Chapter 13

Quantum Dots and Fluorescent and Magnetic Nanocomposites: Recent Investigations and Applications in Biology and Medicine

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Additional information is available at the end of the chapter

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Abstract

This chapter presents a comprehensive and updated review on the ongoing research area of nanostructures with a focus on quantum dots (QDs), fluorescent and magnetic nanocomposites, and their applications in biological and medical field. The study includes the essential characteristics of QDs and fluorescent and magnetic nanocomposites, their structure, properties, and methods that are utilized for their characterization. Some interesting qualities of CdSe/ZnS QDs with reference to the research of the microorganism are emphasized. The bioimaging applications of QDs and fluorescent and magnetic nanocomposites and their role as nanoprobes and as contrast enhancing agents are discussed. So, in this work, an overview is exhibited including the case of the most commonly studied QD-based hybrid NPs, which are called MQDs, such as a dual "two-in-one" fluorescent-magnetic nanocomposite materials, that blend both fluorescent and magnetic properties in a unique concept and show the feasibility for clinical diagnostics, drug delivery, and therapy.

Keywords: quantum dots, magnetic quantum dots, nanocomposites, fluorescence property, magnetic property, microorganism labeling, biological imaging, drug delivery

1. Introduction

Fast progresses in nanotechnology and nanoscience have offered a diversity of nanoscale materials possessing very controlled and distinctive optical, electrical, magnetic, or catalytic properties. The diversity of the composition (organic or inorganic, semiconductors or metals), form (particles, rods, wires, cubes, or triangles), and the availability for the functionalization of the surface (physical, chemical, or biological) allowed the production of the different functional nanoscale tools [1, 2]. The scientists have expanded new types of nanoscale tools that could be utilized for forensic science, biology, medicine, electronic technology, environmental science, computer fabrication, and food industries. The researchers in biological and medical fields already used these nanodevices in an assortment of uses varying from the diagnosis of disease to gene therapies. The combination of biomaterials (proteins, peptides, nucleic acids with semiconductor quantum dots (QDs), and metal nanoparticles is expected to generate important advances in molecular biology, bioengineering, medical, and therapeutic diagnostics.

The current progresses comprise the evolution of the functional nanoparticles (electronic, optical, and magnetic) which are conjugated to biological molecules such as peptides, proteins, and nucleic acids. Today, the magnetic nanoparticles (MNPs) are considered to be primary components in therapies and screening methods that are gradually included in many areas of medical practice. Due to the dimension-dependent properties and dimensional similitudes with biomolecules, the magnetic nanoparticles and their bioconjugates are highly appropriate for intracellular tagging [3, 4] and for image contrast-improving agents in magnetic resonance imaging (MRI) [5–8], magnetic separation [7, 9], targeted drug delivery [7, 8, 10], and for usage in hyperthermia [7, 10–12].

QDs are a unique class of fluorescent nanoparticles that are crystalline semiconductors of variable sizes (1–100 nm) and consist of only a few hundred to a few thousand atoms, in spite of the fact that QDs exhibit the same crystal structure as the bulk semiconductor material. The highest-quality QDs are typically composed of atoms from groups II and VI or groups III and V or groups IV and VI of the periodic table [1, 13, 14].

These nanoparticles, compared to their bulk, have smaller exciton Bohr radius which characterizes their definition [15]. This thing establishes what is described as quantum confinement when distinctive optical and electronic properties are created [15]. The nanometric dimension of QDs determines the quantum-confinement effect, which results in unique optical and electronic properties. Due to the effects of quantum confinement, QDs possess distinct photophysical properties that give QDs tremendous advantages over the conventional organic fluorophores [16–18]. Traditional organic dyes exhibit chemical and photophysical limitations such as pH dependence, susceptibility to photo-bleaching, narrow absorption windows of wavelengths, asymmetric emission spectra broadened by a red tail, small Stokes shifts, and short excited state fluorescent lifetimes [17–19].

The researchers in the field have found many production techniques for QDs, from photolithography to wet chemical synthesis. The most utilized QD construction consists of two materials from group II–VI materials, namely a CdSe core with a thin, protective shell of ZnS. Colloidal QDs are fabricated utilizing surfactant micelles, coprecipitation or organic solvent synthesis at high temperature. The last technique is used to manufacture the highest-quality materials [1, 14].

In contrast with the organic dyes and fluorescent proteins, QDs have distinct electronic and optical properties that comprise high quantum yield, broad absorption, large effective Stokes shifts, the ability to size-tune fluorescent emission as a function of core dimension, simultaneous excitation of multiple fluorescence colors, and high resistance against photo-bleaching

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and against photo- and chemical degradation [19, 20]. QDs have great potential in many applications such as solar cells, light-emitting devices, and photobio-labeling technologies. The unique optical properties of QDs make them appealing *in vivo* and *in vitro* in different biological and clinical applications, such as cell labeling [17, 20], cell tracking, *in vivo* imaging, and DNA detection [19, 21].

The combination of dual-natured parts of optical and magnetic properties on nanometer system can bring new advances in molecular imaging and medical theranosis, which are fundamental for early detection and rapid disease treatment. QDs represent an exciting and versatile category of fluorophores with a bright future, thus increasing the interest in blending the advantages of QDs with those of other materials to obtain composites with multifunctional properties [22, 23].

Nanocomposites, which comprise fluorescent and magnetic particles, represent a basis for multiplexed nanoprobe designs. The area of nanocomposite applications is still in a state of development [24]. The magnetic materials constitute one of the most frequent materials, which when amalgamated with QDs form a captivating class of new materials for bioimaging. In this sense, QD biosensing can be further improved by combination with MNPs (e.g., superparamagnetic iron oxide nanoparticles, SPIONs) or ions (e.g., gadolinium). The fluorescent property of the QDs allows visualization, while the magnetic property of the composite allows imaging, magnetic separation and can bring therapeutic advantages [23]. In this paper, actual investigations using only QDs or MNPs will be reviewed in situations where the applications can be expanded to nanocomposites.

This review examines the properties of QDs and magnetic QDs (MQDs) comprising the applications of these materials. Because the properties of these materials continue to enhance, QDs and MQDs possess the capacity to considerably determine biological imaging, diagnosis, and treatment. The application of QDs for combined targeting and delivery of diagnostic and therapeutic agents can be further developed by a combination with magnetic separation techniques via the recent evolution of MQDs. In this chapter, among many benefits of MQDs-based separation to current procedures, one should also mention the small dimension of MQDs, which are small enough to possibly interact with single-cell biomarkers/cell surface receptors which results in corresponding quantification of the results [22, 25]. These multifunctional fluorescent and magnetic nanoparticles of small dimension, which are MQDs, can target any biomolecule and can be separately controlled by engineering magnetic fields. Some authors reported very useful research papers which refer to a combined result of both types of fluorescent and magnetic properties to approach important biological issues [24, 26, 27]. This work provides a survey of the different application of biosensing technologies which are based on QDs and their MQD correspondents.

2. Properties of quantum dots

In the last decades, NPs were produced as interesting materials, with outstanding results for many applications. As a type of NPs, QDs represent the excellent competitors for optical bioanalysis by virtue of their electronic and optical properties, which can be adjusted by modifying the dimension, morphology, and composition of NPs [18, 28]. A new biological labeling material, QDs are considered that they can bring several important advantages in their applications in comparison with the organic fluorophores [29]. In this paper, these tremendous advantages are considered that determine in special, the fluorescent label comportment and hence the utilization in different cases, which comprise the spectral position, the width of the excitation spectrum, the width of the excitation spectrum, the Stokes shift, the molar absorption coefficient, the fluorescence quantum yield, the photo stability, and the decay lifetime.

The most valuable feature influencing the optical properties is the dimension of the QDs. QDs of varying dimensions change the color emitted or absorbed by the crystal thanks to the energy levels of the crystal [30]. QDs present an electronic structure analogous to atoms, due to the tight confinement of charge carriers in them [30, 31]. So, the discrete size-dependent energy levels of QDs represent the effect of the confinement of the charge carriers (electrons, holes) in three dimensions [18, 20, 31, 32]. As a result, the energy difference between excited and ground state (the bandgap energy) of a QD is a function of the QD size and composition: the smaller the bandgap of QD, the larger the QD [18, 20, 33, 34]. This means that the fluorescence wavelength is a function of the bandgap and therefore a function of the QD size [18, 20, 31]. By modifying the dimension, coating, and composition of the QDs, the emission wavelength can be adjusted from the ultraviolet (UV) to the infrared range of the spectrum such that smaller dots emit higher-energy light that is in the blue range and the larger dots emit lower-energy light that is in the red and near-infrared (NIR) region [15]. Because the dimension of QD is inversely proportional to the bandgap energy level, the frequency light emitted changes and an effect on the color occurs [30, 35].

Many of the conventional fluorophores (organic dyes and protein- based fluorophores) exhibit narrow excitation spectra which necessitate excitation by light of a particular wavelength, which fluctuate between certain fluorophores and present broad red-tailed emission spectra which suggest that the spectra of various conventional fluorophores may overlay to a large extent [20, 32]. Three important properties of QDs are considered to be of interest to specialists in biology, namely the capability of QDs to size-tune the fluorescent emission depending on core size, the broad excitation spectra of QDs, which permit excitation of mixed QDs at a single wavelength [36] and the long luminescent life of QDs, which allows their usage for dynamic imaging of living cells [37].

The narrow emission spectra of QDs permit the multicolor excitation involving the potentiality for simultaneous usage of various functionalized QDs for a number of biological targets at the same time. This fact is suited for the usage of QDs in multiplex immunohistochemistry tests [38–40].

QDs are defined by broadband excitation wavelength, very bright fluorescence even when irradiated only with a light-emitting diode (LED) flashlight [2, 17]. These characteristics of QDs, which have been mentioned earlier, allow simultaneous imaging of many entities in a unique biological experiment. This fact represents a difficult mission with common fluorophores since their relatively narrow excitation and broad emission spectra many times lead to the overlapping of the spectra [41]. QDs exhibit high resistance to physical and chemical degradation (suitable for long-term imaging) high quantum yields and high molar extinction coefficients which are 10–50 times greater than that of organic dyes, which make them much brighter in photon-limited *in vivo* conditions [14].

QDs present photoluminescence (PL), when photons are utilized to excite QDs and another photon of lower frequency is released [42]. QDs are famous for eye-catching photos of differently dimensioned QDs under ultraviolet lighting which exhibit a shining rainbow of photoluminescence [33]. This brilliant PL is obtained like a consequence of high quantum yields ($\varphi = 0.1–0.9$) combined with substantial molar extinction coefficients ($10^5–10^7\ M^{-1}\ cm^{-1}$) [32, 33, 42]. The values of the molar extinction coefficients of QDs are 10–100 times greater than those for most organic fluorophores [41]. In contrast with the organic dyes, another beneficial characteristic of QDs is represented by the very large two-photon action cross section [43].

The majority of QD applications in biology utilize this feature for cellular/molecular tracking and imaging [42]. If a photon excites a QD, but the energy is collected as electricity, QD is utilized as photovoltaic material and represents a good possible choice for the case of the current applications in solar cells [41, 42]. In addition, QD blends the conveniences of inorganic and organic materials. In many QD-based solar cells, QDs do not only help like a light-collecting material but also have numerous purposes in order to assist in load separation and transportation [44]. QDs have also been extensively utilized in solar cells for sensitization. Quantum dot-sensitized solar cells (QDSSCs) have lately captivated a lot of interest due to their benefits over the dye-sensitized solar cells (DSSCs), comprising higher molar extinction coefficient of QDs, tunable energy gaps, and multiple exciton generation [45, 46]. It is also worth mentioning the case in which the higher voltage electrical energy can also segregate electrons from holes to form excitons, and when energy is released in the form of light, QDs are utilized in a new light-emitting diode variation, the QD-LEDs [30, 42].

Compared to organic fluorophores, QDs are about 10–100 times brighter and about 100–1000 times more stable against photo-bleaching [2, 47, 48]. Due to these properties, QDs are excellent for single molecule or, more accurately, particle measurement [33].

The fluorescence time is defined like the average time in which a fluorophore will stay in its excited state before it emits light to return to its ground state [43, 49]. The usual values of the fluorescence lifetimes are from 1 to 10 ns for organic dyes and 10 to 100 ns for QDs [43, 49]. An important property that is used for the diminution of the auto-fluorescence of the biological samples is the possibility to choose any wavelength shorter than the wavelength of fluorescence. This quality of QDs can be obtained by electing the most suitable excitation wavelength for which the auto-fluorescence is reduced to a minimum. Previous studies show that the pushing of the emission wavelength into the near-infrared (650–950-nm) range led to the enhancement of the tissue penetration depth and the decrease of the fluorescence at these wavelengths [14, 50].

QDs have shown other many remarkable advantages compared to traditional fluorophores, such as organic dyes, fluorescent proteins, and lanthanide chelates [15, 32]. One of the most significant properties of QD is the red shift of the emission spectra, called the QD Stokes shift. QD Stokes shift, which can be as large as 300–400 nm, depending on the wavelength of the excitation light, can be utilized for *in vivo* imaging [14, 36, 50]. The high Stokes shift values diminish the phenomenon of auto-fluorescence that enlarges the sensitivity [41].

Considering these advantageous optical properties shown earlier, it is not surprising that QDs have been and are still studied as some alternative fluorophores to conventional organic dyes.

2.1. Quantum dots as fluorescent probes for the bioimaging applications

These benefits of QDs are used in an emerging area of science and technology which blends the biological chemical and engineering sciences and guarantees the achievement of nanometric scale methods in order to study the biological systems in the field of health and disease [51]. The best available QDs for biological applications comprise a semiconductor core (e.g., CdSe, CdS, and CdTe) overcoated with a shell of a semiconductor material with a wider bandgap than the material of the core (e.g., ZnS, CdS) in order to obtain a considerable enhancement in the quantum efficiency [17, 18, 33, 52]. The leader QD material, which is used in almost all biological applications, is certainly represented by CdSe/ZnS core-shell, whose celebrity is imputed to well-determined synthetic protocols, emissions that can be scattered in the visible/NIR region and commercial accessibility [33, 53].

In [17, 20, 54], it has also been shown that CdSe/ZnS core-shell QDs represent an excellent substitute to fluorescent fluorophores utilized to label the microbial cells. In this context, the fluorescence of the CdSe/ZnS core-shell QDs, dispersed in toluene with long-chain amine-capping agents, was studied [17, 20, 54, 55]. The different semiconductor nanocrystals, which were utilized in various research works [17, 20, 54, 55], were purchased from EVIDENT Technologies. The sizes of these QDs are in the field of (3–5) nm and their emission is situated in the domain (490–600) nm. The emission properties of diverse QDs were examined and estimated utilizing Fourier transform visible spectroscopy [17, 18, 54, 55] for two excitation sources (a UV laser or a blue LED). **Figure 1** presents the case of the fluorescence of CdSe/ZnS core-shell QDs with the dimensions of 3.2, 3.8, and 5.0 nm [17].

In this section of the chapter, some recent important bioimaging applications of QDs, which have to do with the study of the microorganisms and toxin detection, are reviewed.

QDs have proven to be convenient in the morphological examination of microorganisms in order to show their shape, position, evolution, number, and so on [17, 20, 54, 56]. The QD-based technologies, which are used for the operations of labeling with QDs, are very relevant in biotechnology medical diagnosis and food safety [17, 20, 54, 56].

Numerous authors described successfully linked QDs to biorecognition molecules such as peptide, antibodies, nucleic acids, or small-molecule ligands for further applications as fluorescent nanoprobes [57, 58], whereas few researchers have reported results obtained in using CdSe/ZnS core-shell QDs in the field of the microbial labeling, for both pure cultures of cyanobacteria (Synechocystis PCC 6803) and mixed cultures of phototrophic and heterotrophic microorganisms [17, 20, 54, 59, 60]. In these last works, the labeling of the biological samples, comprising the cultures of the microorganisms with QDs of 0520 Evidot suspension type, which were incubated in darkness at room temperature, was described. The natural samples including filamentous cyanobacterial cells were microscopically studied (B-352 LD2) by

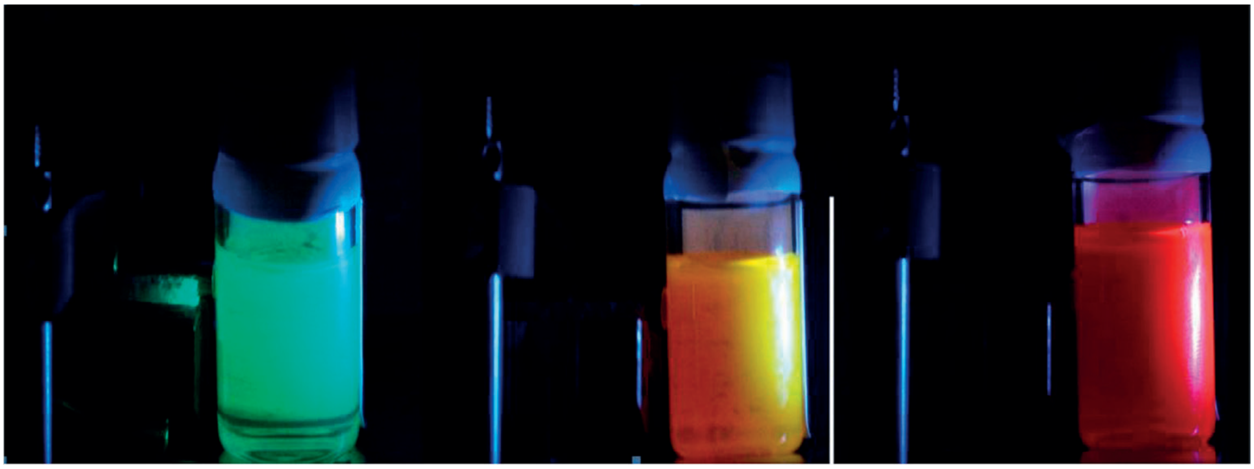

Figure 1. The fluorescence of CdSe/ZnS core-shell, suspended in toluene with long-chain amine-capping agent, under ultraviolet illumination. The various colors are correlated with the various wavelengths of the fluorescence maxim according to the sizes of the QD in the suspension. From left to right, according to the specifications of the EVIDENT Technologies catalog three kinds of CdSe/ZnS core-shell QDs were used: 0490 QDs fluid (with the crystal diameter of 3.2 nm and the color of Lake Placid Blue type), 0520 QDs fluid (with the crystal diameter of 3.8 nm and the color of Hops Yellow type) and 0600 QDs fluid (with the crystal diameter of 5.0 nm and the color of Fort Orange type) [17].

transmission in white light or by epifluorescence, with the help of the blue and green filters [17, 54]. **Figures 2** and **3** show the easy visualization of the individual cyanobacterial cells due to the green fluorescence of QDs. These two figures present the case of the individual filamentous cells in two types of natural samples indicated in the visible microscopy (A), the case of microscopic aspect of the QD-labeled cyanobacterial cells for the blue filter (B) and the case of the microscopic aspect of the same samples for the green filter (C) [17, 54].

Another research paper examined the nonspecific labeling of cyanobacteria in natural samples and enriched cultures with CdSe/ZnS core-shell and the impact of CdSe/ZnS core-shell QDs on the global color of epifluorescence microscopy images [20]. The same paper [20] exhibited the use of the digital color analysis method for the study of the epifluorescence microscopy images, demonstrating the color transformation of the epifluorescence images of filamentous cyanobacteria and showing in this way the potential toxic effects of QDs on cyanobacteria.

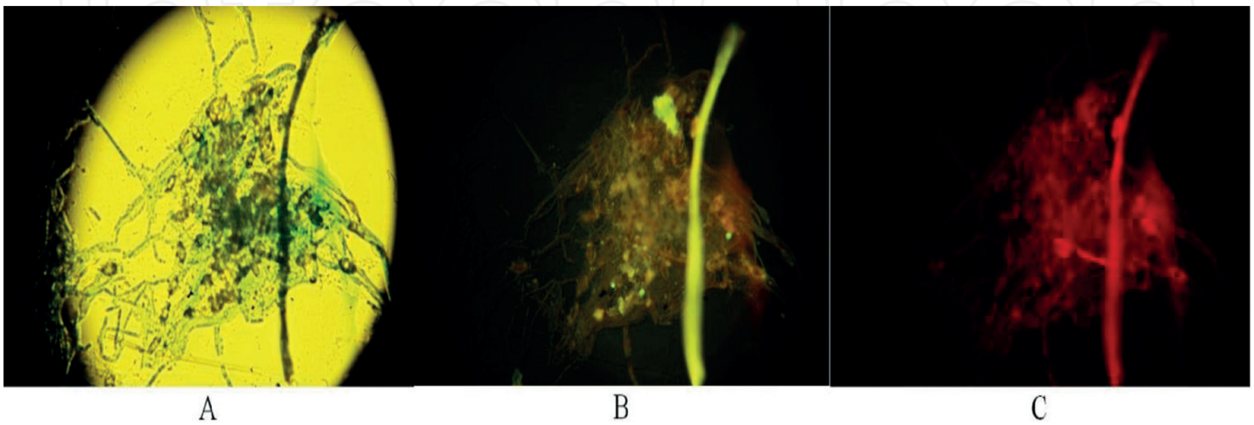

Figure 2. Microscopic aspect of the labeling of the cyanobacterial cells with QDs in the case of the sample 1: A: Transmission in white light; B: Epifluorescence utilizing a blue filter; C: Epifluorescence utilizing a green filter [54].

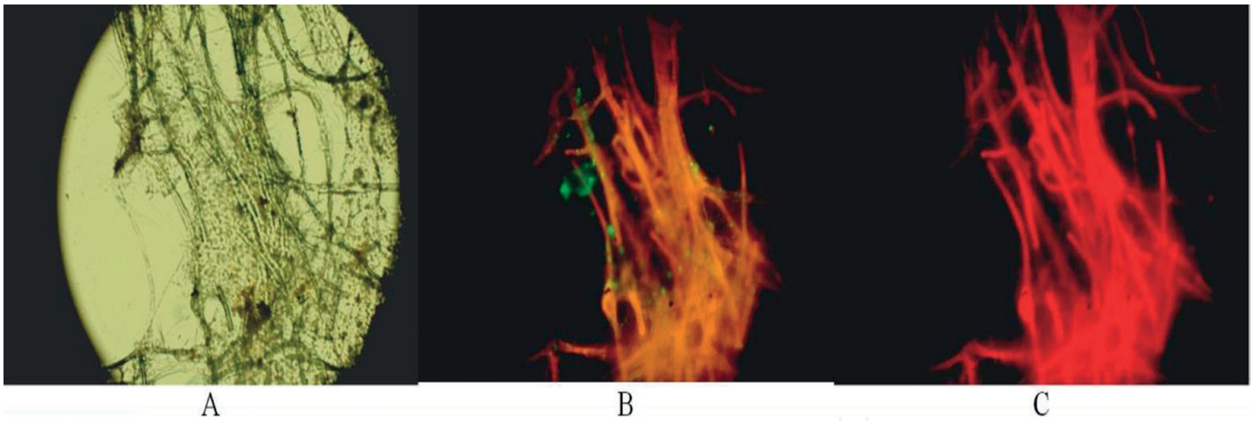

Figure 3. Microscopic aspect of the labeling of the cyanobacterial cells with QDs in the case of the sample 2: A: Transmission in white light; B: Epifluorescence utilizing a blue filter; C: Epifluorescence utilizing a green filter [54].

3. Fluorescent and magnetic nanocomposites as nanoprobes for multimodal imaging applications

QDs represent a new category of molecular imaging instruments which created a significant effect in biological and medical research, thus helping to further develop new applications. Using new layers, QD appears as a fundamental element for further manufacture of multifunctional nanostructures and nanodevices which can be manufactured by integrating QDs with NIR emission, paramagnetic or superparamagnetic nanomaterials [15]. In the next part of the paper, the latest applications of the nanocomposites are exhibited, which comprise fluorescent and magnetic particles and help for the construction of the novel multiplexed nanoprobe models.

Fluorescent-magnetic nanocomposites comprise a diversity of materials which integrate silica-based, dye-functionalized MNPs and QDs-MNPs composites. Different papers have described various types of techniques to fabricate composites of fluorescent semiconductor QDs and MNPs, such as the mixing of the two materials for the construction of a single heteromeric particle with optical and magnetic properties, the enclosing of separately synthesized fluorescent and magnetic particles in a polymer or silica matrix, the enclosing of the single particles in a polymer or silica gel, magnetically doped QDs and ionic aggregates, which are composed of a magnetic core and fluorescent ionic composites [24, 61].

These multifunctional fluorescent magnetic nanocomposites can be utilized in a range of biological and biomedical applications in nanobiotechnology, such as imaging and therapy, cell tracking and sorting, separation, and drug delivery.

Corr et al. [61] emphasized the fact that the merging of a magnetic and fluorescent entity offers novel two-in-one multifunctional nanomaterials, with a wide gamut of feasible applications, for two reasons: the first reason is that multimodal magnetic-fluorescent tests would be an advantage for *in vitro* and *in vivo* bioimaging applications (magnetic resonance imaging and fluorescence microscopy) and the second reason is that these multifunctional fluorescent

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magnetic nanocomposites can be used as instruments in the nanomedicine realm. Thus, fluorescent magnetic nanocomposites are utilized to visualize and synchronously treat diverse diseases [61].

Koole et al. described four diverse techniques of obtaining a single nanoparticle, which comprises the fluorescence and magnetic properties and represents new sensitive bimodal contrast instrument for two extremely powerful and highly complementary imaging methods: fluorescence imaging and MRI [27].

In some research papers [21, 53], new approaches of the therapeutic procedures and imaging modalities (such as the technique of the correlation between MRI and ultrasensitive optical imaging) are exhibited in order to be developed and to become mainstream clinical methods for the visual detection of the microscopic tumors during an operation and the complete elimination of the diseased cells and tissues. The authors of these research works show that medical imaging methods can detect the illness, but do not furnish a visual template during a certain surgery. This matter can be resolved with the help of some MQD probes. MQDs are a form of magnetic contrast agents in MRI. In this regard, paramagnetic and superparamagnetic agents Gd(III) and different forms of iron oxide (Fe_2O_3) in molecular form and in nanoparticle form are attached to QDs to utilize in a variety of MRI applications with the scope of the improving image contrast [21, 53].

Many researchers have investigated paramagnetic QDs (pQDs) [62–65]. So, in Refs. [62, 64], a model of multifunctional fluorescent magnetic nanocomposites, comprising silica-coated Fe_3O_4 and TGA-capped CdTe QDs, was communicated. This type of nanocomposite has been used for the labeling and imaging of HeLa cells in a magnetic separation. In Refs. [63, 65], pQDs were improved by coating CdSe/ZnS core-shell QDs with a PEGylated phospholipid and a Gd lipid, making the particles biocompatible and MRI active. The pQDs were also conjugated by maleimide to cyclic RGD peptides for targeting angiogenic vascular endothelium as proved by *in vitro* investigations with human umbilical vein endothelial cells (HUVECs).

Ahmed et al. [66] developed a novel technique for the manufacture of QDs enclosed MNPs based on layer-by-layer (LbL) self-assembly method in order to be used for cancer cells imaging. In a research study, Park's group [67] reported long-circulating, micellar hybrid nanoparticles (MHNs) which include MNs, QDs, and the anticancer drug doxorubicin (DOX) in a single poly(ethylene glycol) (PEG)-phospholipid micelle and furnish the first models of concomitant targeted drug delivery and dual-mode near-infrared fluorescence imaging and MRI of diseased tissue *in vitro* and *in vivo* [24, 67].

A very useful review study, which includes the mention of the specialized literature on the applications of MQDs, which represent one of the most currently explored QD-based hybrid NPs, was realized by Wegner and his colleague [68]. In this study, a principal result is indicated, which was obtained by Qiu et al. [69]. These researchers blended QDs, superparamagnetic iron oxide nanoparticles (SPIONs), and gold (Au) NPs in a single poly(lactic-co-glycolic acid) (PLGA) NP. This type of particle is significant for imaging, tracking, and manipulating neutrophils and is used for *in vivo* applications and localized photothermal treatment.

4. Conclusions

QDs and fluorescent and magnetic nanocomposites, which have essential physicochemical characteristics, represent some excellent candidates for numerous applications in bioanalysis and bioimaging. In this review, the important properties of these nanoprobes are summarized and the recent developments of the applications of the QD-based techniques in biomedical uses (biological imaging, cell tracking, magnetic bioseparation, and bio- and chemo-sensoring) are highlighted.

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