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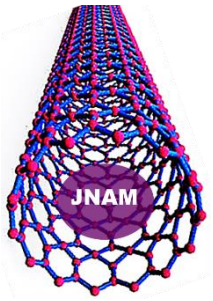
Superparamagnetic Iron Oxide Nanoparticles (SPIONs): Preparation and Recent Applications



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Abstract: Superparamagnetic iron oxide nanoparticles (SPIONs) resemble a unique class of nanomaterials with distinguished magnetic properties and biocompatibility, thus they have recently grasped the attention of researchers. SPIONs have various applications in fields such as -but not limited to- diagnostics, drug delivery, biosensing and bioimaging. The ability to control these nanoparticles by applying an external magnetic field made them perfect nanomaterials for such wide range of applications. Moreover, SPIONs have unique surface chemistry allowing for surface functionalization/coating with different organic or inorganic materials and thus making them suitable for different aspects. This review summarizes the most recent methods proposed for synthesizing SPIONs suitable for different applications. In addition, the amazing properties of SPIONs are discussed herein. Finally, an overview about some of the recent applications of SPIONs is introduced.
Keywords: SPIONs; Drug delivery; Magnetic nanoparticles; Paramagnetic materials; Surface functionalization; Functional materials.

1 Introduction

Nanotechnology represents a novel platform in the development of most types of effective biomaterials which have a contribution in treatment processes either in therapeutic or diagnostic applications. Superparamagnetic iron oxide nanoparticles (SPIONs) have grasped special attention due to their proven biocompatibility and strong magnetic properties making them super candidates for different bioapplications. SPIONs are paramagnetic and exhibit super magnetization behavior at particle size of 10-80 nm at certain temperature [1,2].

SPIONs show significant response towards external magnetic field and lose their magnetization in absence of that magnetic field. In addition to their magnetic properties, SPIONs have other properties that make them potential agents for several bioapplications such as their high surface area-to-volume ratio, their unique surface chemistry and biocompatibility [3]. Basically, surface-functionalized SPIONs consist of three main components: a) iron oxide (Fe_3O_4) core, b) a coating material (usually a polymeric material) and c) a targeting agent that makes them more specific for a certain mission [4]. SPIONs with the previously-mentioned properties and structure contributed significantly in fields such as drug delivery, hyperthermia for cancer treatment, diagnoses of different diseases, biosensors and MRI technology for bioimaging (**Fig. 1**). Although most of these applications are still in the preclinical stages, they are expected to reshape the future of therapeutic nanomaterials in a promising extent [4].

Recently, SPIONs showed deep penetration into bacterial biofilms while applying an external magnetic field, leading to a high therapeutic index against *S. epidermidis* and *S. aureus* infections [5]. In a study published by Taylor et al., SPIONs in a concentration range of 10–2000 μg/mL were able to kill up to 25% of *S. epidermidis* populations in a 48-hour old biofilm, proving that SPIONs can be used to prevent implant infections [6]. It was proven that surface functionalization of SPIONs is a crucial factor influencing their antimicrobial activities. For example, coating of SPIONs with materials such as silver or gold promotes their antimicrobial activity against biofilms [7].

Due to their very interesting properties as well as their importance in many applications, we summarize herein the

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possible synthesis routes, properties and recent applications of SPIONs, shedding the light on chemotherapy, hyperthermia, drug delivery, imaging and biosensing.

2 Synthesis of SPIONs

Metallic ferrous NPs are widely applied in therapeutic, diagnostic, and real-time imaging research fields. There are three main iron oxides that fall under the category of SPIONs; namely, magnetite (Fe_3O_4), maghemite (γ-Fe_2O_3) and hematite (α-Fe_2O_3). Moreover, ferrites, which consist of mixed iron oxides along with other transition metal ions (e.g. Cu, Co, Mn, and Ni), are also known to exhibit superparamagnetic properties [8]. The magnetic properties of these metal oxides vary significantly with variations in particle size and crystallinity. Magnetite is predominant amongst its counterparts. It is composed of Fe^{2+} and Fe^{3+} ions in a ratio of 1:2.

During the 1970s, an exhaustive research exploring the magnetic properties of iron oxides NPs and their synthesis was implemented [9]. Sugimoto *et al.* were the pioneers in establishing a co-precipitation method to prepare well-defined spherical magnetite NPs using ferrous salt in the presence of potassium nitrate and potassium hydroxide [10]. Recently, the same research group [11] developed a sol–gel method for producing well-structured magnetite, maghemite and hematite with defined size and shape (spherical/ellipsoid). Precipitation from solution is a vital method of crystallization in which monodispersed NPs shall be obtained via an initial uniform nucleation phase followed by crystal growth [12]. Additionally, multiple nucleations were also used to prepare uniform NPs by Oswald ripening [13]. In this approach, large uniform crystals form by crystal growth through the dissolution of small crystallites. Moreover, aggregation of small crystallites through coalescence can lead to the formation of uniform larger sized particles [14]. Alternatively, Massart [15] attempted the addition of base to an aqueous solution of ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions in a 1:2 stoichiometry in an oxygen-free environment which successfully produced a black precipitate of spherical magnetite NPs of uniform size. Massart's methods for magnetite synthesis produced smaller (<20 nm) spherical particles compared to Sugimoto's method which produced larger particles (30-200 nm) of rhombic (stirred condition) and spherical (static condition) morphologies [16], making it the most commonly used method.

Crystal growth in solution is interface-controlled up to a certain critical size beyond which the growth gets controlled by diffusion. Thus, controlling the crystal growth step in the co-precipitation route is crucial for obtaining nanometer-sized SPIONs [17]. To this end, the microemulsion (water in oil) method, in which water droplets act as nanoreactors promoting the precipitation of iron oxides, is the preferable method used. In this method, water droplets are surrounded by micelles with the organic solvent acting as unreactive continuous phase. Conceivably, the size of the synthesized NPs is dependent on the size of water droplets [18].

Fig.1: Some of the important applications of SPIONs.

Many different SPIONs synthesis approaches are available. The solvothermal route has been recently deployed by Zhang *et al.* [19] to fabricate hollow magnetite NPs. Moreover, solvent-free thermal decomposition route was also used recently for the preparation of SPIONs [20]. Furthermore, biomimetic synthesis of SPIONs using magnetotactic bacteria has been performed [21]. Interestingly, Jia *et al.* [22] successfully synthesized single-crystal magnetic nanorings on a large scale using the hydrothermal route.

Amongst the recent approaches with promising commercial scale-up potential are spray and laser pyrolysis. In spray pyrolysis, a solution of Fe^{3+} salt and reducing agents is sprayed through a series of reactors followed by evaporation of the solvents along with solute condensation within the aerosol droplets. Further drying and thermolysis of the precipitated product at high temperature takes place resulting in microporous solids [23]. On the other hand, laser pyrolysis deploys a continuous-wave carbon dioxide laser to heat a flowing mixture of gases, in-turn initiating and sustaining a chemical reaction. Homogenous nucleation of particles is promoted within the reaction zone above a certain pressure and laser power [24].

From the abovementioned section, it is clear that the synthesis method dictates the applicability of SPIONs. Accordingly, SPIONs can be classified according to their size ranging from micrometer-sized (300 nm–3.5 µm) to standard (10–150 nm) and to ultra-small (<10 nm) iron oxide crystals. Such variation in size imposes advantages and disadvantages that should be taken into consideration when using SPIONs. Generally, for *in-vivo* biomedical applications, NPs biodistribution is size-dependent which should be optimized to avoid either sequestration or an early renal clearance. Moreover, the NPs life-time in the blood stream as well as enhanced local accumulation are also size-dependent [25]. Having this mentioned, the characteristics and biomedical applications of SPIONs will be comprehensively discussed onwards.

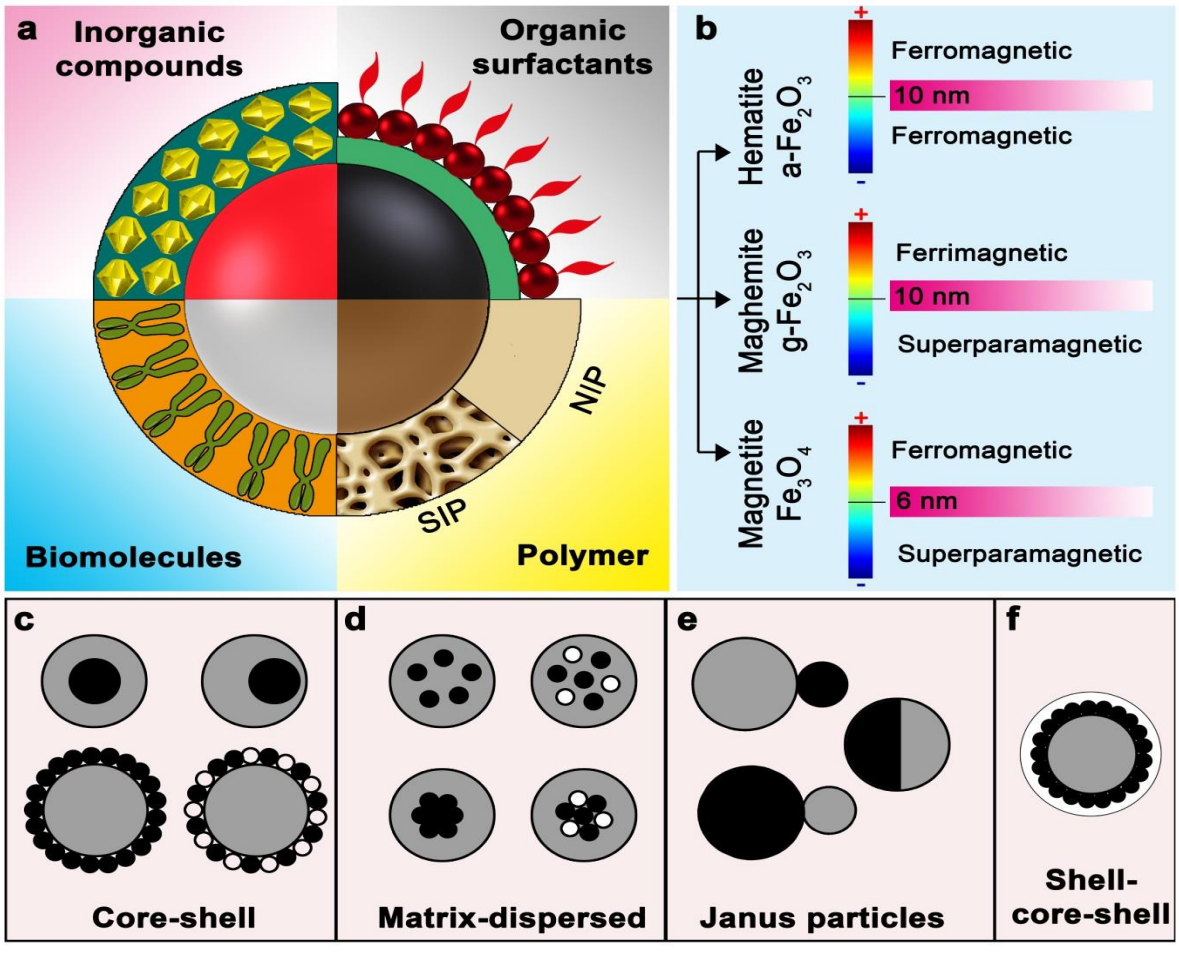

Fig. 2: Surface functionalizations, properties and structures of SPIONs. (a) Possible ways of SPIONs surface modificaton (the four basic SPIONs colors are depicted in the central nanoparticle; SIP: surface-imprinted polymer; NIP: nonimprinted polymer), (b) the three chemical structures of SPIONs and their size-dependent magnetic properties, and (c-f) structural differences of SPIONs which can be obtained by applying various synthesis protocols (black: SPION; grey: functional material A; white: functional material B).

3 Characteristics of SPIONS

3.1 Color and Stability of SPIONs

Iron oxides vary significantly in their color according to their oxidation state and composition (**Fig. 2**). This not only makes them distinguishable but also affects their stability. Ferrous oxide, known as Wüstite, exhibits a black color. Ferric oxides are classified into four different subtypes (α, β, γ and ε) whose colors are among grey, brown and red. Hematite, made of α-Fe_2O_3, is both kinetically and thermodynamically stable. On the contrary, maghemite which is composed of γ- Fe_2O_3 is only kinetically stable. Furthermore, maghemite is known to be metastable meaning that it turns slowly into a stable iron oxide form (hematite) accompanied with significant reduction of magnetization. Finally, magnetite is composed of mixed black iron oxides, Fe_3O_4 or $FeO.Fe_2O_3$ and is known to exhibit the most powerful magnetic behavior [26].

3.2 Magnetic Properties of SPIONs

SPIONs exhibit the phenomenon of *"superparamagnetism, SPM"*, which means that they get magnetized till the saturation magnetization upon the application of an external magnetic field, and they lose any residual magnetic interaction once the magnetic field is removed. Saturation magnetization of SPIONs and their size are reported by Varanda *et al.* to be linearly correlated [27]. This phenomenon generally arises at a size range of 10–20 nm due to the accompanying changes in the surface curvature. At such a small size, these NPs do not possess multiple domains as found in bulk magnets; but they become a single magnetic domain acting as a *"single super spin"* that exhibits high magnetic susceptibility. Thus, upon exposure to a magnetic field, these NPs respond rapidly with minimal residual magnetization and coercivity [25].

Thus, the magnetic property is clearly size-dependent (**Fig. 2**), as magnetite and maghemite both exhibit SPM at room temperature when the size is <6 nm and <10 nm, respectively. However, magnetite (≥6 nm) and hematite are both ferromagnetic, and maghemite (≥10 nm) is ferrimagnetic. Unlike the previously-mentioned iron oxides, hematite does not show SPM at a size <10 nm at room temperature, but it rather demonstrates Morin transition (a.k.a. spin-flop transition) below a critical temperature (~260 K) to be antiferromagnetic. Such transition can be suppressed by reducing crystallinity and/or size of the NPs (≤10–20 nm) [26]. More in-depth explanation about magnetic properties and terminology can be found in the review reported by Wallyn *et al.* [28].

The main advantage of employing SPIONs in biomedical applications is to use SPM nanostructures exhibiting the highest magnetic saturation along with least toxicity. SPM behavior enables the targetability of SPIONs to their site of action guided by the applied external magnetic field. Moreover, once the applied magnetic field is removed, the magnetic particles retain no remnant magnetism at room temperature with low tendency of agglomeration, thus evading uptake by phagocytes and increasing their half-life in the circulation, and minimizing the risk of thrombosis. Although SPM of NPs can be improved through using larger sizes, yet its application is limited by increased toxicity [29].

3.3 Surface Charge of SPIONs

The surface charge is crucial for colloidal stability and biodistribution of SPIONs. Surface charge is controlled by surface groups in electrolyte solutions of certain pH. Sun *et al.* [30] studied the effect of excess surface concentration of Fe^{2+} and Fe^{3+} ions on the zeta potential of SPIONs. Zeta potential of magnetite had positive and negative values in the absence of multivalent cations in acidic and basic solutions, respectively. Furthermore, in the presence of excess iron cations, specific adsorption took place at the surface of magnetite, considerably affecting its zeta potential. In a given medium, crystallinity, smoothness/roughness, hydrophobicity/hydrophilicity of SPIONs are important for their *in-vivo* applications; all of which determine the residence time of SPIONs in the circulation [31]. One other factor affecting surface charges is the oxidation state of the iron ions on the surface of SPIONs, which can be affected by medium composition including surfactant exposure. It has been reported that the oxidation state of the iron ion can have a potential effect on the morphology of the prepared nanoparticles. For instance, iron ions in the trivalent state (3+) favor the formation of the spherical shape, whereas metal ions in the divalent state (2+) favor the formation of nanorods [32].

Finally, for biomedical applications, the chemical composition, size distribution, shape and angle of curvature of SPIONs control their interactions with biological fluids. Coey *et al.* [33] found that the surface charge of SPIONs regulates their cellular interaction, especially during endocytosis and phagocytosis. Recently, Osaka *et al.* [34] reported a correlation between the surface charge of magnetite NPs and their cellular uptake efficiency into different cell lines. Moreover, surface charge controls the *in-vitro* or *in-vivo* opsonization process (i.e. adsorption of plasma proteins that facilitate phagocytosis of the particles by macrophages) [35]. Moghimi *et al.* [36] proved that the lower the size and the higher the hydrophilicity of the NPs, the less efficient is the opsonization process.

4 Applications of SPIONs

4.1 Drug Delivery and Cancer Targeting

The main aim of drug delivery is to improve dynamics of a pharmaceutical compound inside the body by increasing its efficacy, limiting its toxicity and reducing its effective dose. SPIONs gained high research interests due to their unique physical and chemical properties. Their surface properties allow for easy coating of the particles with different types of polymeric materials either via physical interaction or direct chemical bonding. In addition, SPIONs have high surface-to-volume ratio that enables higher loading capacity for the loaded drug. After coating, SPIONs are biocompatible and safe so that the cytotoxicity could be significantly limited [4].

SPIONs have greatly contributed in developing drug delivery especially in cancer chemotherapy. Loading such chemotherapeutics on SPIONs as a delivery system helped to reach the cancerous tissue more effectively and avoid the healthy cells as well. There are two basic targeting approaches in drug delivery, active and passive approaches. The passive approach takes the advantage of the enhanced permeability and retention effect (EPR) of the cancer tissue. In that case the blood supply to the cancer tissue is increased and its leaky vasculature enables the blood to cross the tissue carrying the loaded chemotherapeutics in SPIONs. Although EPR effect is useful in passive targeting it has some drawbacks such as low selectivity and high distribution of SPIONs through the whole body. Hence a new targeting method, active targeting, was developed in order to increase the selectivity of the drug carriers. The main idea of this approach is adding a targeting agent on the surface of the carrier particles possessing receptors with high expression in the cancer tissues such as vitamins, antibodies and peptides so the distribution could be limited only to the cancer region [4].

One of the most effective polymeric coatings of SPIONs is the combination of folic acid (FA) and polyethyleneimine (PEI) conjugate. FA receptors have significantly higher expression in cancer tissues than in their normal counterparts making them a potential tumor targeting agent. PEI increases SPIONs stability and prevents their agglomeration besides making them biocompatible and safe for absorption. In one of the studies [37], FA-PEI-SPIONs conjugate was prepared and characterized, and the resultant cellular uptake was observed to be higher than control samples indicating the significant improvement in selective targeting [37].

Another study in modifying SPIONs as a potential drug targeting system was reported based on chitosan as a coating material. Chitosan is a natural polymer which grasped researchers' attention due to its biocompatibility and positively charged surface functional groups. This surface chemistry makes it strongly attractable towards the negatively charged cell membrane to serve the targeting sake. In this study [38], SPIONs were prepared with chitosan as a coating and capping agent via co-precipitation method, and then the anticancer drug doxorubicin (DOX) was loaded on the coated SPIONs. The prepared drug conjugate showed higher cellular uptake than the free DOX, in addition to the desirable slow and sustained release pattern [38].

4.2 Hyperthermia for Cancer Control

Hyperthermia is one of the techniques used for cancer control and treatment. The name comes from a Greek origin, "*hyper*" means rise and "*therme*" means heat [39]. This treatment method is based on the idea that normal cells can withstand elevated temperatures ranging from 41°C to 46°C while cancer cells cannot and start apoptosis (programed cell death) [40,41]. Despite the great benefits of hyperthermia, this technique also has several limitations and constrains represented in some undesirable side effects such as burns, some biological dysfunctions, blisters and pain which limit its application to only the localized solid tumors and make the process impossible in some cases such as dynamic leukemia [40]. Nanotechnology represented by SPIONs offers significant improvements to hyperthermia in order to overcome the previously-mentioned limitations. SPIONs produce focus generated heat inside the targeted cells after having the advantage of specific targeting either by being manipulated by a strong external magnetic field or being linked with ligands specific to cancerous cells [40,41].

In 1957 the first SPIONs-based hyperthermia for cancer treatment was reported. In this study, SPIONs were prepared in size between 20 nm and 100 nm and then heated by 1.2 MHz. The recorded temperature was around 43-46°C and the final result was significant death of metastases stages in lymph nodes [42]. Other preclinical trials on esophagus and prostate cancers were reported in which the co-treatment with SPIONs hyperthermia shows greater improvement when coupled with surgery and chemotherapy [43,44]. The effective heat generated by SPIONs depends on several factors such as magnetization strength, colloidal stability and the rate of surface absorption. In fact SPIONs have a promising surface chemistry making them suitable for different types of coatings to produce variable modified particles and to allow best control for the previously mentioned factors in order to a) increase SPIONs stability, b) reduce their toxicity and c) increase their magnetization response [45].

4.3 Biosensing Applications

The biosensing mechanisms are based on the ability of a bio-recognition element to interact with a specific analyte and trigger a specific change inside the biological environment which can be transduced into a corresponding signal by a suitable transducer. Interestingly, SPIONs are suitable candidates for biosensors applications because they exhibit high electrocatalytic activity and large surface area for adsorption (**Fig. 3**). Moreover, iron oxide nanoparticles are usually produced with a controlled crystallinity, thus

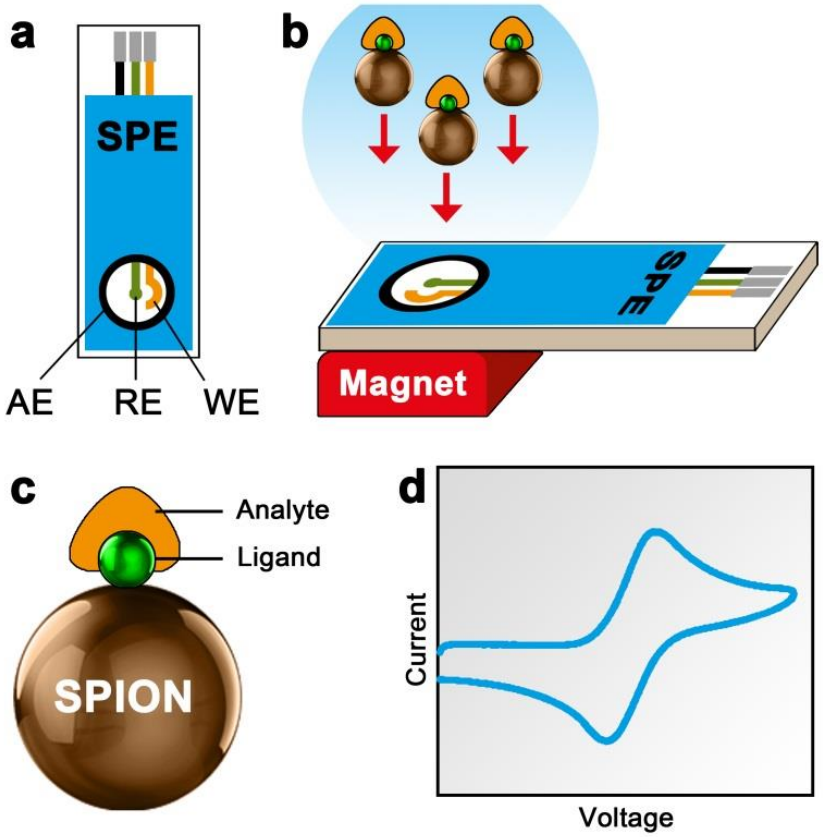

Fig. 3: Application of SPIONs in electrochemical (bio)sensing. (a) a screen-printedelectrode (SPE), (b) role of SPIONs in the attachment of analyte molecules to the electrode surface, (c) a SPION attached to an analyte molecule via a specific ligand and (d) typical cyclic voltammogram.

provide the desirable conductance (the conductivity of most of metal oxides strongly depends on their crystallinity). However, one of the common drawbacks of iron oxide nanoparticles is that they show higher reactivity with the decrease in particle size, hence they may show fast degradation upon direct exposure to certain environments. Therefore, caution should be taken while selecting a method for SPIONs preparation. In other words, the selected method should permit the control over the particle size, shape and the size distribution.

Sensing strategies relying on SPIONs offer competitive advantages compared to the non-magnetic based counterparts in terms of some analytical figures of merit including high sensitivity, low detection limit, enhanced signal-to-noise ratio and fast analysis. SPIONs are used in sensing applications in one of three ways: (i) integration into the transducer material, (ii) direct application of tagged supports to the sensor, or (iii) dispersion in the analytical sample followed by attraction by an external magnetic field onto the surface of the sensor [46].

A general limitation of most sensing mechanisms is the inability of the analyte to reach the active sites of the sensor surface by overcoming all the barriers existing in the biological matrix. SPIONs introduce two major advantages to develop the targeting aspect in such biosensors. Firstly, SPIONs surface could be coated with several kinds of ligands which could be linked to the corresponding analyte with a specific targeting moiety. Secondly, SPIONs can be used for amplifying the signals measured by some kinds of sensors (e.g. electrochemical sensors). Hence SPIONs could be manipulated and controlled by external magnetic field to be directed and concentrated directly towards the sensor's active surface [47].

Hausmann and coworkers developed a microfluidic platform for the preparation of magnetic microparticles with *"birefringent properties"* (i.e. magneto-optical coupling properties) [48]. Birefringent particles have refractive index which depends on the polarization and the direction of propagation of light. In order to achieve this goal, they applied a microfluidic emulsification process where water-based SPIONs-containing droplets are stretched into anisotropic shapes and then converted into particles through photo-polymerization. These magneto-optical microparticles open new horizons for numerous applications including sensing and viscosity measurements via the conversion of external magnetic field into optical signals. In other words, when the particles are suspended in a fluid, they can be magnetically controlled by applying a relatively weak magnetic field and hence they allow for remote control of light.

Metal ions can be assayed using SPIONs-based fluorescence probes. Hg(II) ions were accurately determined using a turn-on fluorescence probe with incorporated SPIONs [49]. In this work, the researchers developed a nanoprobe combining fluorescent carbon quantum dots (CQDs) as fluorophores and SPIONs

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functionalized with –SH and –COOH for efficient removal and accurate determination of Hg(II) ions. The calculated detection limit was 0.38×10^{-9} mol/L. The proposed probe was used successfully for the removal and monitoring of mercury in bacterial and fish samples.

For instance, SPIONs have been recently utilized for constructing bacterial sensors. A novel SPIONs-based ultra-high sensitivity magnetic biosensor for *Escherichia coli* was developed. The detection relied on measuring the consequent change in the magnetic response [50]. Other SPIONs-based biosensors are developed based on the advantages of carrying the analyte-SPIONs composite to the transduction platform under the external magnetic field domain while a significant agglomeration of that composite is observed at the site of action [51]. In addition to bacteria, tumor cells were also detected using surface-enhanced Raman spectroscopy (SERS)-based sensors. In this context, Lin, Zheng and Wu published a valuable review article summarizing the SERS biosensors including those containing SPIONs as sensor modifiers [52].

5 Conclusions

SPIONs are advanced materials with great advantages and applications in different aspects of science; that is why they have attracted the attention of researchers for decades. Here, we gave a concise background about the methods utilized for the synthesis of SPIONs and their most common applications such as drug delivery, cancer treatment, hyperthermia and biosensors. Moreover, the various structures of functionalized SPM nanostructures and their properties (i.e. color, shape and magnetic properties) were highlighted herein. This review may be very important for scientists interested in various areas of research because it opens new avenues for introducing these advanced materials into other novel applications. Here are some precautions to follow while preparing and using these functionalized materials (i.e. SPIONs):

- There is no an optimal method for SPIONs synthesis, indeed the best method for synthesis is the method which ends up with the desired size, biocompatibility, magnetic properties, *etc*. In other means, selecting a method for SPIONs synthesis largely depends on the target application.
- Different applications usually require a certain size threshold of SPIONs. For example, SPIONs can be used for magnetic resonance imaging (MRI), where the suitable particle size should not be more than 20 nm [53].
- Poly(ethylene glycol) (PEG, a FDA approved water-soluble biologically safe polymer) is usually used as a coating material for SPIONs in order to enhance their biocompatibility, circulation time and stability.
- When surface functionalization of SPIONs is desired, it is necessary to keep in mind that the surface iron ions act as Lewis acids. Therefore, functional groups capable of electron donation (carboxylates, sulfates, phosphates, *etc*.) are the most suitable groups for this purpose.
- Naked SPIONs are chemically reactive, thus suitable stabilization methods should be used for preventing their aggregation which leads to the formation of larger magnetic structures. Some materials such as chitosan (alkaline, biocompatible, hydrophilic and nontoxic polymer), polyvinyl alcohol (PVA), polyetherimide, polyvinylpyrrolidone (PVP), poly(acrylic acid) and poly(caprolactone) (PCL) are suitable stabilizers.
- Further effective applications of SPIONs are still challengeable due to the lack of control over some key characteristics such as biodegradability, relaxivity, particles diameter and size distribution.

Although inspiring researches and significant advances in SPIONs applications have been achieved, further researches should be performed. It is necessary to find a suitable mean for getting rid of SPIONs after the application in order not to cause any hazards to humans and/or the environment. Moreover, the dynamics and kinetics of SPIONs inside the human body are still mysterious. These issues will open new avenues for more SPIONs applications in the near future.

Conflict of Interest: There are no conflicts to declare.

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