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Review Article

Mussel-Inspired Polydopamine Coated Iron Oxide Nanoparticles for Biomedical Application

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Mussel-inspired polydopamine (PDA) coated iron oxide nanoparticles have served as a feasible, robust, and functional platform for various biomedical applications. However, there is scarcely a systemic paper reviewed about such functionalising nanomaterials to date. In this review, the synthesis of iron oxide nanoparticles, the mechanism of dopamine self-oxidation, the interaction between iron oxide and dopamine, and the functionality and the safety assessment of dopamine modified iron oxide nanoparticles as well as the biomedical application of such nanoparticles are discussed. To enlighten the future research, the opportunities and the limitations of functionalising iron oxide nanoparticles coated with PDA are also analyzed.

1. Introduction

Magnetic iron oxide nanoparticles are of great interest due to the unique properties stemmed from their extremely small size and large specific surface area [1]. They have been extensively investigated in recent years for the promising biomedical applications, such as drug delivery [2, 3], immunoassay analyzer [4, 5], magnetic resonance imaging [6, 7], and cancer hyperthermia [8]. For most of these applications, surface modification of iron oxide nanoparticles plays an important role in improving their hydrophilicity, colloidal stability, biocompatibility, and conjugation of bioactive functional groups. To this end, many materials have been employed to design stable surface coatings for iron oxide nanoparticles, such as polymers, surfactants, or inorganic shells [9, 10]. Surface modification of magnetic nanoparticles is mainly aiming at how to render their functionality and to control their solubility. For biomedical applications and bioanalysis, the ability to solubilize the nanoparticles in water and to modify their surfaces with molecules, proteins, oligonucleotides, or other targeting agents is a crucial step toward their widespread use [11]. However, the cumbersome steps and harsh conditions, such as toxic organic solvents utilized as reaction media, are often seemed as the barriers to the modification processes. Therefore, surface modification with aforementioned materials is still a challenge so far to us, which appeals for a facile, feasible, and aqueous approach to achieve controllable surface coatings for iron oxide nanoparticles.

Nowadays, dopamine and its derivatives have enjoyed success as agents for the masking of magnetic nanoparticles, often so as to provide their biocompatibility with medium to long-term colloidal stability in the various biological milieu [12]. Recently, Lee et al. pioneered a one-step formation of robust adherent polydopamine (PDA) films based on mussel-inspired polymerization of dopamine at alkaline pHs on various substrates [13]. Because of the ease of the use as well as its fascinating properties, PDA has attracted great interest for wide applications. Notably, the application of PDA to iron oxide nanoparticles has emerged as a particularly important field. Controllable PDA films can be formed on the iron oxide nanoparticles by simply dispersing them in an alkaline dopamine solution and mildly stirring at room temperature [9]. Dopamine derivatives provide a novel and useful alternative for surface immobilization schemes. For example, dopamine derivatives have been used to anchor

small functional biomolecules onto ferromagnetic nanoparticles for protein separation [14, 15]. Obviously, dopamine and its derivatives open a new route to the modification of iron oxide nanoparticles [16].

In this review, certain aspects on PDA coated iron oxide nanoparticles, including the synthesis of iron oxide nanoparticles, the mechanism of self-oxidation of dopamine, the interaction between iron oxide nanoparticles and dopamine, and the functionality and safety assessment of dopamine modified iron oxide nanoparticles as well as their biomedical application, are discussed. The opportunities and the limitations of functionalising the surfaces of iron oxide nanoparticles coated with PDA are also analyzed.

2. Synthesis of Iron Oxide Nanoparticles

The quality of iron oxide nanoparticles, such as crystallization, size, and shape, highly depends on the synthesis approaches, which can produce well-crystallized and size-controlled iron oxide nanoparticles and offer more opportunities for their biomedical applications. Among all the chemical synthesis methods, hydrothermal may be one of the most widely reported [17, 26, 27]. In such method, a relative high temperature and a high pressure were often employed to induce or affect the formation of nanocrystals. The advantages of this method, such as high reactivity of the reactants, facile control of product morphology, and good crystallization of products, are apparent. Ge et al. reported a one-step hydrothermal approach to the synthesis of iron oxide nanoparticles with controllable diameters from 15 to 31 nm, narrow size distribution, and high saturation magnetization in the range of 53.3–97.4 emu/g, in the presence of $FeCl_2{\cdot}4H_2O$ in basic aqueous solution under an elevated temperature and pressure [17] (see Figure 1). With $FeSO_4{\cdot}7H_2O$ and $FeCl_3$ as precursors and NaOH as hydrolysis reactant, Khollam et al. achieved spherical iron oxide nanoparticles with a size range of 150–200 nm via a microwave hydrothermal reaction [26]. Obviously, the solubility of reactants and desired products via this method is critical.

Coprecipitation is another one of most widely reported methods to fabricate iron oxide nanoparticles [18, 28, 29]. In general, an alkaline solution, such as NaOH and $NH_3{\cdot}H_2O$, was often employed to precipitate Fe^{2+} and Fe^{3+} ions in an aqueous solution. Due to the nanoparticles achieved by dehydration from the intermediate iron hydroxides, the surfaces of as-prepared nanoparticles were covered with large number of hydroxyl groups and the nanoparticles could be well suspended in an aqueous solution. Roth et al. prepared superparamagnetic iron oxide nanoparticles with size between 3 and 17 nm and saturation magnetizations from 26 to 89 emu/g via coprecipitation. They found that particle saturation magnetization could be enhanced by addition of more iron salt into the reaction system and employment of a molar ratio of Fe^{3+}/Fe^{2+} below 2 : 1 [28]. Basuki et al. reported their work to prepare magnetic nanoparticles with in situ coprecipitation of Fe^{2+} and Fe^{3+} ions in aqueous solutions in the presence of functional block copolymers. They varied the ratio of copolymer to Fe to wield control over nanoparticle diameters within the range of 7–20 nm. They found that the amount of polymer employed during the coprecipitation proved critical in governing crystallinity and colloidal stability [18] (see Figure 2). In addition, Xia et al. developed a complex-coprecipitation method to synthesize iron oxide nanoparticles with triethanolamine as ligands to govern the quality of iron oxide nanoparticles. In this case, triethanolamine was used mainly for limiting nanoparticles growing rate due to its chelation to Fe^{3+} and Fe^{2+} [29]. Because the most coprecipitation reactions carried out at low temperature and their reaction kinetics can be only controlled by changing reactants, it is difficult to optimize the size and size distribution of nanoparticles and to achieve high crystalline or control the particle shape in coprecipitation route.

Recently, high-temperature decomposition of organometallic precursors was found to be one of the most efficient approaches to fabricate iron oxide nanoparticles with well-controlled size and shape [30–33]. Sun and Zeng gave the first report on iron oxide nanoparticles preparation by thermal decomposition of $Fe(acac)_3$ in the presence of surfactants, oleylamine, and oleic acid. With this method, uniform iron oxide nanoparticles with size between 4 and 16 nm were achieved [30]. Kucheryavy et al. synthesized magnetite nanoparticles in the size range of 3.2–7.5 nm with high yields using high-temperature hydrolysis of the precursor Fe^{2+} and Fe^{3+} ions alkoxides in diethylene glycol solution. The average sizes of the particles were adjusted by changing the reaction temperature and time and by using a sequential growth technique [31]. Alternatively, Fe–oleate complex was also employed as the precursor for large scale synthesis, up to 40 g of iron oxide nanoparticles obtained in a single reaction, by Park et al. [32]. Moreover, the work that iron oxide nanoparticles with 4.5 nm core size were synthesized by thermal decomposition of $Fe(CO)_5$, followed by air oxidation with a ligand 4-methylcatechol, was also reported by Xie et al. [33].

3. Self-Oxidation of Dopamine on Iron Oxide Nanoparticles and Their Interaction

Dopamine, known as a small-molecule mimic of the adhesive proteins of mussels, is liable to be oxidized to generate a thin PDA layer on iron oxide nanoparticles surface (see Figure 3) [19]. At a weak alkaline solution, dopamine is susceptible to undergo self-oxidation to produce adherent PDA coatings on virtually any substrates and catechol groups are oxidized to the quinine form [13, 25, 34]. The catechol functionality of dopamine is primarily responsible for moisture-resistant adhesion and the oxidized o-quinone functionality is primarily responsible for cross-linking [35]. Virtually any substrate can be functionalized by first depositing PDA followed by secondary derivation reaction including self-assembled monolayers through the deposition of long-chain molecular building blocks, metal films by electroless metallization, bioactive functionalities, and even cross-linking reaction [19].

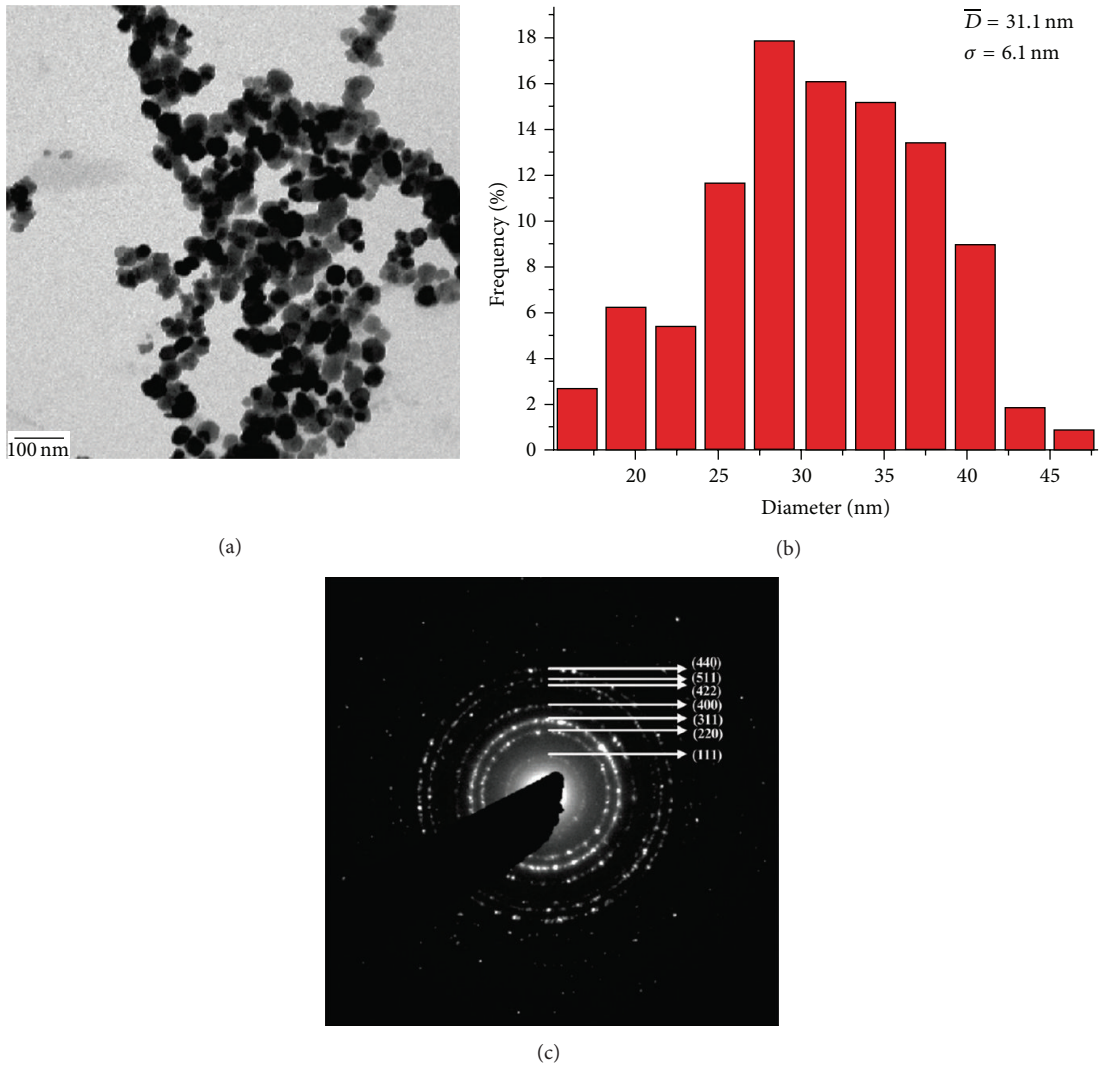
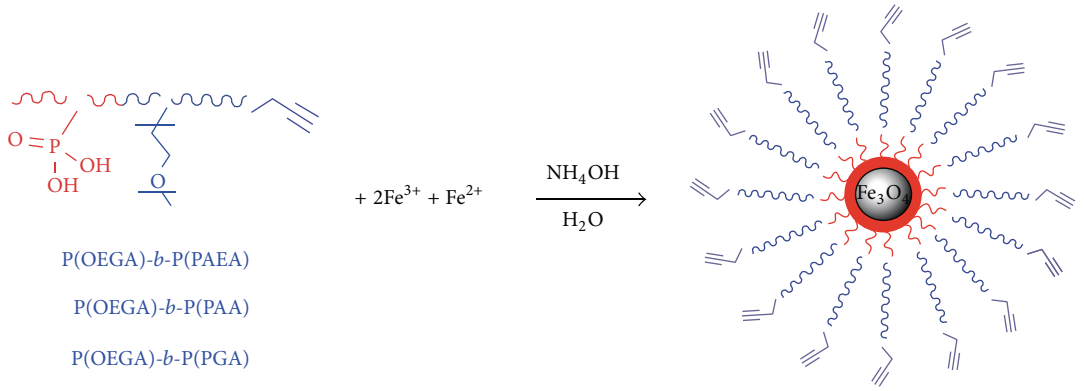


Figure 1: A typical TEM image (a), size distribution histogram (b), and SAED pattern (c) of iron oxide nanoparticles [17].

Shultz and his coworkers [20] found that an initial PDA structure formed with coordination to the surface of magnetic nanoparticle resulted from improved orbital overlap of the five-membered ring and a reduced steric environment of the iron complex (see Figure 4). A semiquinone is therefore formed via transfer of electrons to the iron cations on the surface and rearrangement of the oxidized dopamine. Oxygen on the surface was liable to be protonated because of free protons in the system and form Fe^{3+} in the aqueous solution. Consequently, the reactivity between Fe^{3+} and dopamine quickly facilitates the degradation of the nanoparticles.

The solvents also play an important role in the self-oxidation of dopamine. The presence of ethanol is found to significantly slow down the polymerization rate of dopamine and make the surface modification of nanomaterials with PDA more controllable in comparison to the water-phase polymerization [21, 36]. PDA can provide a simple and versatile method for surface modification of iron oxide nanoparticles and a promising building block towards functional materials (see Figure 5).

The interaction between PDA and iron oxide nanoparticles has been widely investigated by many groups. The method of Park and coworkers [32] was used for the preparation of iron oxide nanoparticles from iron(III) oleate. Mussel adhesive protein served as the inspiration for their surface coatings, which was composed of a polysaccharide containing pendant dopamine anchors. This composite ligand made use of multiple surface-dopamine interactions for surface attachment. Due to the large difference in the affinities of PDA-hyaluronic acid and oleic acid for the particle surface, the initial electrostatic interaction between the positively charged particle layer and the ligand-conjugate was replaced by a covalent interaction between the particle surface and the dopamine catecholates. Amstad et al. [22] synthesized dopamine derivative anchor groups possessed irreversible binding affinity to iron oxide which can optimally disperse magnetic nanoparticles under physiologic conditions. This not only leads to ultrastable iron oxide nanoparticles but also allows close control over the hydrodynamic diameter and interfacial chemistry (see Figure 6). Iron(III) in solution



Polymer/Fe ratio	IONP@P(PAEA)-*b*-P(OEGA)	IONP@P(AA)-*b*-P(OEGA)	IONP@P(GA)-*b*-P(OEGA)
1 : 4	Black	Black	Black
1 : 2	Brown	Brown	Black
1 : 1	Brown	Orange	Black
2 : 1	Orange	Yellow	Black
4 : 1	Yellow	Yellow	Brown

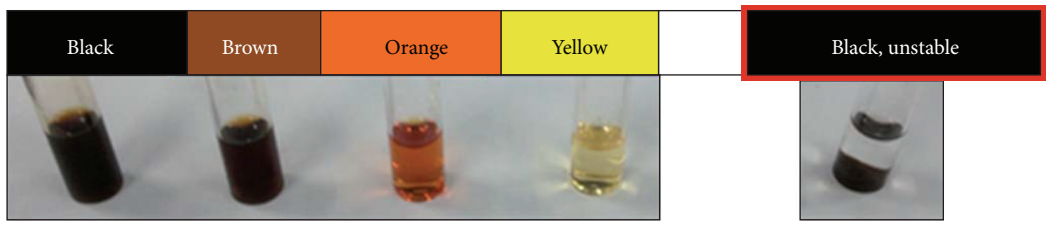


Figure 2: In situ coprecipitation of IONPs at different polymer-to-iron ratio [18].

forms extremely stable complexes with bidentate dopamine. For example, a stability constant of 1044.9 has been determined for the octahedral complex. Given the large stability constants for these complexes, it is no doubt that catecholate groups are found in siderophores, molecules which evolved to sequester iron from the external environment and in adhesive proteins. Hence the widespread use of dopamine-derived surface modification for iron oxide nanoparticles functionalisation is based on the well-studied bonding interactions in iron dopamine complexes [12].

4. Functionality of PDA Coated Iron Oxide Nanoparticles

As mentioned above, PDA provides a number of advantages, such as ease and convenience to modification on iron oxide nanoparticles for further functionalization with biomolecules, chemical reactivity, near-infrared absorption, and high fluorescence quenching efficiency [37–39]. Besides, PDA film exhibits a special zwitterionicity: PDA layer is positively charged and allows good permeability of negatively charged small molecules at low pH, while it is negatively charged and allows good permeability of positively charged molecules at high pH. The fully reversible and pH-switchable permselectivity may be conferred with potential applications in drug delivery or other biomedical applications [40]. PDA shell can also be further surface functionalized to improve selective recognition with cells [41, 42]. PDA coatings with significant ability of enhancing the adhesion and proliferation of cells show good biocompatibility and promise for tissue engineering [43, 44]. PDA-coated iron oxide nanoparticles were also proved to have negligible cytotoxicity [45]. Furthermore, the functional properties of nanoparticles, including

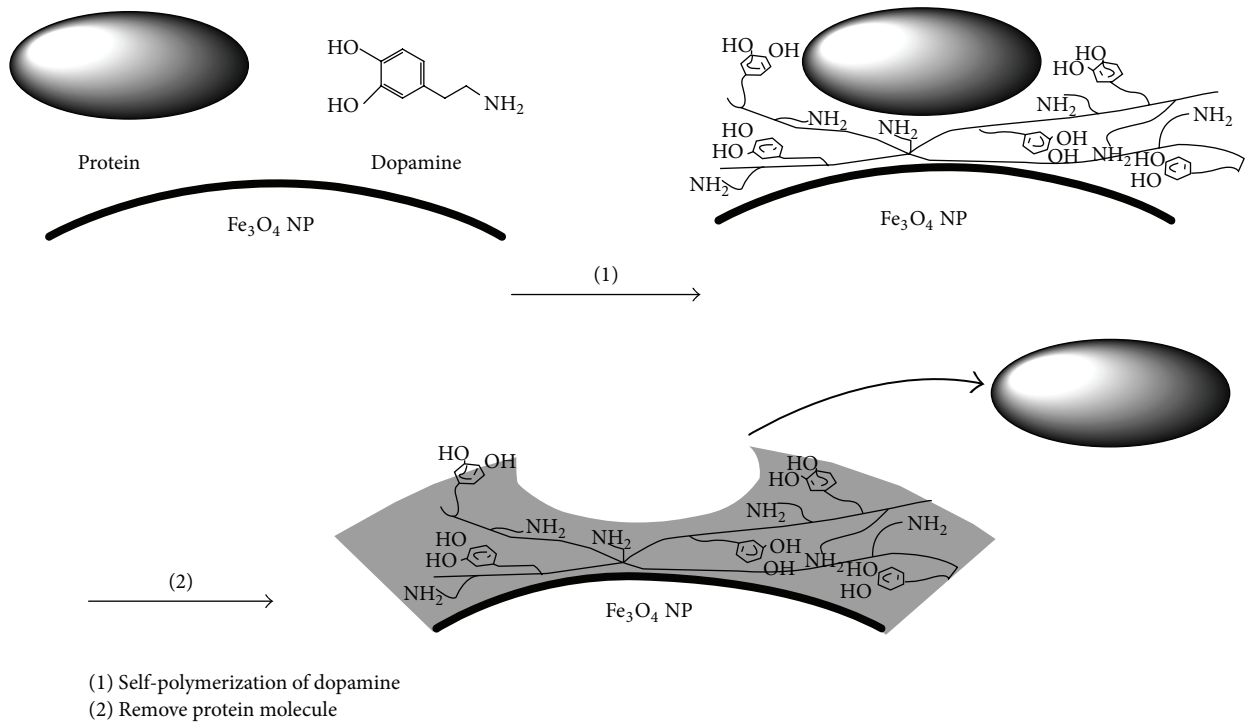


Figure 3: Formation of template imprinting PDA layer on Fe_3O_4 nanoparticles surface [19].

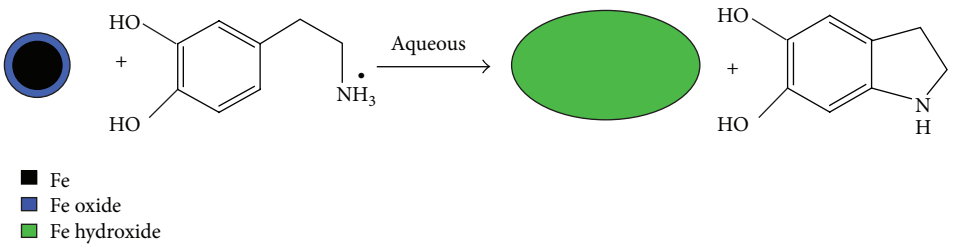


Figure 4: Illustration of reactive nature of dopamine as a surface functionalization agent in iron oxide nanoparticles [20].

enhanced magnetization and increased superparamagnetic blocking temperature, could be significantly improved via dopamine adsorption on iron oxide nanoparticles [46]. This was attributed to change from microstructure of the magnetic dead layer on the particle surface, which promoted magnetic ordering in the surface layer. A one-step reaction strategy was employed by Mazur et al. [23] to integrate several reactive sites onto iron oxide nanoparticles. Such particles, with size of 25 nm, were achieved by simultaneous modification with differently functionalized dopamine derivatives. Different termini, amine, azide, and maleimide functions enable further functionalization of iron oxide nanoparticles by the grafting-on approach (see Figure 7).

To enhance the functionality and thus to broaden the application of PDA coated iron oxide nanoparticles, many groups have done lots of effort. Kemikli et al. [47] obtained monosize sub-7 nm porphyrin coated magnetite nanoparticles via dopamine anchor with high crystallinity and well defined superparamagnetic behavior at room temperature. Zhou et al. [19] encapsued iron oxide nanoparticles with PDA in the presence of human hemoglobin, yielding imprinted particles with preserved magnetic properties for their separation after exposure to targeting proteins. The versatility of the hemoglobin imprinted iron oxide nanoparticles was tested in a competitive binding assay using five different nontemplated proteins. In all assays, the relative binding of hemoglobin was over 80%, suggesting that those iron oxide nanoparticles have the potential to serve as affinity materials for protein separation and detection. With an ethanol-mediated oxidative polymerization of dopamine, Yue et al. [21] have achieved surface modified iron oxide nanoparticles. They found that the PDA coatings can dramatically reduce the cytotoxicity of nanomaterials and enhance their biocompatibility.

With the application environments (pH, temperature, ionic strength, illumination and time) in mind, the stability of PDA layer on iron oxide substrates is especially important for their application. A comparison of the stabilities of dopamine hydrochloride and 3,4-dihydroxybenzaldehyde for magnetic nanoparticles was carried out by Basti et al. [48] aiming at preparing novel MRI contrast agents.

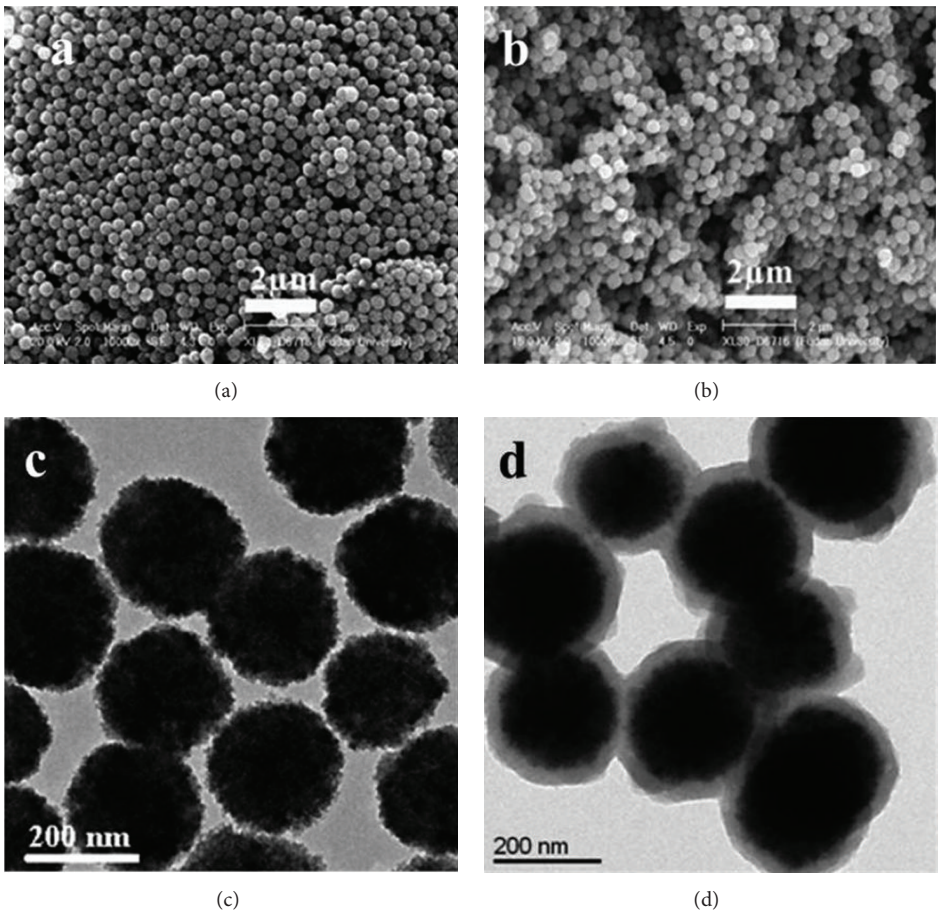


Figure 5: SEM (a and b) and TEM (c and d) images of (a and c) the Fe_3O_4 nanoparticles and (b and d) the Fe_3O_4@PDA core–shell particles [21].

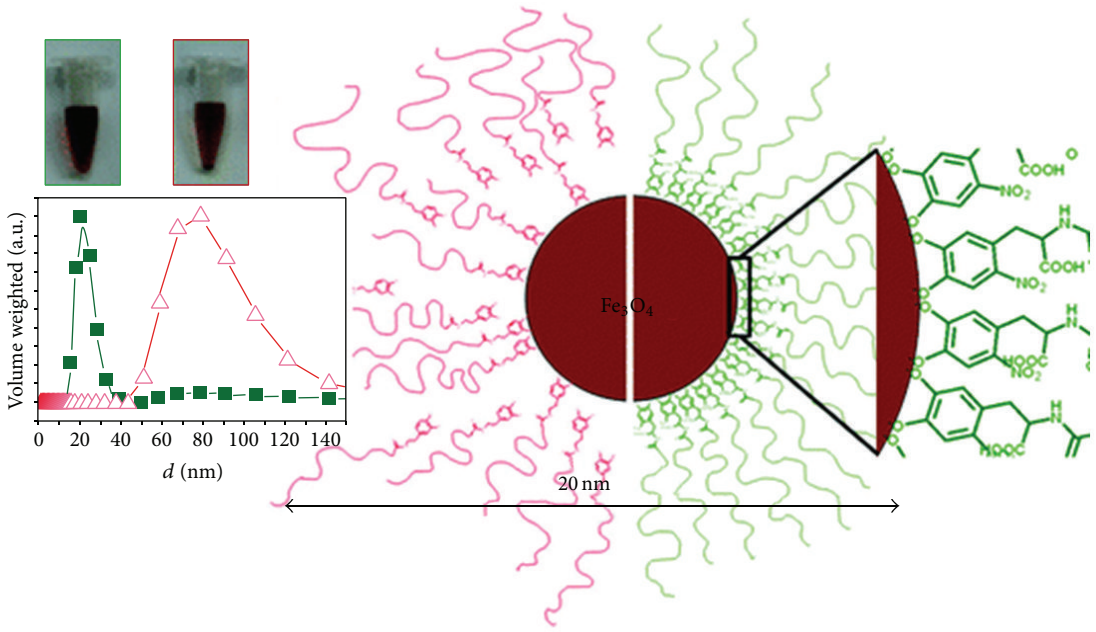


Figure 6: Dopamine-derivative anchor groups with irreversible binding affinity to iron oxide and optimal dispersity to superparamagnetic nanoparticles under physiologic conditions [22].

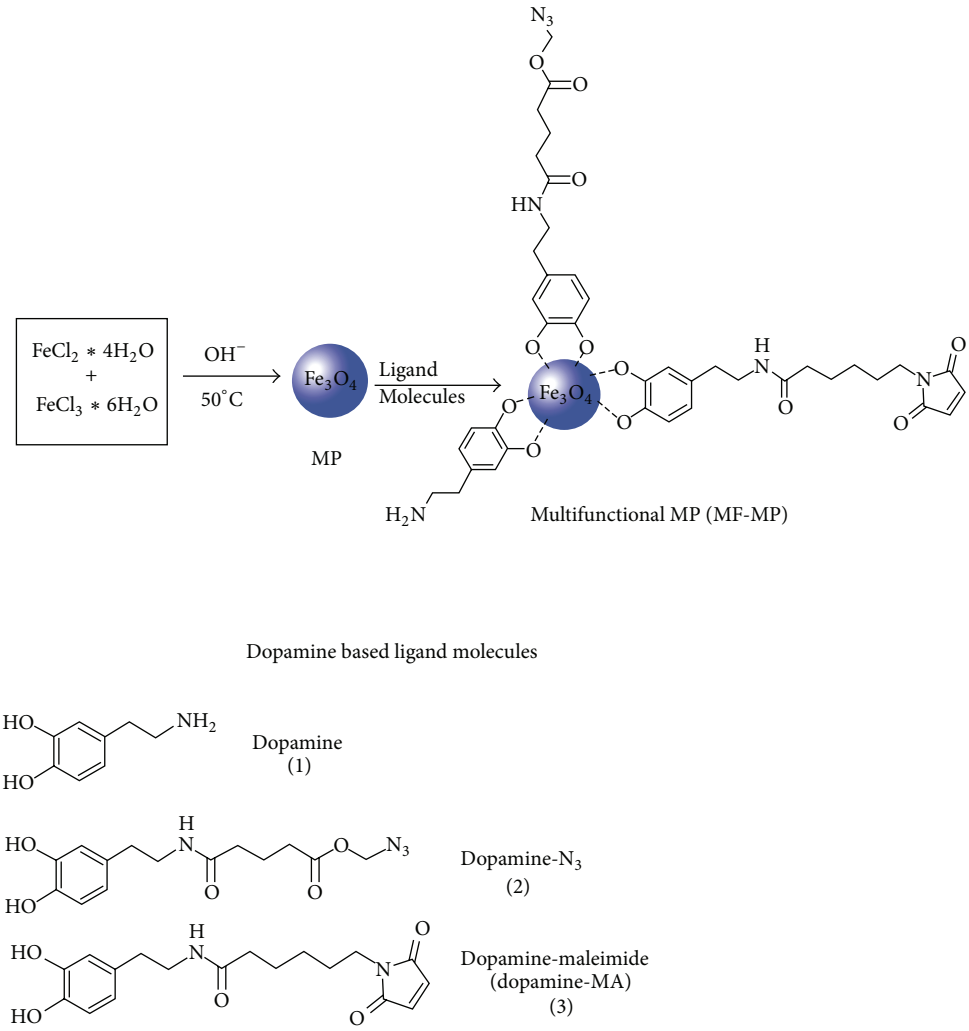


Figure 7: Schematic illustration of the formation of iron oxide nanoparticles with several reactive sites based on the use of differently functionalized dopamine derivatives [23].

Although both ligands coordinated the particle surface, thermogravimetric and calorimetric analyses indicated that 3,4-dihydroxybenzaldehyde did not have as high a grafting density as dopamine for magnetic nanoparticles. Hence, only dopamine was found to be suitable for stabilisation in aqueous environments, owing to its dense surface coverage. The formation of PDA layers on surfaces in aqueous solution probably indicates its good stability in aqueous environment. Dopamine is susceptible to oxidation itself, whereas PDA is more stable. The mPEG-dopamine-coated magnetite nanoparticles were stable at 70°C in the buffers when pH values are greater than 7 [49]. Moreover, dopamine-based anchor on iron oxide surfaces exhibited exceptional stability to heating and high salt concentration [50], with its thermal stability satisfying the requirement of hyperthermia therapy [14]. Amstad et al. reported dopamine derivative anchor groups having irreversible binding affinity to magnetite nanoparticles under physiological conditions [22]. Iron oxide nanoparticles modified with PEG-dopamine could be freezedried and stored as a powder for at least three months or alternatively redispersed in pure water and stored for at least four months without noticeable change in particle stability. Particularly, the suspensions of PEG-nitrodopamine modified iron oxide nanoparticles can experience multiple cycles of diluting and heating free of nanoparticle agglomeration. Recently, highly crystalline and hydrophobic magnetite nanoparticles have been modified at the surface in the presence of dopamine with the advantages that the stability provided by a polypeptide shell covalently bonded to the magnetite surface through a dopamine anchor molecule instead of other noncovalent interactions [51].

For some potential applications, the PDA layer on magnetite nanoparticles must prove their robustness in variable environments, but relevant data are, so far, very rare. For example [16], the stability of PDA shell in vivo should be seriously taken into account. It is known that PDA will degrade oxidatively with the existence of strong alkaline or hydrogen peroxide [52]. For the in vivo case, Bettinger et al. [43] showed that the implant dopamine thin films seemed to degrade in tissue within eight weeks, where the gross

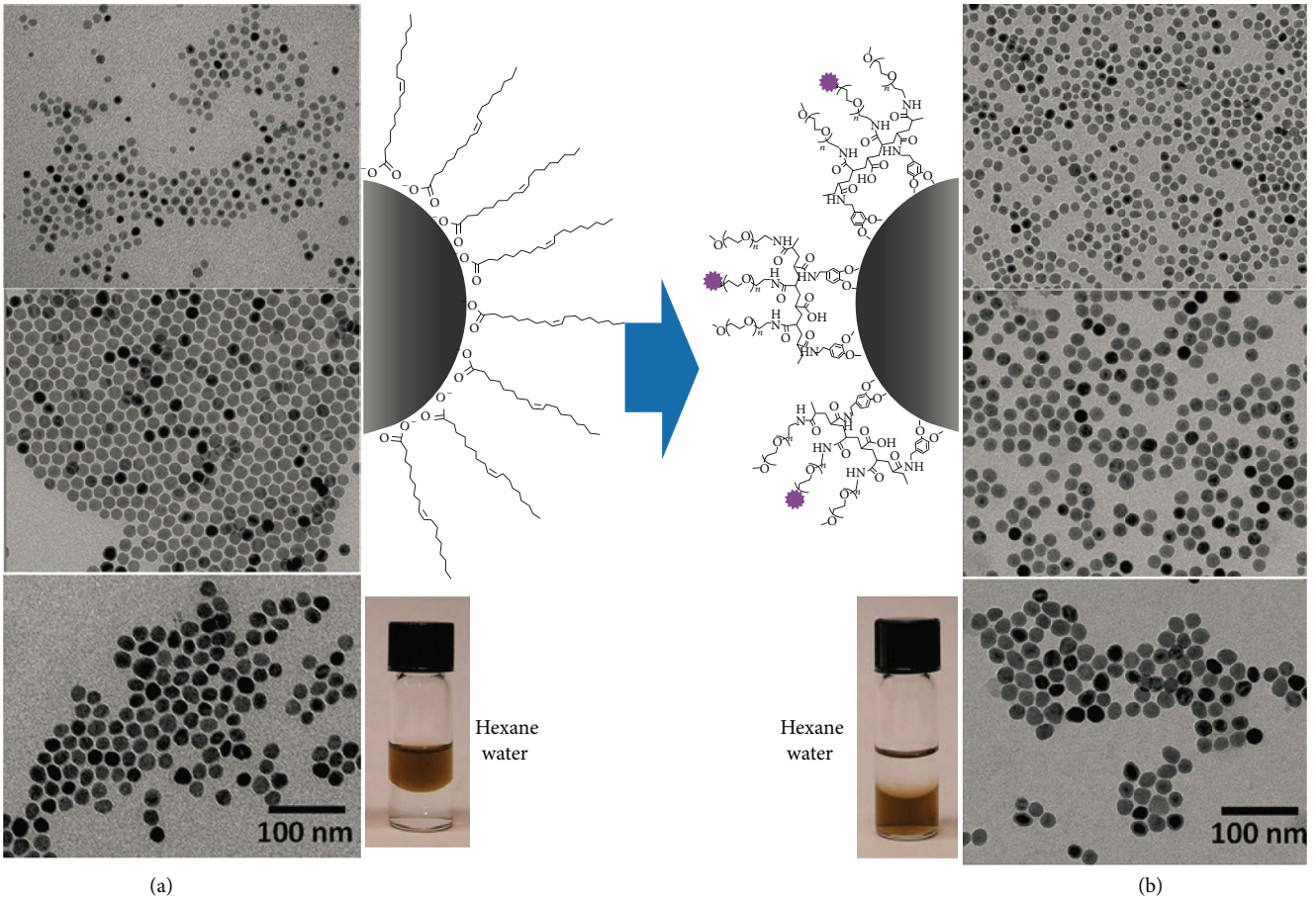


FIGURE 8: TEM images of Fe_3O_4 NPs with 11, 17, and 23 nm core size before (a) and after (b) ligand exchange with OligoPEG-Dopa. Schematic representation of the NP with the corresponding surface cap along with images of the organic and aqueous dispersions are shown [24].

erosion of the dopamine implant was fully completed. It could be attributed to the rigid properties of dopamine implants, which resulted in fracture of the implant after insertion into the host. The existence of dopamine nanoparticles could have allowed immediate uptake by macrophages and giant cells. However, it is still unanswered whether PDA, especially at the nanoscale, is degradable in vivo as well as within cells [53].

5. Safety Assessment on Polydopamine Coated Iron Oxide Nanoparticles

As mentioned above, PDA coating served as a useful method of surface functionalization on iron oxide nanoparticles due to the ability of this compound to form a nanometer-scale organic thin film on virtually any material surface to which many molecules are able to be attached. But a fact should not be neglected that dopamine is potentially individually highly neurotoxic molecule [54]. Thus evaluation of toxicity of PDA coated iron oxide nanoparticles should be carried out before their application, but to date less reference was found closely related to these aspects except the reports from Na et al. [24], Postma et al. [55], Xie et al. [15, 56], and Wei et al. [57].

Na et al. prepared a set of PDA and polyethylene glycol- (PEG-) derivatized oligomers, OligoPEG-Dopa on iron oxide nanocrystals (see Figure 8), which served as MRI T2 contrast, and applied MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay to test the potential cytotoxicity of these NPs to live cells. Finally, they found no measurable toxicity to live cells [24]. Postma et al. carried out the cell experiment with PDA/Fe_3O_4 capsules via a cell viability assay, showing that the 1 μm capsules at the tested concentrations are not inherently cytotoxic for LIM1215 cells [55]. The work of Xie et al. demonstrated that the uniform PEG-Fe_3O_4 nanoparticles with catechol bonding brought about negligible aggregation in cell culture condition and much reduced nonspecific uptake by macrophage cells, meaning that these particles can escape from the innate immune system [15]. In addition, Xie et al. utilized dopamine modified iron oxide nanoparticles to yield nanoconjugates that could be easily encapsulated into human serum albumin (HSA) matrices. In order to assess their biophysical characteristics, the HSA coated iron oxide nanoparticles were labeled with both 64Cu-DOTA and Cy5.5 and tested in a mouse model via subcutaneous U87MG xenograft. The particles were manifested a prolonged circulation half-life

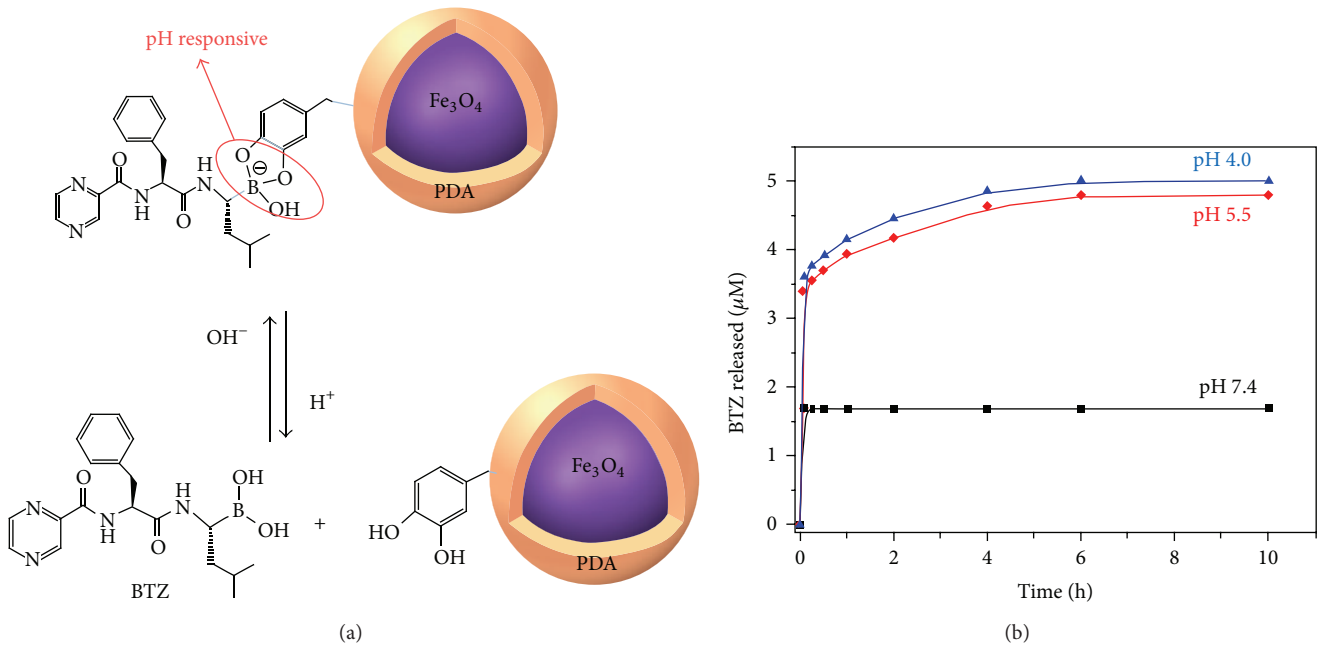


FIGURE 9: (a) Schematic of pH-dependent boronic acid–catechol conjugates on hybrid core–shell nanoparticle. (b) Time-dependent release of BTZ from Fe_3O_4@PDA core–shell nanoparticles as a function of solution pH ranging from 4 to 7.4 [25].

and showed massive accumulation in lesions, high extravasation rate, and low uptake by macrophages at the tumor area [56]. Compact and water-soluble zwitterionic dopamine sulfonate (ZDS) ligand coated superparamagnetic iron oxide nanoparticles were prepared by Wei et al. [57] and their in vitro performance and in vivo performance relative to nonspecific interactions with HeLa cells and in mice were both evaluated. They found that those particles showed only small nonspecific uptake into HeLa cancer cells in vitro and low nonspecific binding to serum proteins in vivo in mice.

6. Biological Applications

The synthesis of dopamine functional magnetic nanoparticles is one of the most active areas in advanced materials as their surfaces allow conjugation of biological and chemical molecules, thus making it possible to achieve target-specific diagnostic in parallel to therapeutics [23]. Surface modification of diatom frustules with dopamine terminated iron oxide nanoparticles was confirmed active and available for the attachment of targeting ligands by Losic et al. [58]. Sustained release over 2 weeks of poorly water-soluble drug indomethacin from magnetic diatom structures has been demonstrated and is expected to serve as magnetically guided microcarriers with the potential to open new prospects for noninvasive and targeted drug delivery.

Polymer capsules are considered to be another desirable mean as drug delivery vehicles. Emulsion droplets, loaded with magnetic nanoparticles prior to the PDA deposition, yield about 1 μm sized cargo-loaded PDA capsules [59]. A pH-sensitive manner was also used on Fe_3O_4@PDA NPs for the controlled drug release via reversible bonding between catechol and boronic acid groups of PDA and the anticancer drug bortezomib (BTZ) [25] (See Figure 9). The released amount of BTZ was pH dependent, with a greater concentration observed at lower pH values.

As universal nonfouling materials, PEGs were linked to surfaces using dopamine [13] and showed excellent resistance to serum protein adsorption [60]. A dopamine-PEG based ligand was used to stabilize uniform 9 nm magnetic nanoparticles in physiological conditions and against nonspecific uptake by macrophage cells. Such advantages provide an opportunity for enhancing the efficiency in target-specific drug delivery and increasing the signal-to-noise ratio in MRI [15].

Peng et al. [61] have linked dopamine as spacer molecules to iron oxide nanoparticles. They found that the existence of the spacer molecule on magnetic nanoparticles could greatly improve the activity and the storage stability of bound trypsin through increasing the flexibility of enzyme and changing the microenvironment on nanoparticles surface compared to the naked magnetic nanoparticles. Yuen et al. [12] prepared core-shell magnetic molecularly imprinted polymers for protein recognition. The lysozyme-imprinted Fe_3O_4@PDA nanoparticles show high binding capacity and acceptable specific recognition behavior towards template proteins.

In addition, magnetic nanoparticles have been largely used for efficient magnetic resonance imaging. Xie et al. [62] reported an approach to prepare dopamine-plus-HSA (human serum albumin) to functionalize iron oxide nanoparticles, resulting in nanoconjugates with high efficiency in labeling various types of cell lines, and the application in vivo MRI on xenograft and focal cerebral ischemia models was further demonstrated. Lin et al. [39] prepared Fe_3O_4@PDA

NCs with the ability to act as theranostic agents for intracellular mRNA detection and multimodal imaging-guided photothermal therapy. Generally speaking, the staining of the target cells by nonfouling nanoparticles is the prerequisite for this technique. The application usually requires designated molecules to be anchored onto the surfaces of magnetic nanoparticles. However, there are not very effective methods to modify Fe_3O_4, to which solution dopamine provides great opportunity by displaying very good affinity to Fe_3O_4. For example, Xie et al. reported peptide coated iron oxide nanoparticles via dopamine that act as a contrast agent used in MRI in vivo tumor detection. Moreover, the cellular uptake was dramatically increased due to multivalent binding of the functionalized iron oxide nanoparticles [33].

Immobilization of lipase on appropriate solid supports has been considered as an effective way to improve their stability and activity and could be reused for large scale applications. Ren et al. developed a lipase immobilization method by use of PDA coated iron oxide nanoparticles. 73.9% of the available lipase was immobilized on PDA coated iron oxide nanoparticles under optimal conditions, yielding a lipase loading capacity as high as 429 mg/g with enhanced pH and thermal stability compared to free lipase and the ease of isolation from the reaction medium by magnetic separation. This work made the immobilization of enzyme onto magnetic iron oxide nanoparticles via polydopamine film more economical, facile, and efficient [63].

Taking the advantages of PDA coatings into account, the applications will expand in the near future. Although biomedical application by such reports show promise, their potential needs to be further determined [64].

7. Conclusions and Perspectives

Dopamine and its derivatives can efficiently and facilely modify iron oxide nanoparticles and yield functional surfaces. The surface modification relies largely on the interactions between nanoparticles substrate and PDA or their derivatives. Modified iron oxide surfaces exhibited the best stability due to the stronger adhesion [65, 66]. Although the details of the thermodynamics, kinetics, and mechanisms of dopamine self-oxidation keep unclear to date, the strong binding of dopamine represents a robust and feasible approach for the surface modification of iron oxide nanoparticles [16]. A large number of functionalities of such nanoparticles have been developed via the optimization of polymerization, the selection of dopamine ligands, or even more deeply insight with the quick appearance of advanced instruments.

This strategy may be utilized in increasing areas, including but not limited to biomedical application because of potential long term stability in wet conditions and resistance to oxidation. Future research may be directed towards an even more universal dopamine in physiological environments or at other complex conditions. For better application in biomedical areas, in vivo and in vitro safety assessment of PDA coated iron oxide nanoparticles should be carried out completely. Thus more questions about the modification, the functionality, and the application of PDA coated iron oxide nanoparticles, according to those environments or conditions, should be better answered with broad and deep interdisciplinary content.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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