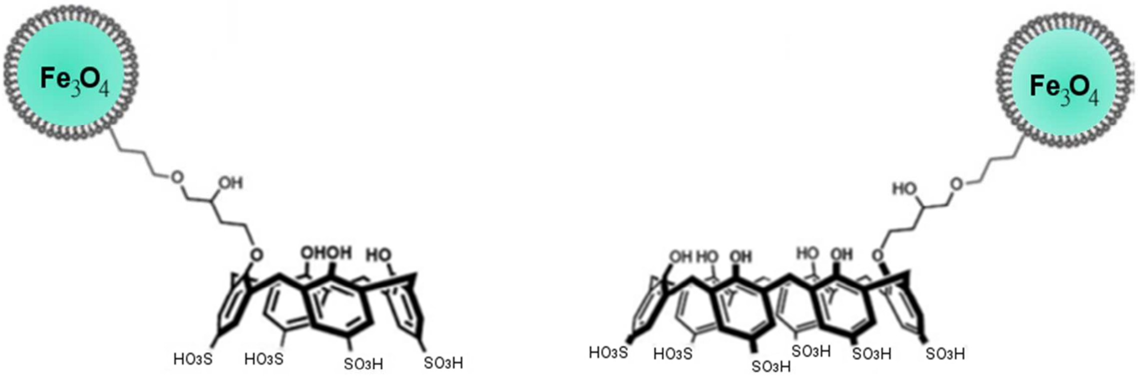


Fig. 17. MnO nanoparticles functionalized using a multifunctional polymeric ligand through suitable anchor groups and carrying amine moieties. Protoporphyrin is bound to PEG800 shell via an amide bond. The protoporphyrin IX tagged MnO nanoparticles are used as photodynamic therapeutic agents to induce localized and intracellularly induced apoptosis in Caki-1 cells.



p-C[4]-MN *p*-C[6]-MN

Fig. 18. Water-soluble calix[4,6]arene appended magnetic nanoparticles. Reproduced with permission of *Springer* {Aksoy, T.; Erdemir, S.; Yildiz, H.B.; Yilmaz, M. Novel Water-

Soluble Calix[4,6]arene Appended Magnetic Nanoparticles for the Removal of the Carcinogenic Aromatic Amines. *Water Air Soil Pollut*., **2012**, *223*, 4129-4139.}.

Among functionalizing compounds, a variety of water-soluble *polymers* occupy indeed the first place in the experiments to solubilize MNPs; we will show only the most representative examples. Thus, highly monodispersed magnetite NPs were prepared in organic solvents and subsequently transferred to water using a biocompatible amphiphilic polymer were prepared to be used as suitable materials for *Magnetic Fluid Hyperthermia*[96] {It is known[97] that, in this method above, the heat dissipated from superparamagnetic nanoparticles, in an alternating magnetic field can be used to locally raise the temperature by 5°C or more above the physiological temperature (37°C), in targeted tumor tissues, thereby encouraging either cell damage or death.}. Indomethacin-loaded bilayer-surface magnetite nanoparticles (9 nm in size) are also described.[98] The particles were first stabilized with oleic acid as a primary surfactant, followed by poly(ethylene glycol) methyl ether-poly(3-caprolactone) (mPEG–PCL) amphiphilic block copolymer as a secondary surfactant to form nanoparticles with hydrophobic inner shell and hydrophilic corona. Studies on the transferring efficiency of the particles from hexane to water phases showed that the dispersibility of the particles in water was promoted by increasing mPEG block lengths. This enables for possible tuning their dispersibility in water by adjusting the ratio of hydrophilic to hydrophobic moieties in the copolymer composition. Percent of magnetite transferred to water phase ranged between 78.9 and 91.2% with the standard deviation ranging between 1.0 and 1.5%. The particles were stable in water with some aggregation observed after one month period.

In addition to the example of PEG-containing polymers above, iron oxide nanoparticles were decorated onto the surface of fullerene (C_{60}), and then PEGylation was performed to improve the solubility and biocompatibility of C_{60}-IONP, obtaining a multifunctional C_{60}-IONP-PEG nanocomposite with strong superparamagnetism and powerful photodynamic therapy capacity (Fig. 19).[99] The resulting C_{60}-IONP-PEG exhibited excellent stability in water (Fig. 20) and various physiological solutions including saline, cell medium and serum. Then, hematoporphyrin monomethyl ether (HMME), a new photodynamic anti-cancer drug, was conjugated to C_{60}-IONP-PEG, forming a C_{60}-IONP-PEG/HMME drug delivery system (Fig. 21). In the *in vitro* and *in vivo* studies, C_{60}-IONP-PEG/HMME showed excellent PDT efficacy, magnetic targeting property and MRI ability, indicating that there is a great potential of C_{60}-IONP-PEG/HMME for cancer theranostic applications.

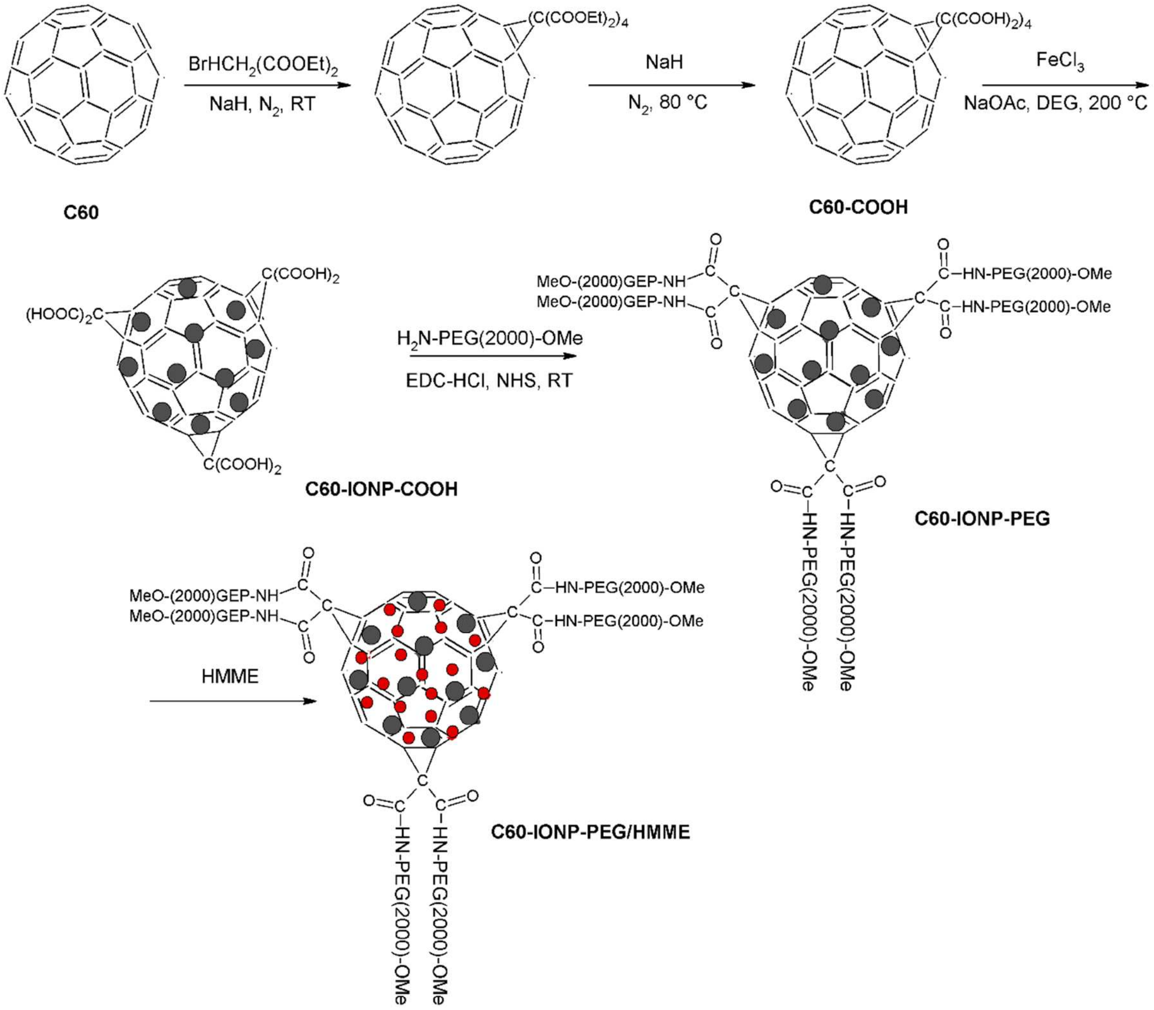


Fig. 19. A schematic illustration of C_{60}-IONP-PEG/HMME nanocomposite preparation.

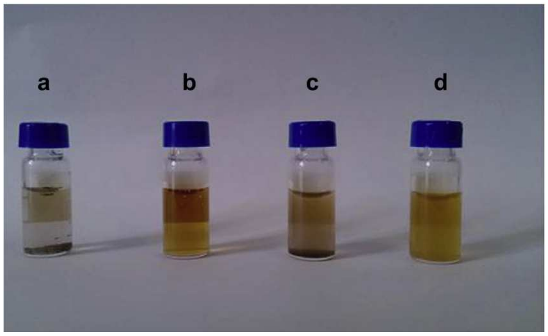


Fig. 20. Characterization of fullerenes: photos of a) C_{60}, b) C_{60}-COOH, c) C_{60}-IONP and d) C_{60}-IONP-PEG in water. Reproduced with permission of *Elsevier Science* {Shi, J.; Yu, X.; Wang, L.; Liu, Y.; Gao, J.; Zhang, J.; Ma, R.; Liu, R.; Zhang, Z. PEGylated fullerene/iron oxide nanocomposites for photodynamic therapy, targeted drug delivery and MR imaging. *Biomaterials*, **2013**, *34*, 9666-9677.}.

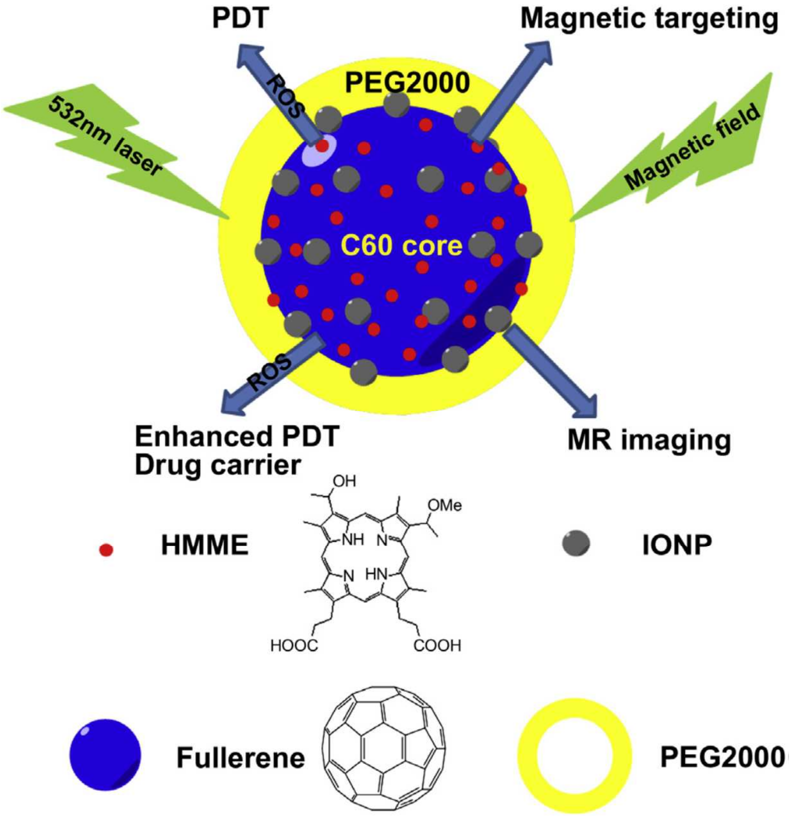


Fig. 21. Scheme of C_{60}-IONP-PEG/HMME and its biofunctions. Reproduced with permission of *Elsevier Science* {Shi, J.; Yu, X.; Wang, L.; Liu, Y.; Gao, J.; Zhang, J.; Ma, R.; Liu, R.; Zhang, Z. PEGylated fullerene/iron oxide nanocomposites for photodynamic therapy, targeted drug delivery and MR imaging. *Biomaterials*, **2013**, *34*, 9666-9677.}.

The gold surface of the Fe@Au NPs was functionalized (Fig. 22) with stained PEG thiol conjugates that provided dispersion of the Fe@Au NPs into aqueous media.[100] By using a redox transmetalation process, the Fe core served as a nanoelectrode for the spontaneous deposition of gold onto the surface of NPs without the need of any additional agent. 70% (w/w) of particles were found to be magnetic and the thickness of the gold layer was about 1.8 nm. In addition, water-soluble cobalt ferrite and manganese ferrite were used as model nanocrystals to illustrate the flexibility of sucrose gradient ultracentrifugation, since they are representative examples of two bimetallic ferrites with biomedical applications.[101] This method is a cost-effective and easily scalable preparative technique that allows sensitive evaluation and isolation of homogeneous, water-soluble nanoparticles. In particular, cobalt ferrite nanocrystals with a mean diameter of 6.0 nm were coated with 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] (DSPE-PEG-2000) by hydrating a dry film containing a mixture nanocrystals stabilized by oleic acid and DSPE-PEG-2000 (Fig. 23).

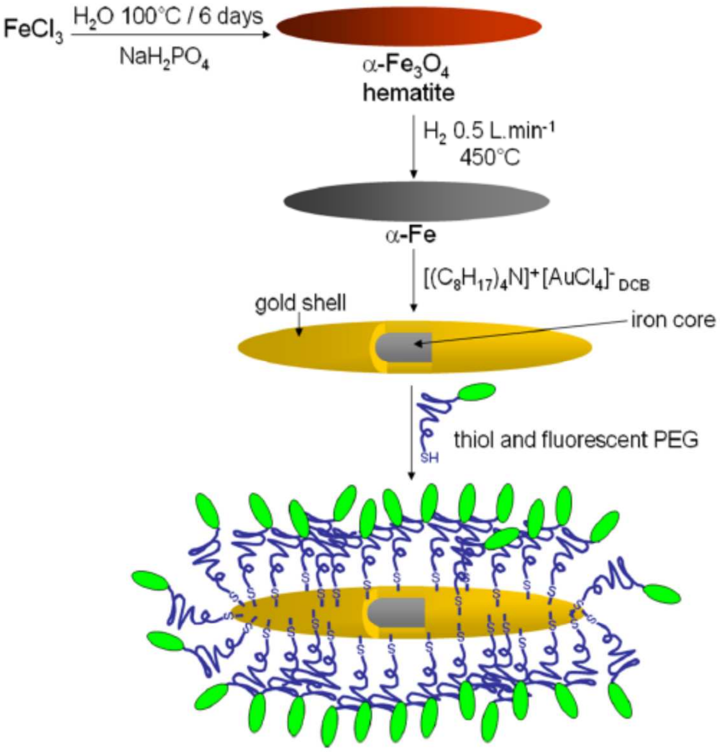


Fig. 22. General procedure to obtain the pegylated iron@gold (core@shell) NPs.

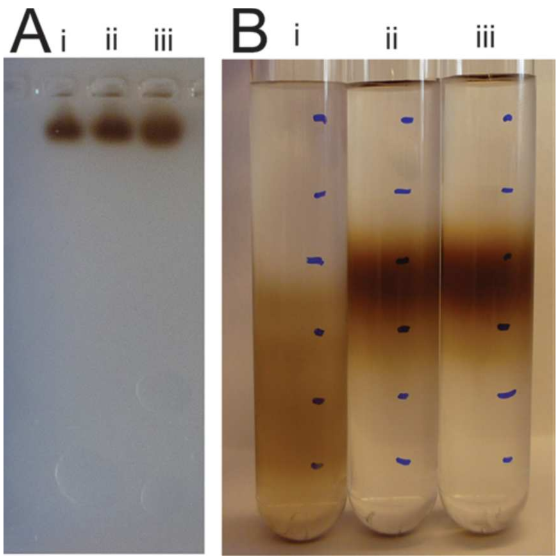


Fig. 23. Qualitative evaluation of nanoparticle preparations. Samples were initially prepared at an iron to DSPE-PEG-2000 weight ratio of (i) 1:5, (ii) 1:10, and (iii) 1:20 by solvent exchange. (A) Samples were analyzed by agarose gel electrophoresis (0.6%, 100 V, 60 min) prior to (B) sucrose gradient ultracentrifugation. The markings in B indicate the approximate position of the density gradient steps (water, 30, 40, 50, 60, 70, and 80%

sucrose). Reproduced with permission of *The American Chemical Society* {Prantner, A.M.; Chen, J.; Murray, C.B.; Scholler, N. Coating Evaluation and Purification of Monodisperse, Water-Soluble, Magnetic Nanoparticles Using Sucrose Density Gradient Ultracentrifugation. *Chem. Mater*. **2012**, *24*, 4008−4010.}.

Three kinds of water-soluble magnetic nanoparticles (20-30 nm in size) capped with different surface functional groups such as 2-pyrrolidone, triethylene glycol (TREG, see also the section on the "polyol strategy" below), and polyacrylic acid were synthesized by the thermal decomposition method from $Fe(acac)_3$ (Fig. 24).[102] To investigate and improve the hydrophilicity of nanoparticles, polyacrylic acid (PAA, third route) was selected by authors for functionalization of the magnetic nanoparticle surface because of the copious carboxylate groups along the polymer chain. These functional groups may enhance the interaction between water and magnetic nanoparticles because the free carboxylate groups extended in water may facilitate the dispersibility of polyacrylic acid magnetic nanoparticles in the aqueous solution. All three kinds of magnetic nanoparticles exhibited very hydrophilic properties and are stably dissolved in water even after being stored for 3 months. Their application as novel draw solutes in forward osmosis was investigated. Magnetic nanoparticles capped with polyacrylic acid can yield the highest driving force and subsequently highest water flux among others. The used magnetic nanoparticles can be captured by the magnetic field and recycled back into the stream as draw solutes in the forward osmosis (FO) process.

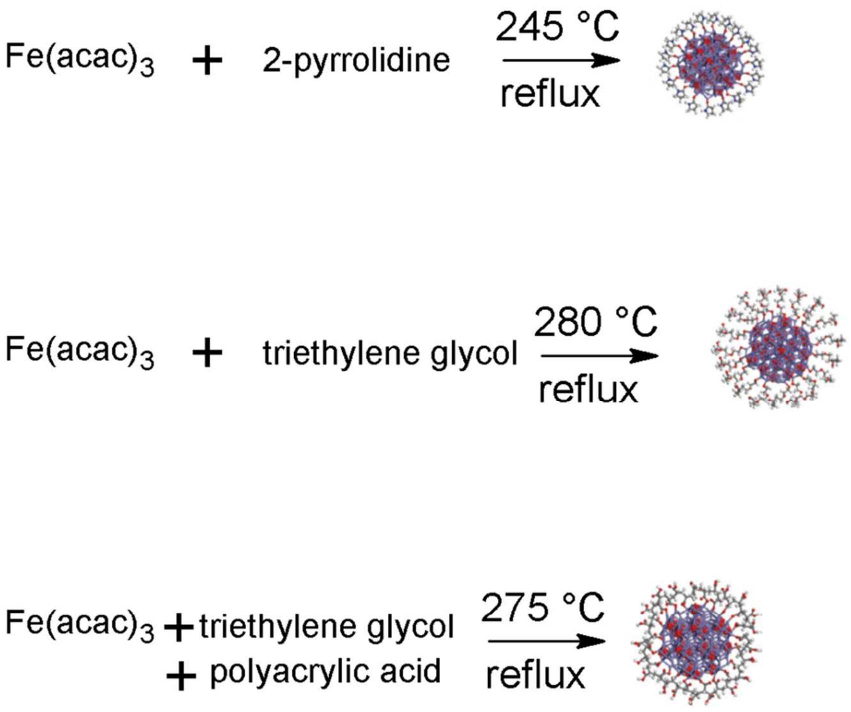


Fig. 24. Routes of synthesis of surface-functionalized magnetic nanoparticles. Reproduced with permission of *The American Chemical Society* {Ming Ming Ling; Kai Yu Wang; Tai-Shung Chung. Highly Water-Soluble Magnetic Nanoparticles as Novel Draw Solutes in Forward Osmosis for Water Reuse. *Ind. Eng. Chem. Res.* **2010**, *49,* 5869–5876.}

Hydrophobically modified water-soluble polymers (HMWSPs) {comprised of a poly(sodium methacrylate) (PMANa) or poly(sodium acrylate) (PANa) backbone and pendent dodecyl methacrylate (DMA) or dodecyl acrylamide (DAAm) chains, respectively} were synthesized and the hydrophobic $CoFe_2O_4$@OAm {oleyamine coated, solvothermally prepared from $Fe(acac)_3$ and $Co(acac)_3$ as precursors} MNPs were encapsulated into the hydrophobic cores of the structures formed by the copolymers above CMC (critical micelle concentration) through a solvent mixing procedure, resulting hydrophilic $CoFe_2O_4$@HMWSP nanohybrids (Fig. 25).[103] Two alternate phase transfer approaches were also used to convert $CoFe_2O_4$@OAm MNPs to hydrophilic ones: (a) addition of a coating layer by cetyltrimethyl ammonium bromide (CTAB) and (b) by the ligand exchange procedure with 2,3-dimercaptosuccinic acid (DMSA). Aqueous $CoFe_2O_4$@HMWSP, $CoFe_2O_4$@CTAB, and $CoFe_2O_4$@DMSA dispersions were prepared and compared in terms of their stability. Related applications of polymethacrylic acid (PMAA)[104] and PAA[105] to obtain water-soluble NPs of iron oxides are also known.

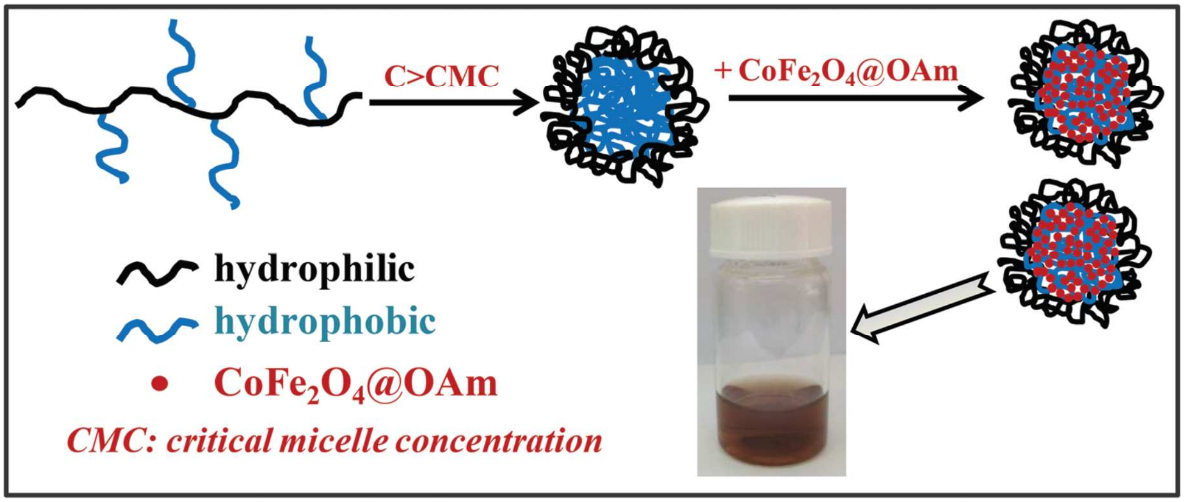


Fig. 25. Schematic depiction of the stabilization of $CoFe_2O_4$@HMWSP nanohybrids in water.

Among other uses of polymers for MNPs solubilization, a one-step, template-free synthesis method (Fig. 26) for preparing superparamagnetic polymeric microcapsules with iron oxide (γ-Fe_2O_3) magnetic nanoparticles embedded in the polymer shell (Fig. 27) was reported.[106] Using an emulsification of the multiphase mixture containing liquid prepolymer (UV curable liquid photopolymer NOA 61) and nanoparticles in chloroform solution, double emulsions comprising a chloroform core and MPs/polymer shell were spontaneously formed. Being exposed to UV light, these double emulsions were converted to microcapsules with a polymerized composite shell and could be moved and collected by external magnetic fields. One interesting property of these hybrid microcapsules was their ability to reversibly exchange water with the environment. When the emulsions were exposed to water by dilution of the glycerin medium, their cores readily swelled due to the diffusion of water into the capsule interior. The authors believe that this core swelling is of osmotic origin due to the presence of a small amount of glycerin in the core. Moreover, when the shrunken dried capsules were redispersed in water after the chloroform in the core completely evaporated, they reswelled to their initial spherical shape. Up to seven drying/watering cycles were repeated, and the capsules showed fully reversible shape restoration.

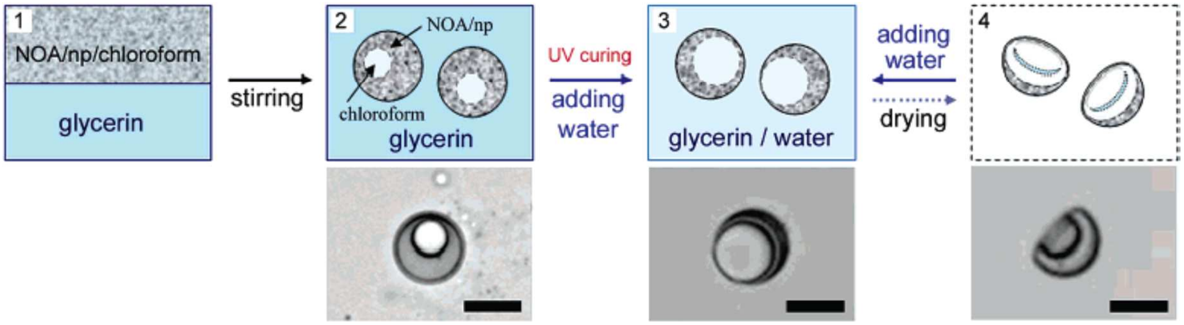


Fig. 26. Schematics of the process for synthesis of the organic/inorganic hybrid microcapsules. The bottom frames are optical micrographs of the actual system (scale bar 10 µm). (1) The mixture containing NOA prepolymer and iron oxide nanoparticles in chloroform is emulsified in the glycerin medium. After emulsification, double emulsions containing the chloroform core and nanoparticle containing polymeric shell are spontaneously formed. (2) After dilution of the glycerin medium with water, the inner chloroform core swells due to water permeation. (3 and 4) Curing and drying of the liquid medium results in organic/inorganic hybrid microcapsules, which reversibly swell in water. Reproduced with permission of *The American Chemical Society* {Hye Young Koo; Suk Tai Chang; Won San Choi; Jeong-Ho Park; Dong-Yu Kim; Velev, O.D. Emulsion-Based Synthesis of Reversibly Swellable, Magnetic Nanoparticle-Embedded Polymer Microcapsules. *Chem. Mater.* **2006**, *18,* 3308-3313.}.

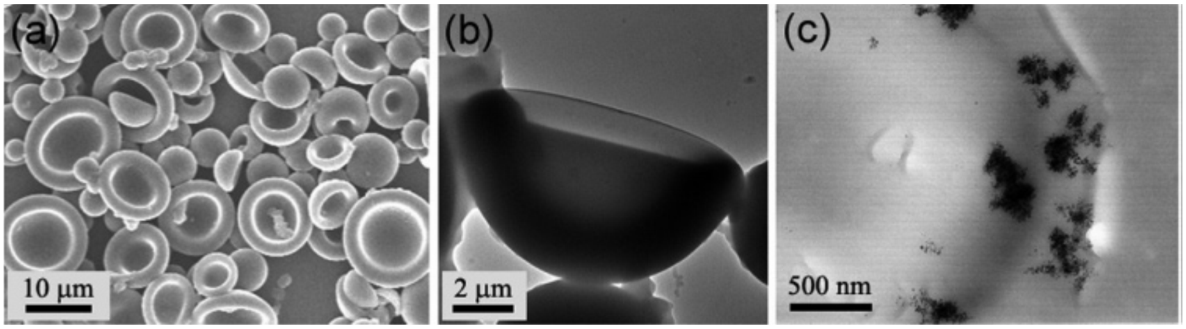


Fig. 27. Microscopy images of the organic/inorganic hybrid microcapsules obtained by (a) SEM, (b) TEM, and (c) ultrathin (100 nm) cross-section TEM of the microtomed capsule. The sample is formed from a 750 µL mixture of the MPs/chloroform and NOA polymer (1:2 v/v), emulsified at a speed of 500 rpm (the average capsule diameter is 12±3.28 µm). Reproduced with permission of *The American Chemical Society* {Hye Young Koo; Suk Tai Chang; Won San Choi; Jeong-Ho Park; Dong-Yu Kim; Velev, O.D. Emulsion-Based Synthesis of Reversibly Swellable, Magnetic Nanoparticle-Embedded Polymer Microcapsules. *Chem. Mater.* **2006**, *18,* 3308-3313.}.

As a rare example of special studies of transformation of initially insoluble MNPs to soluble ones, we note an easy and high-efficient method, described for transferring hydrophobic magnetic Fe_3O_4 nanoparticles from organic to aqueous solution by wrapping a thermo-responsive and photocrosslinkable poly(*N*-isopropylacrylamide) (PNIPAm) terpolymer encapsulating the particles (Figs. 28 and 29).[107] The wrapping procedure was introduced by the co-nonsolvent transition of PNIPAm in the mixing solvent and the polymer can dissolve in water carrying Fe_3O_4 nanoparticles by noncovalent interaction. A related organic system was used to obtain the magnetically responsive ***microgel*** (Fig. 30), consisting of a small IONPs (~15 nm in diameter) embedded in a biocompatible microgel varying from ~65 to ~110 nm in diameter, which was obtained from $FeCl_3 \cdot 6H_2O$ and 8.6 g $FeCl_2 \cdot 4H_2O$ as precursors.[108] Polymeric microgels were prepared by emulsion free copolymerization of thermoresponsive N-isopropylacrylamide and acrylic acid with a water-soluble persulfate initiator.

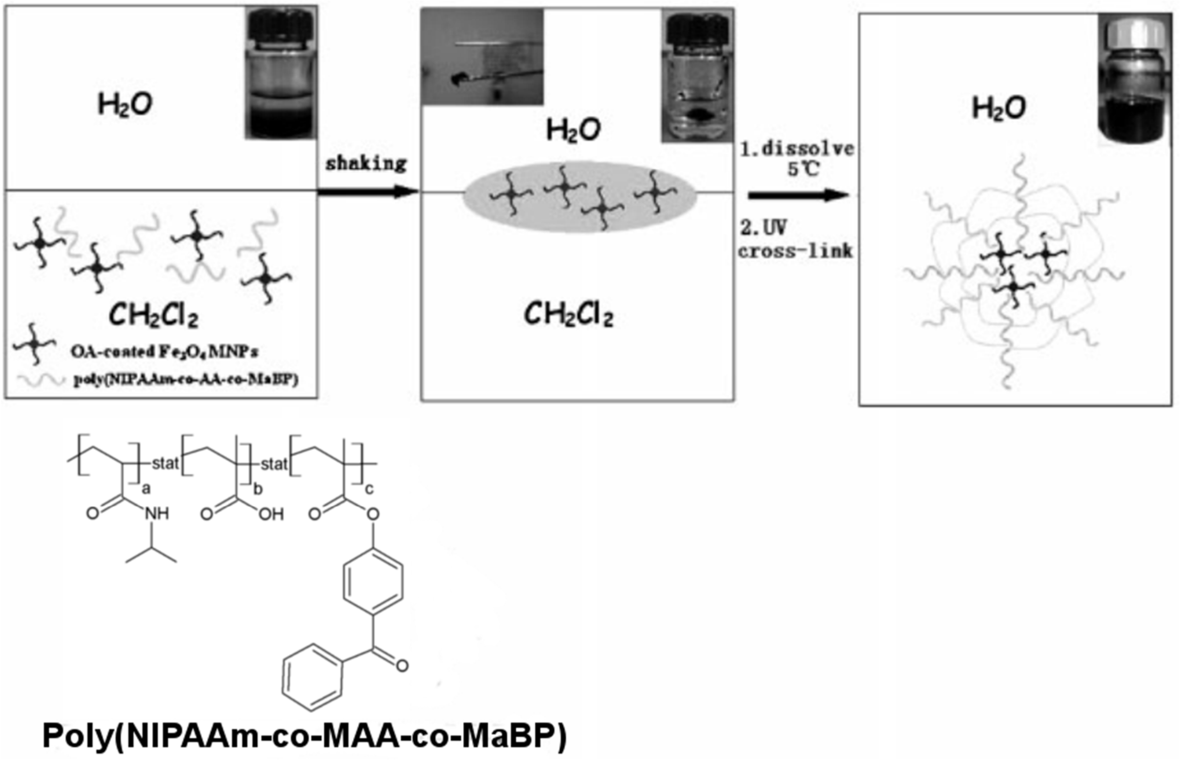


Fig. 28. Schematic depiction of the water-soluble process of hydrophobic Fe_3O_4 MNPs through poly(NIPAAm-co-MaBP-co-MAA) terpolymer and subsequent photo-cross-linking. Reproduced with permission of *Wiley* {Cheng, Z.; Liu, S.; Gao, H.; Tremel, W.; Ding, N.; Liu, R.; Beines, P.W.; Knoll, W. A Facile Approach for Transferring Hydrophobic Magnetic Nanoparticles into Water-Soluble Particles. *Macromol. Chem. Phys*. **2008**, *209*, 1145–1151.}.

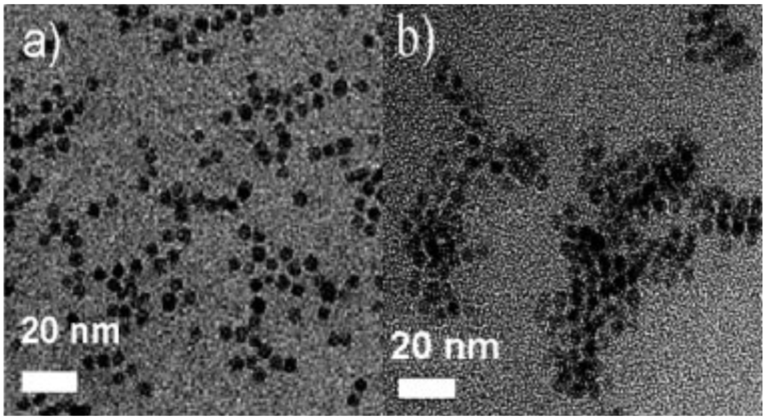


Fig. 29. TEM images of (a) OA-coated Fe_3O_4 nanoparticles (b) hydrogel-encapsulated Fe_3O_4 nanoparticles after photo-crosslinking. Reproduced with permission of *Wiley* {Cheng, Z.; Liu, S.; Gao, H.; Tremel, W.; Ding, N.; Liu, R.; Beines, P.W.; Knoll, W. A Facile Approach for Transferring Hydrophobic Magnetic Nanoparticles into Water-Soluble Particles. *Macromol. Chem. Phys*. **2008**, *209*, 1145–1151.}.

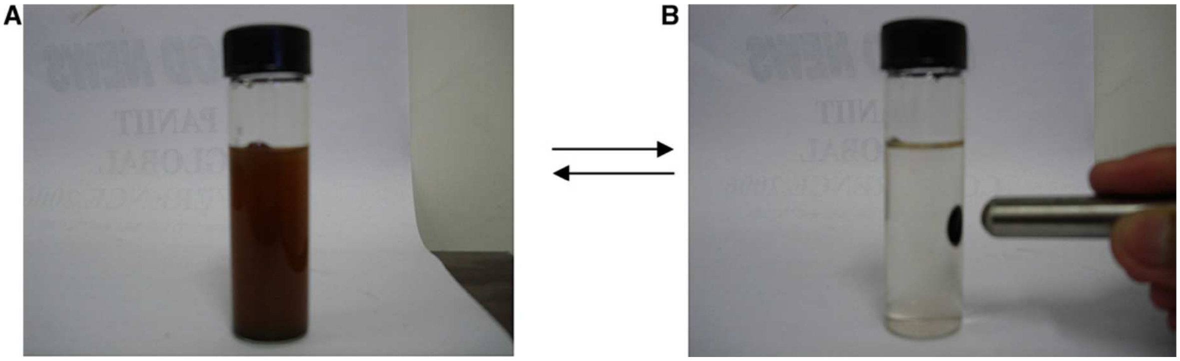


Fig. 30. Photographs of the separation (A to B) and dispersion (B to A) of the microgel magnetic particles (MMP): (A) without external magnetic field, (B) with external magnetic field (the magnetic field strength of the magnet is 2000 G). A color change from saddle brown to transparent was observed when an external magnetic field is applied. Reproduced with permission of *Elsevier Science* {Khan, A. Preparation and characterization of magnetic nanoparticles embedded in microgels. *Materials Letters*, **2008**, *62*, 898–902.}.

Also, superparamagnetic nanoparticles (magnetite Fe_3O_4) with a 5 nm diameter and stabilized in water (pH > 6.5) by a shell of water-soluble poly(ethylene oxide) (PEO) chains were reported.[109] Two types of diblock copolymers, *i.e.*, poly(acrylic acid)-*b*-poly(ethylene oxide), PAA-PEO, and poly(acrylic acid)-*b*-poly(acrylate methoxy poly(ethyleneoxide)), PAA-PAMPEO, were prepared as stabilizers with different compositions and molecular weights. The ferrofluids on the basis of the synthesized nanoparticles should be source of heat when submitted to an alternating magnetic field. In addition, an efficient MRI T_2-weighted contrast agent incorporating a potential liver targeting functionality was synthesized via the combination of superparamagnetic iron oxide (SPIO) nanoparticles with multi-walled carbon nanotubes (MWCNTs).[110] Poly(diallyldimethylammonium chloride)

(PDDA) was coated on the surface of acid treated MWCNTs via electrostatic interactions and SPIO nanoparticles modified with a potential targeting agent, lactose-glycine adduct (Lac-Gly), were subsequently immobilized on the surface of the PDDA-MWCNTs (Fig. 31). Dispersion tests were conducted to determine the water dispersion stability of the product (CNT-PDDA-SPIO@Lac-Gly) in comparison with starting material (MWCNTs) and intermediate (CNT-PDDA). Pristine MWCNTs, CNT-PDDA, and CNT-PDDA-SPIO@Lac-Gly were initially dispersed in water with assistance of ultrasonication for 30 min. As shown in Fig. 32, pristine MWCNTs could not be dispersed in water even with assistance of ultrasound. However, CNT-PDDA and CNT-PDDA-SPIO@Lac-Gly could maintain a stable dispersion for more than 72 h indicating that the PDDA coating improved the MWCNTs dispersions in aqueous solution. Fig. 33 shows TEM images of SPIO@Lac-Gly and CNT-PDDA-SPIO@Lac-Gly, respectively. Most of the SPIO@Lac-Gly particles had diameters of around 9 nm and were spherical in shape; MWCNTs were covered with small clusters of magnetic nanoparticles, and no free nanoparticles were observed. Fabrication of water-soluble magnetic nanoparticles by ligand-exchange with thermo-responsive polymers[111] and chitosan[112 113] is also known.

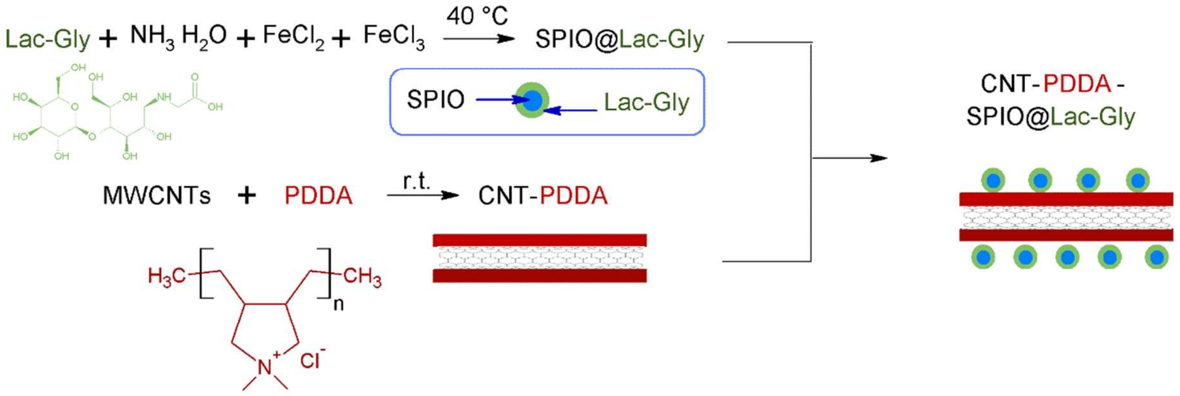


Fig. 31. Synthetic route for the production of CNT-PDDA-SPIO@Lac-Gly nanocomposites.

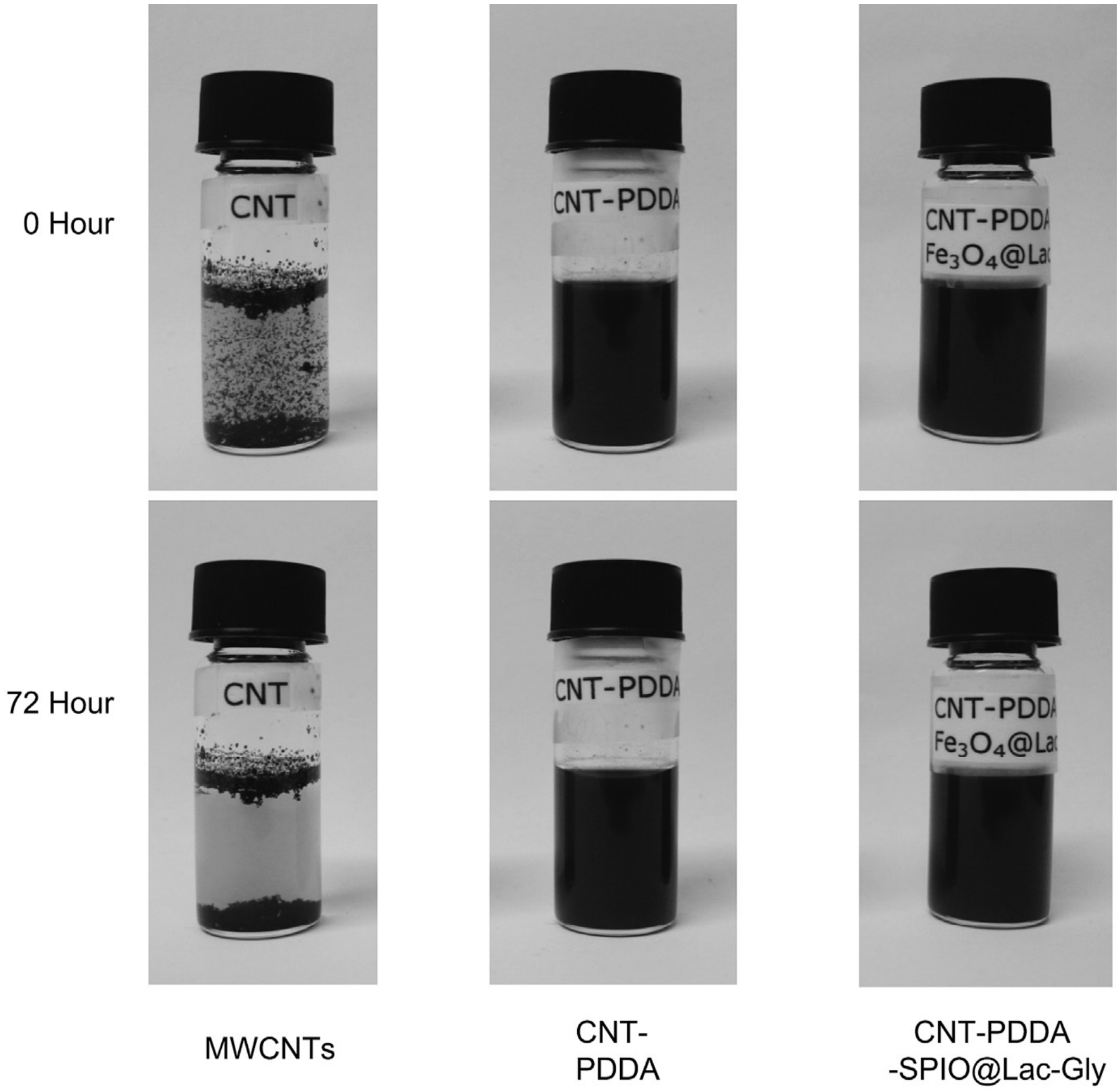


Fig. 32. Dispersion stability test of CNT-PDDA-SPIO@Lac-Gly composite in water. Reproduced with permission of *Elsevier Science* {Liu, Y.; Hughes, T.C.; Muir, B.W.; Waddington, L.J.; Gengenbach, T.R.; Easton, C.D.; Hinton, T.M.; Moffat, B.A.; Hao, X.; Qiu, J. Water-dispersible magnetic carbon nanotubes as T_2-weighted MRI contrast agents. *Biomaterials*, **2014**, *35*, 378-386.}.

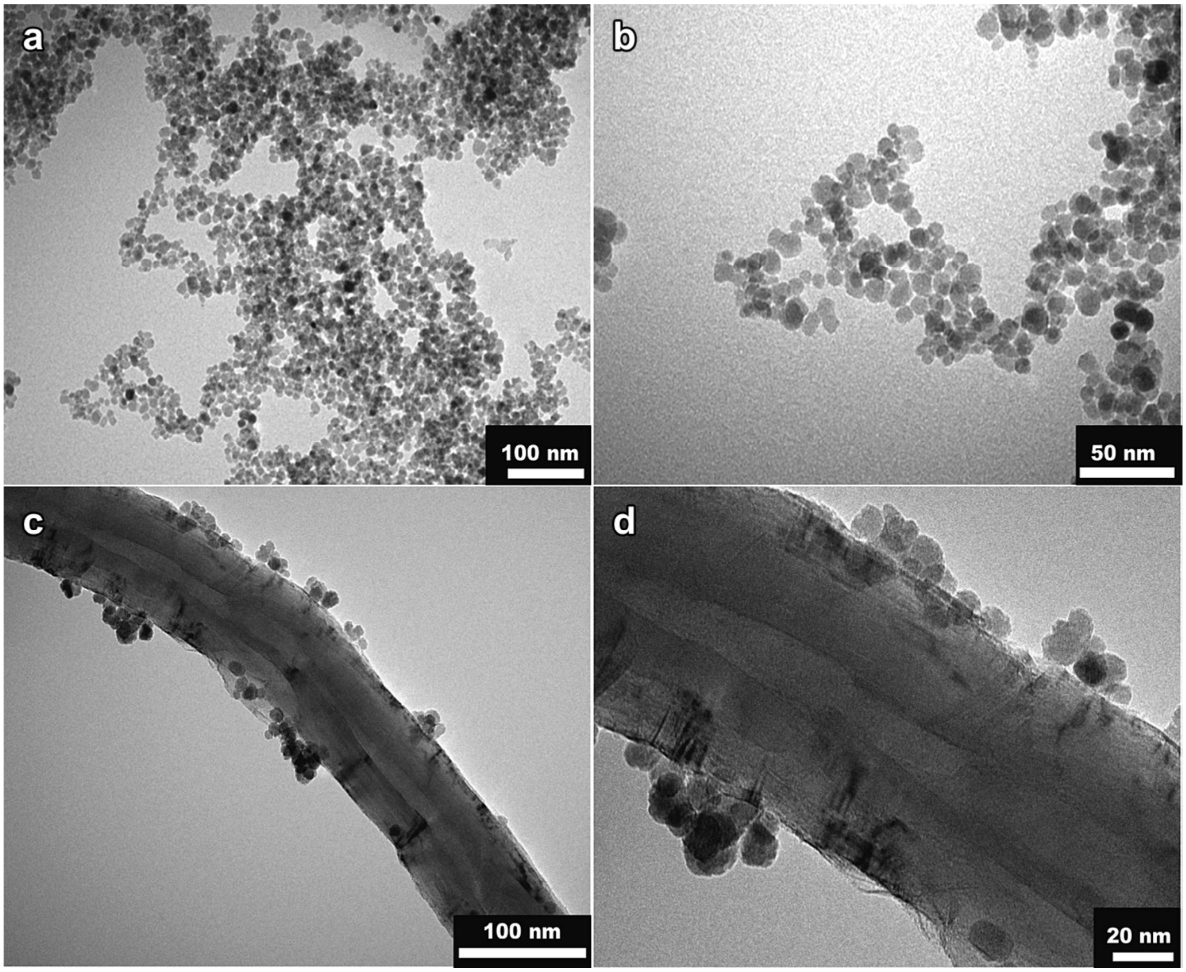


Fig. 33. TEM images of SPIO@Lac-Gly (a, b) and CNT-PDDA-SPIO@Lac-Gly (c, d). Reproduced with permission of *Elsevier Science* {Liu, Y.; Hughes, T.C.; Muir, B.W.; Waddington, L.J.; Gengenbach, T.R.; Easton, C.D.; Hinton, T.M.; Moffat, B.A.; Hao, X.; Qiu, J. Water-dispersible magnetic carbon nanotubes as T_2-weighted MRI contrast agents. *Biomaterials*, **2014**, *35*, 378-386.}.

Additionally to the compounds above for MNPs functionalization, *peptides* can also be used for their solubilization. Thus, a method for selective marking of amyloid fibrils, e.g. insulin and Aβ40, by both fluorescent and non-fluorecent γ-Fe_2O_3 nanoparticles (15 nm in size) was developed.[114] These IONPs of narrow size distribution were synthesized by nucleation, followed by controlled growth of maghemite thin films onto gelatin-iron oxide nuclei, with further surface coatings with a functional fluorinated polymer and peptides, e.g. Leu-Pro-Phe-Phe-Asp (LPFFD) and Aβ40, through various activation methods. The authors note that, in a difference of many fluorescent nanoparticles have their fluorescent moieties bound to the surface, their nanoparticles contain fluorescent dye, covalently encapsulated within the nanoparticles. There is, therefore, retention of the surface properties, including the zeta potential and surface bound ligand capacity.

Co-precipitation

Coprecipitation consists generally in simultaneous reduction of Fe^{2+}/Fe^{3+} or Fe^{n+}/Au^{+} precursors and it is frequently the first step before functionalization of formed "naked" nanoparticles with organic moieties, described above. Several surfactants coating and/or stabilizing agents could be added to the reaction system and temperature could vary. As an example, magnetite Fe_3O_4 nanoparticles were synthesized by coprecipitating a Fe^{2+}/Fe^{3+} mixed solution (the molar ratio $Fe^{2+}:Fe^{3+} = 1:2$) with a NH_4OH solution in air and mixed with oleic acid to coat with a single surfactant layer for further dispersion into methylene chloride.[115] Water-soluble and biocompatible monodispersed ultrasmall magnetic iron nanoparticles (3.3 nm in diameter) were synthesized (Fig. 34) from $FeCl_3{\cdot}6H_2O$ and $FeSO_4{\cdot}7H_2O$ as precursors *via* a high-temperature coprecipitation method using thiol-functionalized poly(methacrylic acid) as stabilizer.[116] In addition, SPION with a mean size of 12 nm were prepared under N_2 atmosphere, with support of natural polymeric starch, by controlling chemical coprecipitation of magnetite phase from aqueous solutions containing suitable salts ratios of Fe^{2+} and Fe^{3+}.[117] The surface of SPION-nanoparticles was treated with a coordinatable agent (starch, dextran, PEG or MPEG) for higher dispersion ability in water and remaining the superparamagnetic behavior.

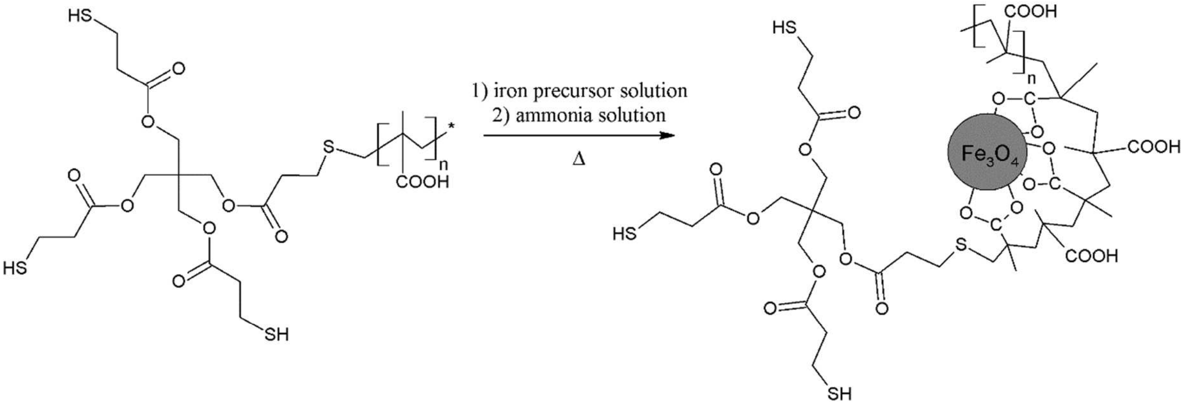


Fig. 34. Preparation of ultrasmall magnetic iron oxide nanoparticles.

Use of surfactants and capping agents

Surfactants are classic agents in the nanotechnology and are widely used to prevent nanoparticle aggregation. As an example, nanoparticles of Fe, Co, FeCo, SmCo, and NdFeB systems with sizes smaller than 30 nm and narrow size distribution were prepared by ball milling in the presence of surfactants (oleic acid and oleylamine, mentioned in the sections above and in Table 1 below) and organic carrier liquid.[118] The nanoparticles prepared by milling Fe and FeCo powders were observed to be close to spherical in their shapes, whereas those of Co, SmCo, and Nd–Fe–B showed elongated rod shapes. The nanoparticles showed superparamagnetic behavior at r.t., except for the SmCo nanoparticles that were ferromagnetic. When surfactant was used along with heptane during milling, a colored liquid (nanoparticles smaller than 30 nm) was obtained along with coarse particles, which sedimented at the bottom of the milling vial; when surfactants were not added to heptane, the solvent remained clear after milling because there were no nanoparticles dispersed in the liquid.

Table 1 contains selected the most representative examples of classic magnetic nanoparticles, soluble mainly in water, as well as in some non-polar organic solvents, examples of solvents, surfactants and capping agents, applied for synthesis and solubilization of magnetic nanoparticles. Here we observe that nanoparticle synthesis, leading to dispersions, could be carried out both in water and in organic solvents. Use of sodium citrate and polyols generally leads to water-soluble polymers, meanwhile very frequent application of oleyamine and oleic acid could result solubility in solvents of distinct nature. 1-Octadecene, polyols, and especially water are the most used solvents; sometimes the same compound has a role of a solvent, surfactant, capping agent and/or reductant (PAA or polyols). Water ("greener" solvent) possesses obvious advantages in comparison with organic solvents and so it is mostly frequently used.

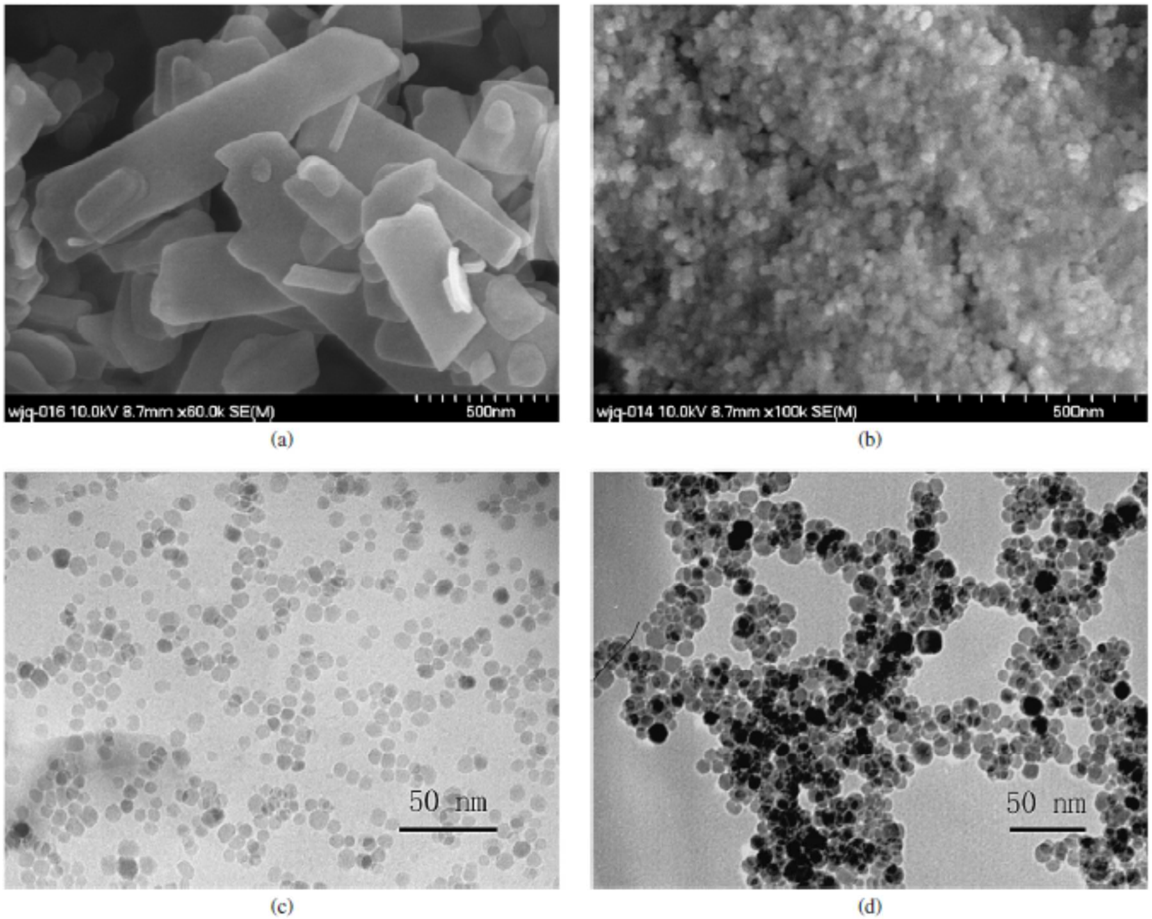
Table 1. Solvents and coating agents in the synthesis of magnetic nanoparticles.

Nanoparticles, size (nm)	**Solvent(s) during the synthesis**	**Coating / capping or functionalizing agent / surfactant**	**NPS solubles in**	**Reference**
Au- and Ag-coated Fe_3O_4, 12 nm.	Chloroform	Au or/and Ag, oleylamine and oleic acid	Non-polar solvents.	88
		Further treatment with CTAB and sodium citrate.	Water.	
Fe_3O_4, 20-40 nm.	Water	Sodium citrate.	Water.	90
Fe_3O_4, 30 nm.	Benzyl ether	Oleyamine	Hexane and toluene.	80
Fe_3O_4 and γ-Fe_2O_3, $CoFe_2O_4$, 6-15 nm; CoO, 50 nm.	1-octadecene	Sodium oleate	Water.	78, 96
Fe_3O_4, 9 nm.	Benzyl ether, further redispersion in hexane.	Oleylamine and oleic acid; PEG diacid.	Water or phosphate buffered saline (PBS).	120
Fe_3O_4, 9 nm.	Benzyl ether.	Oleylamine; mono-methoxypoly(ethylene glycol) (mPEG).	Both hexane and PBS	82
Fe_3O_4, 20 nm.	Ethylene glycol (EG), diethylene glycol (DEG), triethylene glycol (TREG) and tetraethylene	EG, DEG, TREG or TEG.	Water.	

	glycol (TEG).			
Fe_3O_4, 9 nm.	MPEG.	MPEG (used as solvent, reducing agent, and modifying agent).	Water.	125
Fe_3O_4, 5 nm.	1,2-hexadecanediol and phenyl ether; further redispersion in hexane.	Oleylamine; [5,15-bis(phenyl)-10,20-bis(4-methoxy-carbonyl-phenyl)-porphyrin] platinum (t-PtCP)	Water.	92
γ-Fe_2O_3, Fe_3O_4,	Water.	Dextran, sucrose.	Water.	119
Fe_3O_4, 20 nm.	2-Pyrrolidone, triethylene glycol, and polyacrylic acid.	2-Pyrrolidone, triethylene glycol, and polyacrylic acid (PAA).	Water.	102
Fe_3O_4, 5 nm	Toluene.	Poly(ethylene oxide) (PEO).	Water.	109
$CoFe_2O_4$, 5-7 nm.	Diethylene glycol	Diethylene glycol	Diethylene glicol.	123
$CoFe_2O_4$, 6 nm.	-	1,2-Distearoyl-sn-glycero-3-phospho-ethanolamine-N-[methoxy(polyethylene glycol)-2000] (DSPE-PEG-2000).	Water.	101
MnO, 14 nm.	1-octadecene; then chloroform and a solution of 30 mg DA-PEG-NH_2 (3,4-dihydroxy-hydro-cinnamic acid) or DA-PEG-PP (dopamine-PEG-protoporphyrin IX).	Manganese(II) oleate (precursor).	Water.	94

Polyol strategy

Polyol process is a versatile chemical approach, which refers to the use of polyols {for example ethylene glycol (EG), diethylene glycol (DEG), triethylene glycol (TREG) and tetraethylene glycol (TEG)} to reduce metal salts to metal particles, that has successfully been used to prepare a great variety of non-aggregated particles of inorganic compounds. Poly(ethylene glycol) (PEG, amphiphilic polymer and commonly regarded as a non-specific interaction reducing reagent), already mentioned in the sections above, is frequently used for MNPs functionalization.[120] The polyols in this method often serve as high-boiling solvent and reducing agent, as well as stabilizer to control the particles growth and prevent interparticle aggregating. Additionally, PEG is an important biocompatible polymer that facilitates the solubilization and long-term circulation of proteins, viruses and other biological macro- molecules. Thus, magnetite nanoparticles (Fig. 35) were synthesized in liquid polyols at elevated temperature.[121] Polyol solvent was found to play a crucial role in determining the morphology and colloidal stability of the resulting particles. The magnetite nanoparticles were found to be monodisperse, highly crystalline and superparamagnetic at r.t. and can be easily dispersed in aqueous media and other polar solvents due to coated by a layer of hydrophilic polyol ligands *in situ*. A distinguishing property of the magnetite nanoparticles obtained by the current synthesis approach from other non-aqueous route is that the resulting magnetite nanoparticles exhibited excellent water-solubility and no detectable aggregation is found. It is well known that the magnetic colloidal particles attract each other by van der Waals forces and magnetic dipolar interactions. The authors emphasize that the reason of as-prepared magnetite nanoparticles can be easily dissolved in high quantities in water to afford a stable aqueous solution is believed to be the formation of a steric barrier given rise from the strong hydrophilic TREG ligands coated on the particles during the synthesis procedure. In addition, only single iron rich precursor was used and no further reducing agent and surfactants were required, which made this process easy to scale-up for mass production. Also, the size distribution of the nanoparticles is much narrower than those particles produced from traditional methods. The magnetite nanoparticles, obtained from Fe(acac)$_3$ in TREG remained stable for several months without noticeable precipitation.[122]

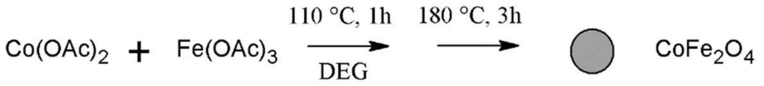


(a) (b)

(c) (d)

Fig. 35. SEM image of the products synthesized in ethylene glycol (a) and diethylene glycol (b); TEM images of the products synthesized in triethylene glycol (c) and tetraethylene glycol (d), the samples are dispersed in ethanol. Reproduced with permission of *Elsevier Science* {Cai, W.; Wan, J. Facile synthesis of superparamagnetic magnetite nanoparticles in liquid polyols. *J. Colloid Interface Sci*., **2007**, *305*, 366–370.}.

The synthesis of spinel-type cobalt ferrite nanoparticles dispersed in diethylene glycol (DEG) was carried out via the polyol–mediated technique (*4*) and the crystal size control through successive synthesis steps.[123] The technique can be repeated in subsequent steps, using each time ferrite particles as seed, to finely tune the average size of the particles in the 5–7 nm range. Final concentrations of cobalt ferrite in stable dispersions for distinctly prepared samples were found to be in the range 0.15÷2.88%. In addition, an interesting finding was observed in case of iron oxide in PEG-containing systems. Thus, the high binding affinity of poly(ethylene glycol)-gallol (PEG-gallol) allows freeze drying and re-dispersion of 92-nm iron oxide cores individually stabilized with 9-nm-thick stealth coatings, yielding particle stability for at least 20 months.[124] Fig. 36 shows the prevention of particle agglomeration *even in the presence of a small external magnet*, when the surfactant is used. In all other interactions "suspended MNPs – magnet", observed in other reports, MNPs were attracted by magnets.



(4)

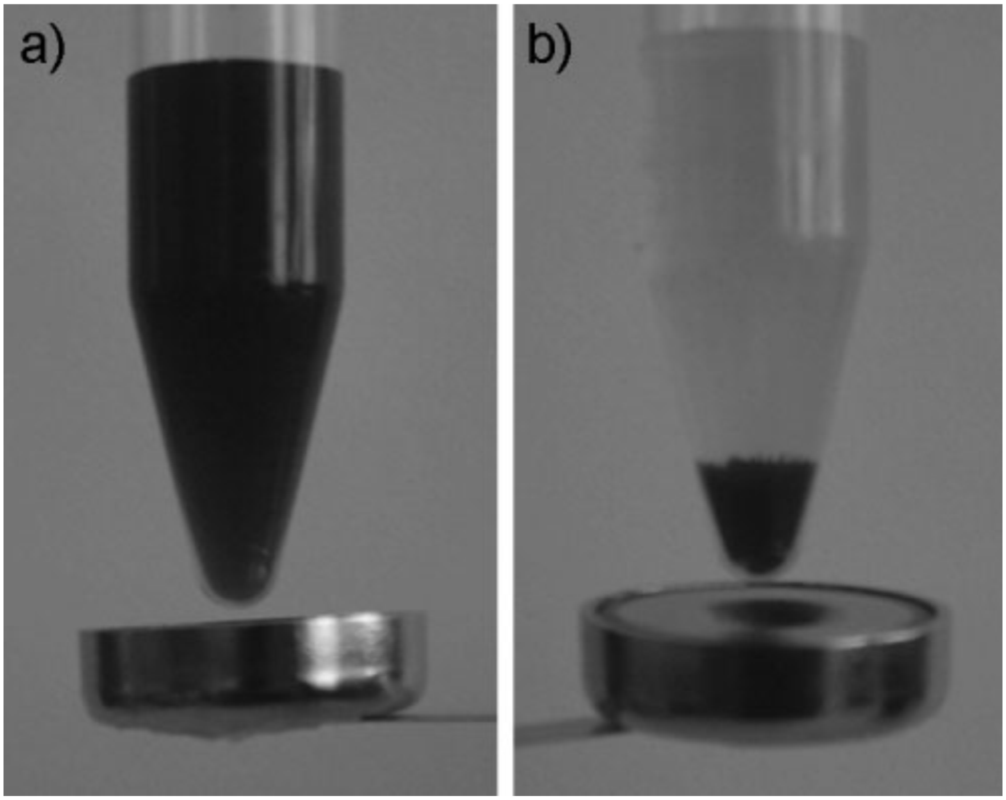


Fig. 36. a) The biotin-PEG(3400)-gallol/mPEG(550)-gallol dispersant layer surrounding the iron oxide nanoparticle cores is stable and thick enough to prevent particle agglomeration in the presence of a small external magnet, even after particles have been dispersed in PBS for more than 1 year. B) In the absence of the dispersant layer, iron oxide cores agglomerate and thus sediment instantaneously upon approaching a small external magnet. Reproduced with permission of *Wiley* {Amstad, E.; Zurcher, S.; Mashaghi, A.; Wong, J.Y.; Textor, M.; Reimhult, E. Surface Functionalization of Single Superparamagnetic Iron Oxide Nanoparticles for Targeted Magnetic Resonance Imaging. *Small*, **2009**, *5* (11), 1334-1342.}.

Thermal decomposition

Thermal decomposition of low-stable precursors of MNPs (generally acetylacetonates or other iron coordination or organometallic compounds) can be carried out with or without use of solvents. If the solvent is chosen appropriately, no other agents might be needed to obtain soluble MNPs. Thus, water-soluble superparamagnetic Fe_3O_4 nanoparticles with an average diameter of 9.5±1.7 nm were synthesized by thermal decomposition of $Fe(acac)_3$ in MPEG (Fig. 37; methoxy polyethylene glycol; it was used as solvent, reducing agent, and modifying agent in this reaction; no further reducing agent and surfactants were required)[125] or TREG (triethylene glycol).[126] MPEG molecules were shown to be covalently bound to the surface of the magnetite nanoparticles *via* the partial oxidation of the terminal OH group of the MPEG.

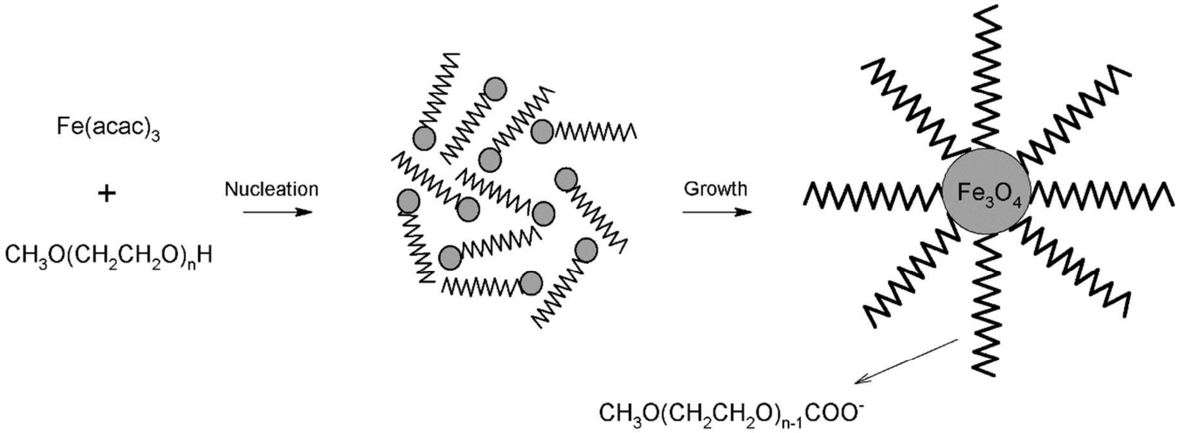


Fig. 37. The preparation of the magnetite nanoparticles in MPEG.

Microwave heating

The reaction system treatment with microwaves (MW) is nowadays a classic tool in chemistry of materials and also in the nanotechnology, having a series of advantages described elsewhere. In general, microwave synthesis has been shown to significantly reduce reaction time, increase yields, reduce side reactions, enhance reproducibility, and provide a more energy efficient, greener process. Microwave heating presents significant benefits over traditional heating methods (*i.e.* oil bath), which rely on conduction and convection for heat distribution. Microwave radiation heats materials through much more efficient dielectric heating; this occurs as molecular dipoles attempt to align with the alternating electric field. As an example of MW applications for preparation of soluble MNPs, a rapid, straightforward microwave-assisted synthesis of superparamagnetic dextran-coated iron oxide nanoparticles was carried out.[127] Two approaches were used: 1) uncoated iron oxide nanoparticles, basically iron cores with no coating, were prepared by hydrazine reduction of ferric chloride with microwave heating at 100°C for 10 minutes. Subsequent coating of the nanoparticles with dextran was achieved in a second stage of microwave heating at 100°C for 2 min. in the presence of additional ferric chloride, sodium hydroxide, and reduced dextran. 2) The nanoparticles were synthesized in a one-pot single step microwave reaction. Ferric chloride and reduced dextran were reacted with hydrazine in the microwave oven at 100°C for 10 minutes. The two methods result in different sized nanoparticles. The dextran coating imparts the water-solubility and biocompatibility necessary for *in vivo* utilization.

Hydrothermal technique

A few reports described the preparation of soluble Fe_3O_4 NPs in distinct reaction systems. Thus, water-soluble Fe_3O_4 nanoparticles with sufficiently high solubility (28 $mg \cdot mL^{-1}$) and stability (at least one month) were synthesized through a hydrothermal approach using sodium citrate and ethylene diamine at 200°C for 12 hours, and found that they exhibited excellent removal ability for heavy-metal ions from waste water.[128] It is important that the adsorption ability of the water-soluble Fe_3O_4 NPs for Pb^{2+} and Cr^{6+} is stronger than water-insoluble Fe_3O_4 NPs. In addition, the water-soluble Fe_3O_4 NPs exhibited relatively high saturation magnetization ($83.4\ emu{\cdot}g^{-1}$), which allowed their highly-efficient magnetic separation from wastewater. The water-soluble magnetite as an adsorbent can directly dissolve in water without the help of mechanical stirring or any extraneous forces. In a related report,[129] water-soluble superparamagnetic Fe_3O_4 nanocrystals, prepared through hydrothermal approach (using Na_2CO_3 and ascorbic acid) at 160°C for 3 h and capped with $C_6H_6O_6$ (the oxidation state of ascorbic acid), could be readily dispersed in hydrated aqueous systems. The formation reactions *(5-7)* are as follows:

$$2Fe^{3+} + 3CO_3^{2-} + 6H_2O \rightarrow 2Fe(OH)_3 + 3H_2CO_3 \quad (5)$$
$$2Fe(OH)_3 + C_6H_8O_6 \rightarrow 2Fe(OH)_2 + C_6H_6O_6 + 2H_2O \quad (6)$$
$$2Fe(OH)_3 + Fe(OH)_2 \rightarrow Fe_3O_4 + 2H_2O \quad (7)$$

It was revealed that ascorbic acid not only serves as a reducing reagent for the reaction, but also the oxidation state of ascorbic acid involves surface coordination which renders the magnetite nanocrystals water soluble and the colloidal solution stable. At the same time, these nanocrystals are difficult to be dispersed in ethanol. In the rinsing process, the products were washed by water, but these nanoparticles could not be separated from the solution by centrifugation. Therefore, the same volume of ethanol was introduced to this solution, and these magnetic particles could be separated either by centrifugation or magnetic separation.

Stabilization of magnetic particles

MNPs, transferred to water or organic solvents or synthesized directly *in situ*, could be present in these phases during very different periods, depending on a series of factors: particle size, surfactant/coating/functionalizing agent, temperature, etc. In terms of practical uses, the aggregation and sedimentation of magnetic nanoparticles can significantly affect their mobility and reactivity and subsequently influence the interaction between them and environmental contaminants, among other applications. So, dispersing bare nanoparticles into a stable suspension within nanoscale range is an important step for studying the interaction of NPs with contaminants (e.g., toxic metals). Such common treatment as ultrasound frequently gives temporal dispersion in the majority of cases, with further precipitation. Stabilization of magnetic particles can be achieved by playing on one or both of the two repulsive forces: electrostatic and steric repulsion (Fig. 38).[130] Controlling the strength of these forces is a key parameter to elaborate particles with good stability. The steric force is difficult to predict and quantify. The electrostatic repulsion can be followed through the knowledge of the diffusion potential that may be very close to the zeta potential and the Debye-Huckel length that mainly depends upon the ionic strength and pH of the solution. Fig. 39 shows main types of stabilizers for magnetic particles.

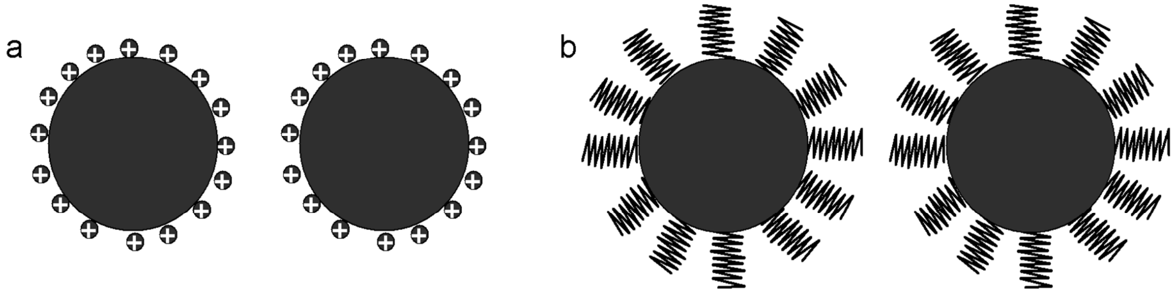


Fig. 38. (a) Particles stabilized by the electrostatic layer. (b) Particles stabilized by steric repulsion.

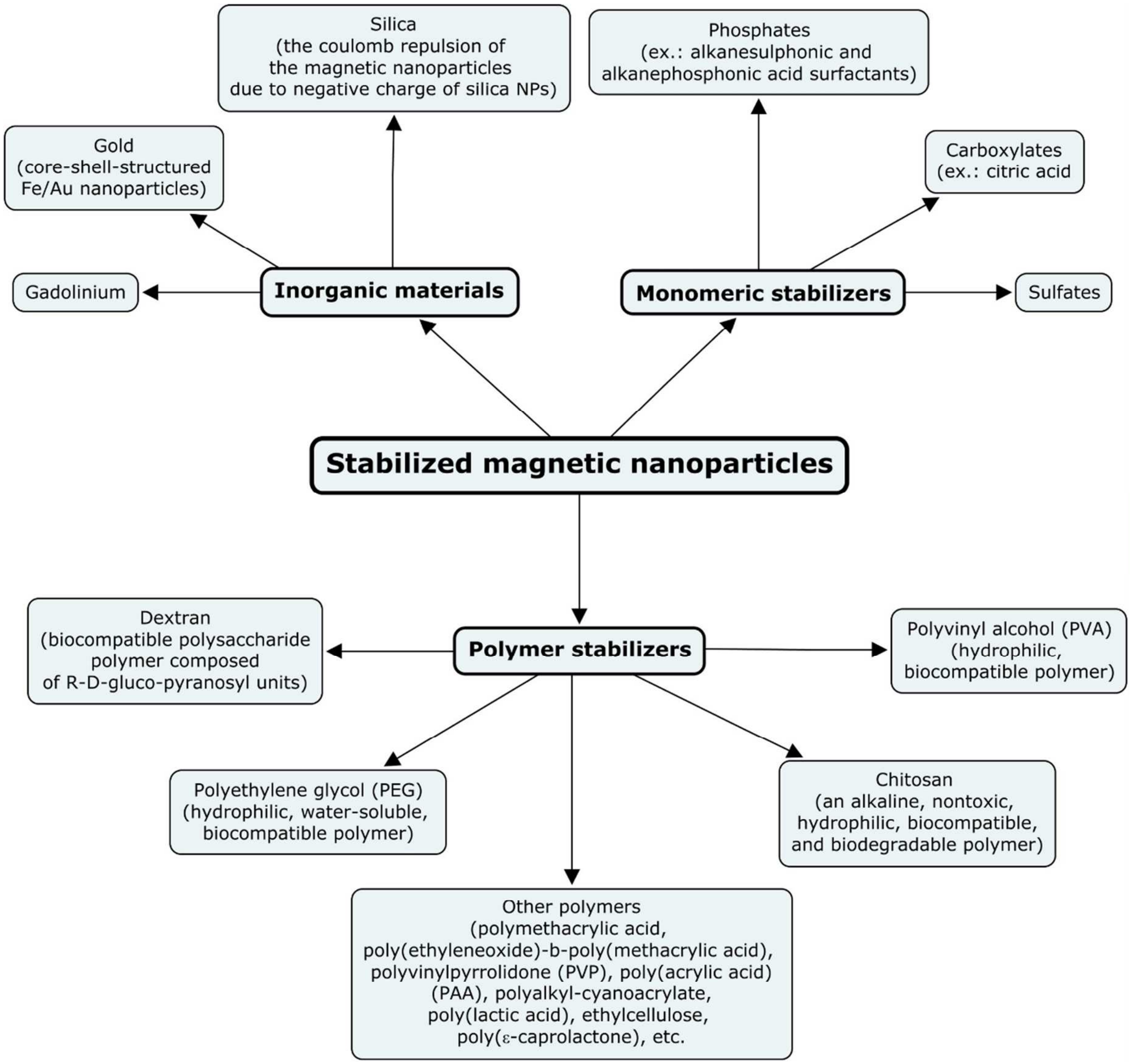


Fig. 39. Compounds used for stabilization of magnetic nanoparticles.

As a representative example of study of stabilization of MNPs in aqueous media, hydrophilic 2,3-dimercaptosuccinnic acid {HOOC-CH(SH)-CH(SH)-COOH, DMSA, Fig.

40} coated monodisperse magnetic nanoparticles (Fe_3O_4) were dispersed in water, RPMI-1640 with 10% (v/v) fetal calf serum, RPMI-1640, PBS and MES (4-morpholineethanesulfonic acid), respectively, to investigate their stability under biologically relevant conditions.[131] It was elucidated that DMSA-Fe_3O_4 nanoparticles exist as aggregate under biological conditions. The stability of DMSA-Fe_3O_4 nanoparticles dispersed in water, RPMI-1640 with 10% (v/v) fetal calf serum, RPMI-1640, PBS and MES, was quantified (Fig. 41). If nanoparticles are not stable and sedimentate rapidly, they can be monitored by a decreased absorbance as a function of time. It is shown that DMSA-Fe_3O_4 nanoparticles dispersed in water and RPMI-1640 with fetal calf serum present excellent stability, whereas those dispersed in RPMI-1640 without fetal calf serum, PBS and MES exhibited poor stability, because the loss of the former is less than 20% after five days, whereas the latter is larger than 80%.

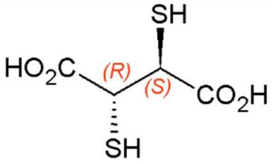
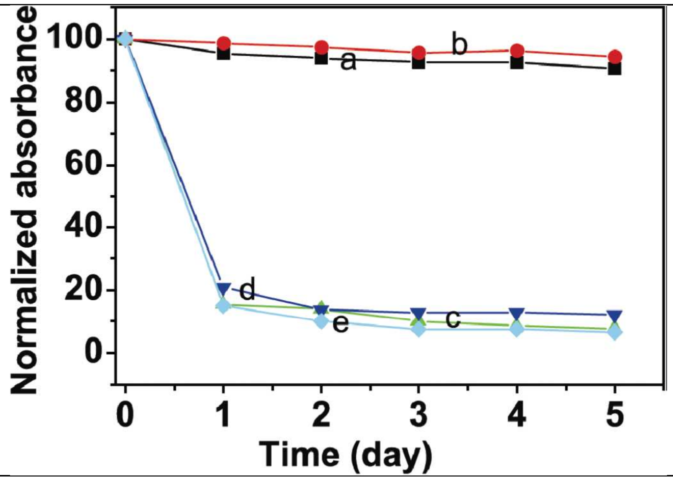
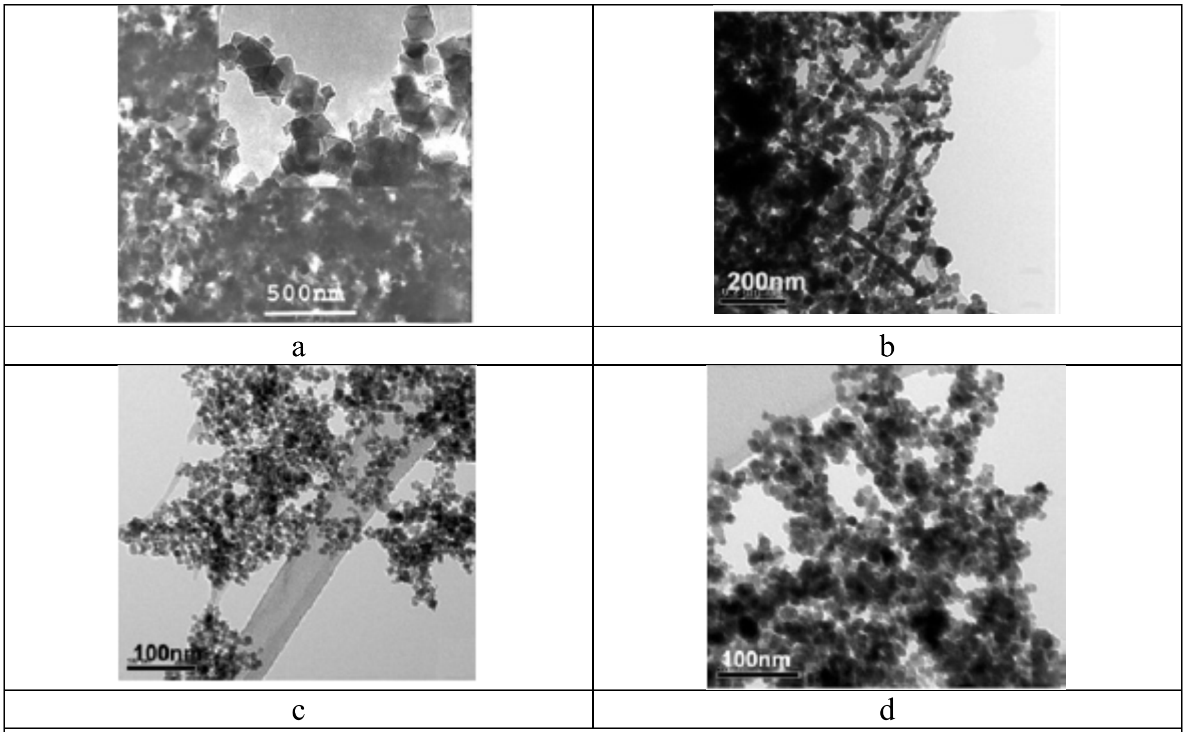
	

Fig. 40. DMSA molecule.	**Fig. 41.** Normalized UV-Vis absorbance of DMSA-Fe_3O_4 nanoparticles dispersed in (a) water, (b) RPMI-1640 with 10% (v/v) fetal calf serum, (c) RPMI-1640, (d) PBS and (e) MES, respectively, as a function of time. Reproduced with permission of *American Scientific Publishers* {Chen, Z.P.; Zhang, Y.; Xu, K.; Xu, R.Z.; Liu, J.W.; Gu, N. Stability of Hydrophilic Magnetic Nanoparticles Under Biologically Relevant Conditions. *J. Nanosci. Nanotechn.* **2008**, *8*, 6260–6265.}.

Special studies on MNPs solubilization and stability

Influence of precursors. Pure magnetite nanoparticles (Fe_3O_4) were synthesized in water by coprecipitation using two different approaches {from a) ferrous sulfate and b) a mixture of ferrous and ferric chlorides}.[132] It was observed that magnetite produced using ferrous sulfate could not be disaggregated, whereas magnetite produced from a mixture of ferrous and ferric chlorides could be disaggregated to a quasi-monodispersed form. The dispersing agents were tetramethyl ammonium hydroxide, Disperbyk 190 and polyacrylic acid (PAA). It was observed that the magnetic response of the washed, dispersed nanoparticles was significantly lower than that of the original material. The authors noted that type a) reactions produced magnetite particles that were rhombic in shape, with sizes ranging from 30 to 150 nm diameter (Fig. 42a), when the reaction was stirred in excess [OH^-], whereas material prepared under unstirred conditions and without excess [OH$^-$] exhibited a nearly monodispersed, spherical morphology of 40 nm diameter. Nanoparticles produced using this method appeared to aggregate in an ordered fashion (chain, Fig. 42b). Type b) reactions produced ultrasmall magnetite nanoparticles with sizes ~10 nm diameter (Fig. 42c). When TMAOH (tetramethyl ammonium hydroxide) was included in the synthesis (replacing NH_4OH), the product represented quasispherical nanoparticles of ~10 nm diameter (Fig. 42d). This material did not appear to aggregate in the same fashion as type a) materials.



a b

c d

Fig. 42. TEM micrographs of magnetite nanoparticles: a) prepared by type "a" reaction in the presence of excess [OH$^-$]; b) prepared by type "a" reaction without stirring and without excess of [OH$^-$] or [Fe^{2+}]; c) prepared by type "b" reaction in the presence of NH_4OH; d) prepared by type "b" reaction in the presence of dispersing agent TMAOH and without NH_4OH.

<u>*Simulation of state of dispersion*</u>. Monte Carlo simulation results predicting the state of dispersion (single, dimer, trimer, and so on) of citric-coated superparamagnetic iron oxide (Fe_3O_4) nanoparticles in an aqueous medium were compared with the experimental data for the same.[133] The simulation was performed by calculating the total interaction potential between two nanoparticles as a function of their interparticle distance (Fig. 43) and applying a criterion for the two particles to aggregate, with the criterion being that the minimum depth of the secondary minima in the total interaction potential must be at least equal to k_BT. The experiments showed that citric acid-coated particles were mostly in the form of aggregates whereas PAA-coated particles were isolated as individual particles. Both of these states of dispersion were predicted by the simulation. It was also observed a minimum shell thickness required for particles with a particular diameter, volume percentage, and grafting density in order for the dispersion to remain as isolated particles

and in a stable state. For both coating agents, suitable ranges of these experimentally controllable parameter values, which can be experimentally realized to obtain a stable dispersion of individual isolated nanoparticles, were established.

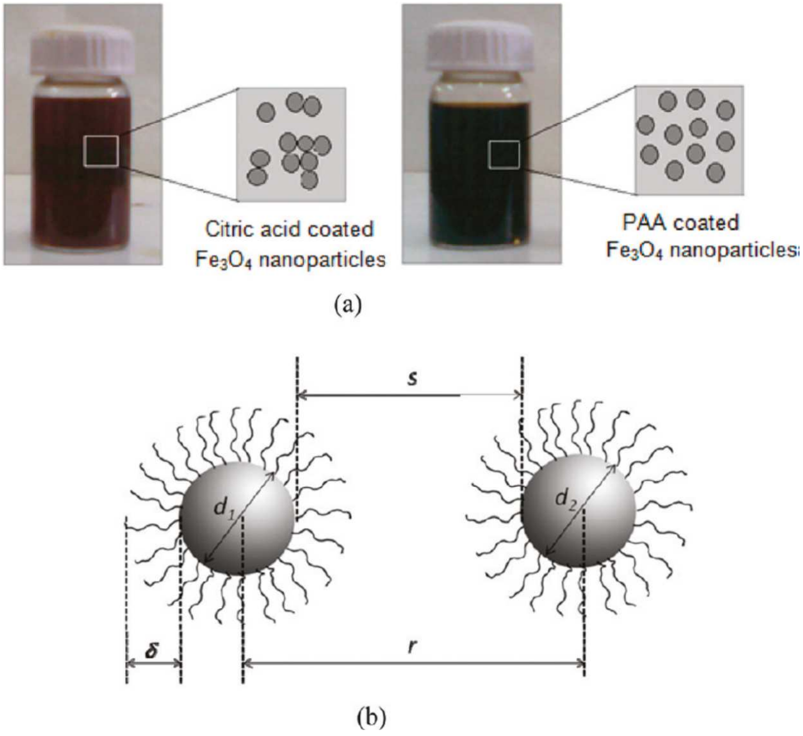


Fig. 43. (a) Stable aqueous dispersion containing citric acid- and PAA-coated Fe_3O_4 nanoparticles. (b) Schematic representation of two particles with diameters of d_1 and d_2 separated by a surface-to-surface distance (s) and a center-to-center distance (r). Reproduced with permission of *The American Chemical Society* {Kumar, S.; Ravikumar, C.; Bandyopadhyaya, R. State of Dispersion of Magnetic Nanoparticles in an Aqueous Medium: Experiments and Monte Carlo Simulation. *Langmuir*, **2010**, *26* (23), 18320–18330.}.

Additional ideas on the direct "hydrophobic → hydrophilic" transformation of MNPs. In addition to the described above, in general, there are three routes to modify hydrophobic NPs and render them soluble in aqueous biological buffers, as illustrated in Fig. 44.[134] In the *first approach*, ligand exchange, the native monolayer of hydrophobic surface ligands is exchanged with ligands containing head groups that bind the magnetic NP surface and hydrophilic tails that interact with aqueous solvent. For the transformation of oil-soluble type into water-soluble type functionalized IONPs, the ligand-exchange reaction is the major approach to realize this last aim. An *alternative solubilization strategy* in which the native hydrophobic ligands are retained on the magnetic nanoparticle surface is performed through the adsorption of amphiphilic polymers onto the nanoparticle. These two general surface modification strategies present water-solubilizing groups such as carboxyl acids and amines are capable of covalent conjugation with appropriate functional groups on the desired biomolecules. The *third route* for magnetic NP surface modification is the fabrication of an inorganic shell, typically consisting of silica or gold, by one of two general schemes: precipitation and reaction at the NP surface or deposition of preformed colloids onto the NP surface. As a representative example of this third approach, magnetic nanoparticles $MnFe_2O_4$ and Fe_3O_4 were stabilized by depositing an $Al(OH)_3$ layer *via* a hydrolysis process.[135] The particles displayed excellent colloidal stability in water and a high affinity to [^{18}F]-fluoride and bisphosphonate groups. The properties of particles were found to be strongly dependent on the thickness and hardness of the $Al(OH)_3$ layer which could in turn be controlled by the hydrolysis method. In particular, nanoparticulate $MnFe_2O_4$ is soluble in hexane, but insoluble in water due to the organic layer (oleylamine and oleic acid) on the surface. Once coated with $Al(OH)_3$, the NPs become soluble in water, but insoluble in hexane (Fig. 45). All these features suggest a coating of $Al(OH)_3$ replacing the oleylamine on the iron oxide NPs. However, it is necessary to take into account no obvious differences in size or morphology before and after coating with $Al(OH)_3$, which were revealed.

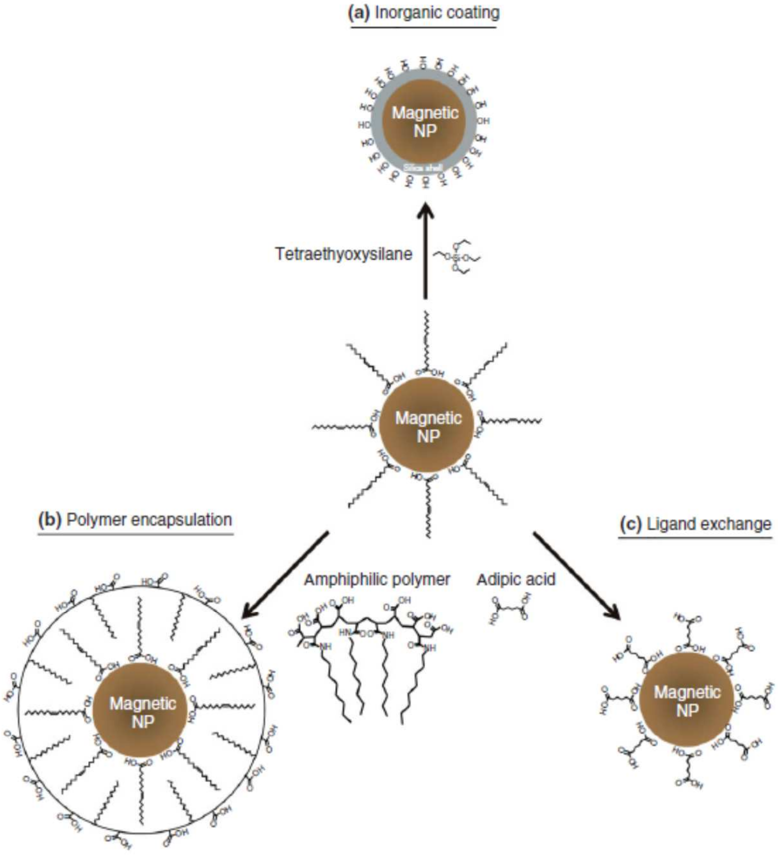


Fig. 44. General surface modification schemes for MNPs. (a) Inorganic surface coating with tetraethoxysilane produces an amorphous silica shell. Polymer coating encapsulates the magnetic NP and native surface ligands (b), whereas the ligand exchange is to replace native surface ligands (c). These routes present polar or charged functional groups onto the outer surface of the NP for water solubility. Reproduced with permission of *Wiley* {Dave, S.R.; Gao, X. Monodisperse magnetic nanoparticles for biodetection, imaging, and drug delivery: a versatile and evolving technology. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.*, **2009**, *1*, 583-609.}.

Fig. 45. Photographs of $MnFe_2O_4$ (*left*) and $MnFe_2O_4@Al(OH)_3$ (*right*) NPs in a two-phase mixture of hexane (upper layer) and water (lower layer).

Ultrasonic treatment: "to be or not to be?" To apply the ultrasonic treatment is the first appearing idea, when one needs to disperse insoluble NPs. Ultrasonic techniques in chemistry and technology are now classic tools described elsewhere. Sometimes, several studies are carried out to compare its effectiveness with other techniques. Thus, different techniques to disperse bare IONPs (vortex, bath sonication and probe ultrasonication) and the effects of important environmental factors such as dissolved organic matter and ionic strength on the stability of IONPs dispersions were investigated.[136] As a result, vortex minimally dispersed IONPs with hydrodynamic diameter outside the "nano-size range" (698–2400 nm). Similar to vortex, bath sonication could not disperse IONPs efficiently. Probe ultrasonication was more effective at dispersing IONPs (50% or more) with hydrodynamic diameters ranging from 120 to 140 nm with minimal changes in size and sedimentation of IONPs for a prolonged period of time, although probe ultrasonication did not break the IONPs down into the primary particle size. In addition, although sedimentation occurred to some extent, a considerable amount of IONPs remained in suspension in the presence and absence of 100 mg/L HA (humic acid) and 0.1 mM NaCl. Authors showed that high ionic strengths increased colloidal instability by compressing the electrical double layer thickness causing rapid aggregation and sedimentation. On the other hand, the electrostatic repulsive force dominated at low ionic strengths resulting in reduced destabilization of the dispersions.

Use of magnetic fields. We observed in different reports that magnetic fields can be applied both for aggregation and deaggregation of nanoparticles in general. Thus, for non-magnetic nanoparticles (for example silica or alumina), magnetohydrodynamic nanoparticle dispersion is an energy efficient method to deaggregate nanoparticles, combining hydrodynamic forces of turbulent flow with Lorentz forces generated by a magnetic field.[137] On the contrary, for MNPs, nanoparticle aggregation influenced by magnetic fields were studied on the example of FeO(OH).[138] The nanoparticles were shown to exist not only in stable (pH 2) and flocculated (pH 6) states, but also in a metastable aggregated state at intermediate pH between 3 and 5. Thus, colloidally stable nanoparticle suspensions of iron hydroxide FeO(OH) at pH 2 were prepared and shown to be non-magnetic. However, when the pH of the dispersion was raised to destabilize the suspension, aggregates near 200 nm diameter were detected and these were influenced by magnetic fields in the 50 kAm^{-1} range. These aggregates were unusual in that they were colloidally stable and did not behave as flocs. The authors called them "*nucleags"* (Fig. 46) to distinguish them from conventional flocculated agglomerates. Increasing pH, flocculation of the nanoparticles was observed and brown sludge, not influenced by magnetic fields, deposited on the base of the container. These metastable aggregates were influenced by small pH changes, showing that the adhesion between nanoparticles was small. The concentration of these metastable aggregates was very low, typically 5 ppb at pH 3.

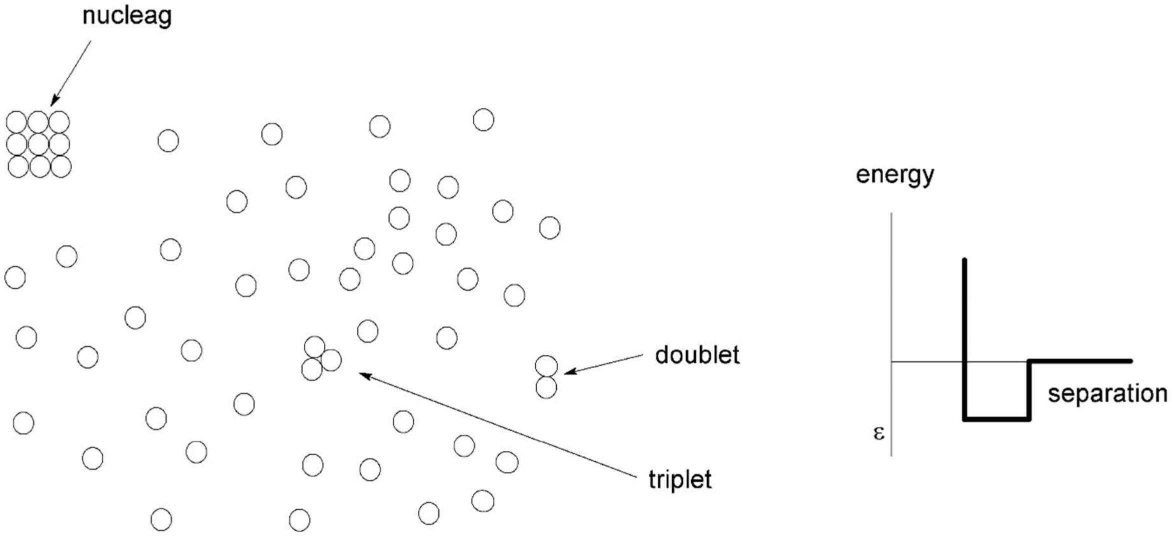


Fig. 46. (a) Schematic of dispersion containing metastable nuclei, defined as *nucleags*; (b) square well interaction potential between nanoparticles.

Conclusions and further outlook

Magnetic nanoparticles (generally on the iron basis) could be solubilized in water (more frequently, because of medical applications) or non-aqueous solvents for short or long time periods. Main approaches, needed to carry out this goal, are the suitable choice of precursors, pH, surfactants/coting agents and solvents, as well functionalizing agents for MNPs. Generally, MNPs are solubilized by functionalization with water-soluble compounds/moieties (in particular soluble polymers, porphyrins and calixarenes), in the conditions of thermal decomposition of low-stable metal complexes, coprecipitation, more rarely by microwave heating and other high-temperature methods. Polyol strategy is frequently applied for increasing MNPs solubility. Stabilization of MNPs could be achieved with aid of inorganic, monomeric and polymeric compounds. Regular functional groups in the surfactants and coating agents, used for dispersion of magnetic nanoparticles, are $–NH_2$ (oleyamine), –COOH and $–COO^-$ {oleic acid, DMSA, sodium oleate, citrates, as well as sodium salts of polymethacrylic and polyacrylic acids (PMANa and PANa)}, -OH {polyols (EG, DEG, TEG, TREG), Tiron, DA}, acetylacetonate anion. Other compounds include polymers (PNIPAm, PEO), small and larger macrocycles (calixarenes and porphyrin-type molecules), polysaccharides (dextran, sucrose), and biomolecules (peptides), among others.

The syntheses of soluble nanoparticles can be carried out both in water and in organic solvents. Use of sodium citrate and polyols generally results water-soluble polymers, meanwhile very frequent application of oleyamine and oleic acid could lead to solubility in solvents of distinct nature. 1-Octadecene, polyols, and especially water are the most used solvents; sometimes the same compound has a role of a solvent, surfactant, capping agent and/or reductant (PAA or polyols). Water ("greener" solvent) possesses obvious advantages in comparison with organic solvents and so it is mostly frequently used.

Currently, as it was seen above, not all experimental techniques, which are being used for the preparation of magnetic nanoparticles, are suitable for the synthesis of soluble or dispersed MNPs. Taking into account a host of applications for solubilized MNPs,[139] [140] [141] first of all in the area of bionanomedicine and treatment of contaminants in the environment, we believe that the number of solubilization and dispersion techniques precisely for aqueous systems will be increased considerably in the next 5-10 years.

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