Chapter

Magnetic and Quantum Dot Nanoparticles for Drug Delivery and Diagnostic Systems

Erandi Munasinghe, Maheshi Aththapaththu and Lakmal Jayarathne

Abstract

Nanoparticles are being used tremendously in biomedical sciences due to their promising chemical and physical properties. Magnetic nanoparticles and quantum dot nanocrystals are two of the main nanoparticle types used in the biomedical industry. The surface of these nanoparticles is further modified in order to obtain biocompatibility and surface functionalization. Magnetic properties, fluorescence, nanometer size, and availability of sites to modify its surface for bioconjugation provide greater potential to use these nanoparticles in targeted drug delivery technique and diagnostics. As a result, these nanoparticles create massive developments in the industrial operations. In this chapter, an overview of the nanoparticles used in drug delivery and diagnostic systems will be discussed. In addition, advantages in encapsulation of magnetic and quantum dot nanoparticles for bioconjugation and different methods of drug delivery will be addressed.

Keywords: drug delivery, quantum dots, magnetic nanoparticles

1. Introduction

Among many synthetic compounds the general public comes across with, in day-to-day life, nanoparticles are considered highly advantageous in various applications. Nanoparticles in diagnostics and as drug delivery vehicles are coming under the aforementioned beneficial applications in the field of biomedical science. Various types of nanoparticles, for instance, gold nanoparticles [1] and iron oxide nanoparticles [2], are being used in biomedical operations. Due to its magnetic properties and nanometer size, magnetic nanoparticles such as magnetite (Fe_3O_4) [3] and maghemite (γ-Fe_2O_3) [4, 5] are considered highly beneficial for diagnostics and in drug delivery systems. On the other hand, inorganic nanoscale particles with semiconductor properties are becoming very popular in such applications. These semiconductor nanoparticles, called quantum dot nanoparticles, are equipped with extremely favorable characteristics such as high fluorescence and photoluminescence. These nanoparticles have been tested to be used in diagnostics [6], and trials were carried out at laboratory scale as therapeutics, that is, for drug delivery [7]. At the same time, quantum dots are found to be more beneficial over regular chemotherapy, radiation, and ionizing radiation imaging [8] which are used in cancer diagnosis and treatment.

2. Nanoparticles used in drug delivery and diagnostic systems

2.1 Magnetic nanoparticles

Magnetic nanoparticles are used widely in a variety of industrial applications in environmental remediation [9], data storage [10], electronic device development [11], and pharmaceutical industry [12, 13]. Its magnetic properties give a greater potential in delivering the drugs at desired sites. The nanoscale size of the particles gives the ability to permeate through membranes without the interference of biological barriers. Therefore, the so-called properties make magnetic nanoparticles an ineluctable component in the development of drug delivery systems.

2.1.1 Properties of magnetic nanoparticles

Several types of magnetic nanoparticles such as iron, nickel, and cobalt based are available for industrial applications [14]. Due to the greater potential in surface modification and higher magnetic properties, iron oxide nanoparticles are considered as the best magnetic candidate in the development of drug delivery systems. These single-domain iron oxide magnetic nanoparticles are present in three different phases, as magnetite, maghemite, and hematite (α-Fe_2O_3) [15]. These nanoparticles generally demonstrate super-paramagnetic properties at ambient conditions even though their physical and chemical properties largely depend on the synthesis procedure and particle size [16]. According to the motions and interactions of the electrons available in the material, magnetism is divided in to five main classes as diamagnetism, paramagnetism, ferrimagnetism, ferromagnetism, and antiferromagnetism [17, 18]. Iron oxide nanoparticles fall under ferromagnetic and ferromagnetic classes due to their strong collective magnetic interaction [18].

To be used in a biological environment, there are several concerns that the magnetic nanoparticles should conquer. Colloidal and chemical stability of these particles is the main consideration. The stability of magnetic nanoparticles is extremely affected by intrinsic structural properties such as size, morphology, and pH of the particles [19].

2.1.2 Synthesis of magnetic nanoparticles

Synthesis of iron oxide nanoparticles can be conducted in different procedures using physical, chemical, or biological methods [18]. Chemical methods such as coprecipitation, hydrothermal reactions, thermal decomposition, microemulsion, sol-gel reactions, aerosol/vapor phase method, and electrochemical method are the principal preparation procedures. These procedures have the ability to control particle size, surface chemistry, and composition. Most simple, efficient, and cost-effective methods among these procedures are coprecipitation and thermal decomposition, which are also used widely due to the same reasons. In coprecipitation, metal oxide particles are synthesized using a solution of the metal salt. In the synthesis of iron oxide nanoparticles, aqueous Fe^{3+} and Fe^{2+} are coprecipitated by addition of a base, preferably, sodium hydroxide or ammonium [18].

2.1.3 Biomedical applications

As a result of its nanometer size, as small as 3 nm [20], magnetic nanoparticles can reach the biological entities according to the interest. Cells with 10–100 μm size, proteins as large as 5–50 nm or even genes which can be 2 nm wide and 10–100 nm long, or viruses with size ranging from 20 to 450 nm can be targeted using these

magnetic nanoparticles [21]. The property of magnetism, where these nanoparticles can be manipulated by an external magnetic field, enhances its utility by providing the ability to get these nanoparticles to where they are required. Magnetic nanoparticles are used in various applications in the aspects of biomedicine and biology. Magnetic separation has been of greater advantage in biological research, where magnetic nanoparticles are labeled to desired biological substances. These have proven superior sensitivity in cell sorting especially in immuno-magnetic selection of rare tumor cells in blood [22]. Moreover, these magnetic nanoparticles are used in a vast number of biological operations such as targeted drug delivery [23], hyperthermia [24], magnetic resonance imaging (MRI) [25], rapid diagnostics [26], tissue engineering [27], magnetic particle imaging (MPI) [28], etc.

2.2 Quantum dot nanoparticles

Quantum dot nanocrystals are semiconductor nanomaterials with intrinsic chemical and physical properties. These have unique semiconductor energy levels that can be adopted by simply changing size, shape, and charge potential [29]. In quantum dot nanoparticles, excitons are confined in all three dimensions. Quantum confinement is a property of semiconductors where the diameter of the nanoparticle approaches that of the Bohr exciton radius. These nanoparticles have particular optical and electronic properties such as size-tunable absorption bands and emission colors due to the quantum confinement effect [30]. Quantum dot particles are artificially synthesized from II to IV and III to V elements such as Cd, Te, Se, Zn, etc. [31]. These are nanoscale structures typically with a diameter of 2–10 nm, which make them a more reliable and influential candidate in most of the industrial applications. Due to its small diameter, the surface atom to core atom ratio is high [32]. When the surface atom to core atom ratio increases, the properties of surface atoms dominate the properties of the whole particle. The semiconductor lattice of quantum dots is terminating on the surface, and therefore, the surface atoms show a different chemical behavior than the core atoms [33]. This ultimately makes the quantum dots more beneficial in industrial and biomedical operations.

2.2.1 Properties of quantum dot nanoparticles

These nanocrystals display fluorescence and produce distinctive colors which can be determined by the nanocrystal particle size. Fluorescence is a form of luminescence, where a substance absorbs light or other electromagnetic radiation and emits light of a longer wavelength than the absorbed light [34]. In general, luminescence is defined as the emission of photons from the excited electronic state. In contrast, when the atoms of the material absorb energy, these atoms are in the excited state. These excited atoms release absorbed energy as photons, which ultimately discharge light [35]. These quantum dot nanoparticles exhibit extraordinary photoluminescence with increased brightness and stability [36, 37].

As presented in **Figure 1**, there are several types of quantum dots as core type [38], core-shell type [39], and alloyed type (bimetallic) [40], which are classified based on their composition and structure. Core-type quantum dots contain single component inorganic core and can be chalcogenides of metals such as PbS, CdTe, CdSe, etc. [38]. These can be further modified with another layer around the core using many substances, according to the application's requirement. Typically, in biomedical applications, these core structures are stabilized with an organic layer around the core in order to obtain a hydrophobic or hydrophilic surface. The electroluminescent and photoluminescent properties of these core-type quantum dots can be refined by basically altering the crystal size [12].

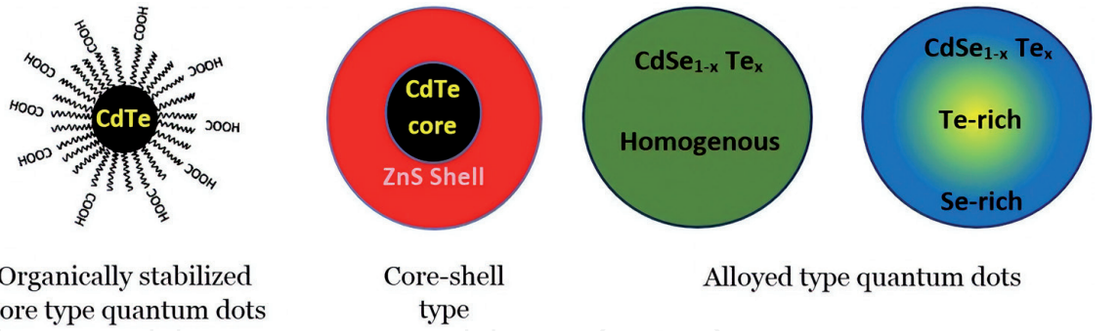

Figure 1.
Types of quantum dots used in drug delivery [44].

Core-shell-type quantum dots, such as CdTe/CdSe [41], CdSe/ZnS [42], CdSe/CdS, etc., are comprised of an inorganic core and an inorganic shell, generally a higher bandgap semiconductor around the core. Core-shell structures of quantum dots are more effective and have an intense brightness, as a result of the diminished chemical damage that can be happened to the fluorescence core. It is believed that inorganic core-shell quantum dots are more robust than organically passivated core-type quantum dots [43].

Alloyed quantum dots are synthesized by alloying two semiconductors with different bandgap energies. This type emits colors by just altering the composition rather than changing the crystallite size as a result of both homogenous and gradient internal structures [44].

2.2.2 Synthesis of quantum dots

Among several methods utilized to synthesis quantum dots, hydrothermal synthesis [45, 46], and organometallic synthesis [47, 48] are the mainly used two techniques. Other methods, for instance, polyol-hydrolysis [49], electron beam irradiation [50], microwave-assisted aqueous synthesis [51], photochemical synthesis [52], UV irradiation [53], and chemical precipitation [54], are also less commonly used for quantum dot synthesis. CdTe quantum dots are highly used in biomedical applications compared to other types of quantum dots. Generally, CdTe quantum dots demonstrate inferior biocompatibility and stability in biological systems. Therefore, methods have developed to modify the surface of CdTe quantum dots during synthesis by capping the quantum dots using different stabilizers such as trioctylphosphine (TOP)/trioctylphosphine oxide (TOPO) [55], etc. Particularly, quantum dots which are capped with stabilizers containing thiol groups [56] make the quantum dots highly biocompatible and more stable inside biological environment [57, 58]. The CdTe quantum dots, which are synthesized in aqueous medium using thioglycolic acid [59], cysteine [60], and glutathione [61], provide high luminescence, stability, and surface functionalization to conjugate biomolecules.

2.2.3 Biomedical application

Recently, quantum dots are used in many biotechnological appliances [6, 62]. These fluorescent nanocrystals are utilized in many immunofluorescence assays [63], tissue engineering [64], DNA array technology [65], and other cell biology techniques [66] where fluorescence measurements are occupied. Single-molecule level studies of living cells [67] and targeted drug delivery for cancer treatment [68] are some other applications in medicine. There are many advantages of using

quantum dots in biotechnology. As the fluorescence of quantum dots is intense than other conventional dyes classically used in immuno-labeling and staining of proteins, quantum dots are currently being used in immunoassays as fluorophores [69] and in immuno-staining of cells [70], DNA [71], etc.

3. Advantages and advances in encapsulation of nanoparticles for bioconjugation

Bare nanoparticles often show undesirable properties in biological systems. These nanoparticles are often hydrophobic or hydrophilic, susceptible to oxidation and agglomeration. The main concern with magnetic nanoparticles is that they may fail to exhibit their super-paramagnetic properties inside or when conjugated to biological systems. This reduction of magnetism occurs as a consequence of their high chemical reactivity and extraordinary surface energy [16]. With the intention of maintaining nanoparticles in the colloidal condition during storage and to increase their constancy and biocompatibility, bare nanoparticles are further modified. Generally, surface modification is performed using polymers or surfactants which are hefty or charged molecules compared to the nanoparticles. These modifications provide several advantages such as increased physical and chemical stability. Therefore, the agglomeration and oxidation which are the most problematic concerns in biomedical applications can be minimized or limited. Ultimately, these modifications make the nanoparticles biocompatible with enhanced surface activity. Following modifications, with the use of functional groups available on the surface of nanoparticles, targeted biomolecules can be anchored on nanoparticles [72]. Magnetic nanoparticles acquire higher surface energy due to its tremendous specific surface area of exposed atoms on its surface [73].

Simply, modification of magnetic nanoparticles can be achieved by surface coating of the nanoparticle with either organic or inorganic materials. Inorganic materials include silica [74] and carbon [74]. Silica is a widely used compound for surface modification of iron oxide nanoparticles. As a result of its low cytotoxicity, silica modified nanoparticles are considered as an excellent combination to be used in biological applications. Silica coatings provide reduced agglomeration along with enhanced stability which ultimately ensures biocompatible-modified magnetic nanoparticles [75]. Organic material coating involves the addition of the material on to the nanoparticle, and the surface structure of the nanoparticle is totally undisturbed. There are many organic materials used for this strategy. Some of them are dextran [76], chitosan [77], alginate [78], and polymers such as polyethylene glycol (PEG) [79], polyvinyl alcohol (PVA) [80], and polyvinylpyrrolidone (PVP) [81].

4. Different methods of drug delivery

In drug delivery systems and diagnostics, nanotechnology has become a leader in the current decade. Since the 1980s there has been a considerable number of research on using nanotechnology in drug delivery systems [82, 83]. Due to its unique properties, such as smaller nanoscale size, magnetism, and fluorescence, nanotechnology-based drug delivery systems have defeated the problems and barriers of drug therapy in the pharmaceutical industry. Studies demonstrate many nanoparticulate drug careers, namely, liposomes [84], microemulsions [85], nano-suspensions [86], and nanoparticles [87]. These can be administrated through parenteral, tablets, capsules (as hard gelatin or soft gelatin), and as oral liquid [88].

These nanoparticles are extraordinary carriers for drug delivery for cancer treatment since they are not uptaken by phagocytosis by the immune system due to its nanoscale size [89].

Nanotechnology-based drug delivery has now come into a point where it has developed a smart drug delivery system. The theory behind smart drug delivery technique is, when the nanoparticle system is provoked by biological, chemical, or physical stimuli (biomolecules, pH, light, temperature, etc.), physicochemical properties of nanoparticle system change rapidly [90]. These smart drug delivery systems can be programmed to release drugs according to the stimuli, and the flow rate of drug release can be regulated according to the environmental condition. It can also predict the drugs required and switch on and off the release of drugs [91]. These advances have made the system more effective and have reduced the toxicity and side effects of the nanoparticulate drug admonition.

4.1 Types of drug delivery

There are several drug delivery methods such as oral method [92], injection-based method [93], transdermal delivery [94], pulmonary drug delivery [95], and carrier-based method [96].

In oral drug delivery, formulations used in oral drug administration range from simple tablets to modified control release tablets. This involves the use of various polymers and hydrogel-based formulations [92]. Injection-based drug delivery provides fast systemic effects bypassing first pass metabolism. Using this method, the drugs can be administered in unconscious or comatose patients, and drugs having short half-life can also be infused continuously [93]. Pulmonary drug delivery involves the administration of drugs by inhalation through the mouth or nose. The alveolar epithelial gets contacted with the drugs, and this provides a good surface especially for lipid-soluble drugs [95]. In transdermal drug administration, adhesive patches containing the drugs are applied on the skin. The drugs pass the skin surface by diffusion and enter the systemic circulation by percutaneous absorption [94]. Carrier-based drug delivery is a novel method which has been experimenting over decades in order to escalate the efficiency and diminish the detrimental side effects of carrier systems. This method serves improved selectivity, effectiveness, and safety of drug administration [96].

4.1.1 Carrier-based drug delivery systems

Carrier-based drug delivery system utilizes several carriers such as liposomes, microemulsions, micellar systems, aquasomes, and nanoparticles.

Liposomes are drug carriers with a spherical structure, constructed from one or several amphiphilic phospholipids and cholesterols. Using liposomes as vehicles in drug delivery provides various conveniences compared to other systems. These carriers are created as small structures (80–100 nm), with bilayers of phospholipids and cholesterols with an aqueous interior. As a result, lipophilic drugs can be encapsulated in the lipid bilayer and hydrophilic drugs in the aqueous interior [85]. Using liposomes are considered as a low-toxic method with minimal side effects, and the drug can be applied without deteriorating its performance [84].

Microemulsions are a thermodynamically stable mixture of two immiscible liquids consisting of two phases called dispersed and continuous phase. These mixtures are typically stabilized with a surfactant and may have droplets with a size of 5–100 nm length [85]. Similar to emulsions, microemulsions can also be constructed as water in oil or oil in water. In drug administration, dispersed or continuous

phases are determined by the hydrophilicity of the drug. Microemulsions provide increased solubility and stability of drugs enhancing high absorption rate through biological membranes.

Composed of copolymers and amphiphilic macromolecules with distinct hydrophobic and hydrophilic properties, polymer micelles form nanoscopic supramolecular core-shell structures. These structures show different types of morphologies, such as spheres, rods, vesicles, tubules, and lamellae. Core-shell structure of these particles grants a number of positive factors to be used in drug delivery applications [85]. As a result of the copolymers used in the formation of the micelles, the half-life of the system is expanded. Another consideration is that water-insoluble drugs can be solubilized by encapsulating the drug within the core structure. Due to its nanoscopic size, the permeability is intensified making it convenient for injections [97].

Aquasomes are spherical particles with 60–300 nm in size. These are used as vehicles for drug delivery as well as to deliver antigens to evoke antigen-specific immune responses [85]. These nanoparticles are comprised of a nanocrystalline core, which is responsible for the structural stability, and an oligomer coating, which protects the system from dehydration. As shown in **Figure 2**, the drugs or biomolecules of interest are adsorbed on the oligomeric coating of the aquasomes, making them conducive for drug delivery [98].

Nanoparticles are solid colloidal particles with 1–1000 nm size [18]. Currently, a number of different types of nanoparticles along with various macromolecules are used for drug delivery. Nanoparticles in different structures are produced depending on their configuration and utility such as nanotubes [99], nanowires [100], nanoshells [101], quantum dots [102], nanopores, nanobots [103], nano-erythrocytes [104], etc. Drugs or biomolecules are attached to the nanoparticles by adsorption, covalent attachment, or entrapment [18]. To be included in the drug development process, utilization of potentially toxic compounds or organic solvents in the nanoparticle synthesis procedure is inadvisable [44]. The components used in synthesis should ideally be biodegradable and safe for in vivo use. Further, these complexes should not induce immunological responses, and also, these should be stable under storage conditions [105]. In drug delivery, magnetic nanoparticles are being used in several approaches. The first approach is localized drug delivery, where the magnetic nanoparticles attached to the appropriate drug and administered systemically. When the magnetic field is applied on the required site of the body, these drug-containing magnetic nanoparticles will accumulate on the diseased site, and the drugs will be released for treatment [106]. The second approach is the usage of an alternate magnetic field to generate heat by magnetic nanoparticles which are conjugated to drugs via thermos-liable linker molecules [107]. These magnetic nanoparticles have the ability to generate heat when an alternate magnetic field is focused on a diseased site. Thus, under the alternate magnetic field, these thermos-liable linkers get cleaved, releasing the drugs [108].

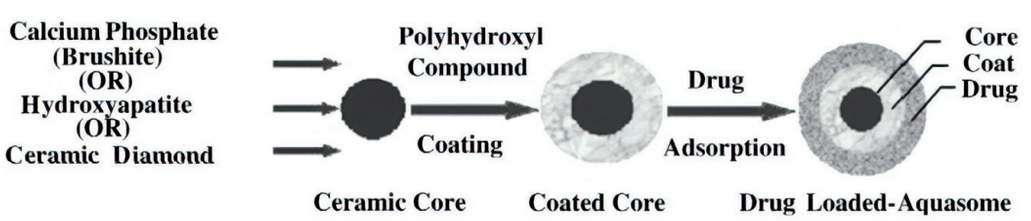

Figure 2.
Preparation of aquasomes [98].

5. Conclusion

Recent advances of nanotechnology which is used in biomedical science have given a great opportunity for the consumers to utilize the technology in a very efficient manner. Special focus on smart drug delivery technique which provides utmost advantages can prove this statement without hesitation. Nanoparticles, being considered as highly useful components in drug delivery, therapeutics, and diagnostics, can also affect its users negatively as a result of its inherent toxicity and inferior levels of biocompatibility. Even though different types of nanoparticles show diverse levels of toxicities, current appliances have made precautions to minimize its toxic effect and increase biocompatibility, by encapsulation. Magnetic nanoparticles and quantum dot nanoparticles, as discussed in this chapter, are used widely in the aforementioned applications with modified surface fabrications. The future prospects of nanotechnology in biomedical applications could lead to a highly sophisticated user-friendly technology where smarter appliances will reach consumers with the least challenges which they encounter in the present systems.

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Author details

Erandi Munasinghe[1*], Maheshi Aththapaththu[2] and Lakmal Jayarathne[3]

1 Molecular Medicine Unit, Faculty of Medicine, University of Kelaniya, Sri Lanka

2 Biotechnology Unit, Industrial Technology Institute, Colombo, Sri Lanka

3 National Institute of Fundamental Studies, Kandy, Sri Lanka

*Address all correspondence to: erandieran@hotmail.com

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