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REVIEW

Applications of functionalized nanomaterials in photodynamic therapy

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Abstract

Specially designed functionalized nanomaterials such as superparamagnetic iron oxide, gold, quantum dots and up- and down-conversion lanthanide series nanoparticles have consistently and completely revolutionized the biomedical environment over the past few years due to their specially inferring properties, such as specific drug delivery, plasmonic effect, optical and imaging properties, therapeutic thermal energy productionand excellent irresistible cellular penetration. These properties have been used to improve many existing disease treatment modalities and have led to the development of better therapeutic approaches for the advancement of the treatment of critical human diseases, such as cancers and related malaise. In photodynamic therapy, for example, where the delivery of therapeutic agents should ideally avoid toxicity on nearby healthy cells, superparamagnetic iron oxide nanoparticles have been shown to be capable of making photodynamic therapy (PDT) prodrugs and their associative targeting moieties tumor-specific via their unique response to an external magnetic fields. In this review, the nanomaterials commonly employed for the enhancement of photodynamic therapy are discussed. The review further describes the various methods of synthesis and characterization of these nanomaterials and highlights challenges for improving the efficacy of PDT in the future.

Keywords Nanomaterials · Photodynamic therapy · Superparamagnetic iron oxide nanoparticles · Gold nanoparticles · Quantum dots · Lanthanide

Introduction

Nanotechnology has played vital roles in many fields of human endeavor. In medicine, for example, nanomaterials have been used to improve both the diagnosis of disease and therapeutic functions of existing chemotherapeutics (Bae et al. 2011). Nanomaterials exist at the nanoscale level and thus have some unique properties not present in their bulk counterparts. These properties, such as size, shape, surface chemistry, superparamagnetism, therapeutic heat generation and specific light absorptions and emissions, have enabled them to be used in a wide array of biomedical applications, such as magnetic resonance imaging (Vu-Quang et al. 2012), specific-site drug delivery (Huang et al. 2013) and disease-treatment modalities, such as immunotherapy (Xu et al. 2016), gene therapy (Ramamoorth and Narvekar 2015), photothermal therapy (Zhou et al. 2009), photodynamic therapy (PDT) (Banfi et al. 2004; Li et al. 2013; Hu et al. 2014) and magnetic hyperthermia (Silva et al. 2011). For example, well-dispersed hydrophilic functionalized gold nanorods exhibit unique plasmonic effects which can be sensitized by near-infrared light to generate thermal energy capable of destroying cancer cells (Huang et al. 2008; Huang and El-sayed 2011). Also, water-soluble surface-capped superparamagnetic iron oxide nanoparticles (SPIONs) have unique magnetic properties capable of generating a high contrast images for detection of cancer cells in magnetic resonance imaging (Shevtsov et al. 2014) and therapeutic heat efficient for the destruction of tumor cells under the influence of alternating current magnetic fields (Mohammad et al. 2010; Muñoz de Escalona et al. 2016). Quantum dots on

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the other hand (Drbohlavova et al. 2009; Bera et al. 2010) are uniquely capable of improving the optical properties of new and existing therapeutic agents.

For nanomaterials to be useful in medical applications, certain criteria need to be fulfilled. Hydrophilicity (water solubility) is important since the body fluid is an aqueous system which helps to convey the materials round about the body and in and out of cells. In addition, the size and surface chemistry including functional groups and charge of the nanomaterials are highly important. These two factors are essential to avoid being recognized and thus eliminated from the circulation by the body's defense system (Weinstein et al. 2010; Kim et al. 2012). Biocompatible polymeric materials, such as polyethylene glycol (Ichikawa et al. 2005) and dextran, capable of by-passing the defense system without being recognized may therefore be highly desired for capping the surface of nanoparticles. Also, cells are generally negatively charged at the physiological pH. Thus, positively charged nanomaterials may have relatively better access to the cell interior via electrostatic interaction with the cell surface.

Cancer is one of the most life-threatening human diseases (Aziz et al. 2003). It occurs in many parts of the body including the vital organs such as lung (Vermaelen and Brusselle 2013), prostate (Turkbey et al. 2009), breast (Eckstein 2011) and brain (Silva et al. 2011). Its major cause has been linked to destruction of DNA of normal cells by reactive oxygen species generated as a consequence of certain social lifestyles such as tobacco smoking (Chang et al. 2009) and alcohol drinking (Kanavos 2006), exposure to environmental toxins (Goubran et al. 2014), lack of physical exercise and inherited genetic defects. Many interventions, such as chemotherapy, ionizing radiotherapy (Chiaviello et al. 2011) and surgery (Anand et al. 2012), are employed to combat the disease. However, these methods have several disadvantages (Aziz et al. 2003; Zhao et al. 2014), and side effects such as non-specific therapeutic functions, recurrence and evolution of drug-resistant cancer cells over time (Eckstein 2011; Aljarrah et al. 2012), cosmetic disillusion often experienced after surgical operation and the high cost of therapeutic methods especially for people living in low-income developing countries (Katz and Wright 2006; Cavalli 2013). As a result, efforts have been made to improve the existing treatment methods and search for better alternatives. The alternatives for cancer treatment currently being exploited include immunotherapy, gene therapy (Mulens et al. 2013; Song et al. 2014), photothermal therapy (Huang and El-Sayed 2011), magnetic hyperthermia (Shah et al. 2014) and PDT (Lu et al. 2014; Yan et al. 2014; Sarkar et al. 2015). Although each technique has its own advantages and disadvantages, photodynamic therapy has been increasingly exploited over the last few decades. This is due to many reasons. Firstly, the procedure is simple and cost-effective. It involves the administration of the cancer-treating prodrug (otherwise known as the photosensitizer; PS) via intravenous or topical routes and activation of the drug after some time using non-toxic light of suitable wavelength (Chiaviello et al. 2011; Allison and Moghissi 2013). Secondly, tuneable prodrugs are employed which become cytotoxic only in the presence of light. Thirdly, it employs non-toxic visible and near-infrared light for both superficial and deep-seated treatment, respectively. Lastly, the technique can be used to treat non-cancerous diseases (Hu et al. 2014), such as age-related eye disease (macular degeneration) (Huang 2005). The prodrugs used in PDT can be classified as porphyrin and non-porphyrin photosensitizers (Chiaviello et al. 2011). The porphyrin photosensitizers include the free base porphyrin molecule and its derivatives, such as benzoporphyrins, chlorins and bacteriochlorins. These can be further classified as first- (e.g., PHOTOFRIN®) and second- (e.g., chlorins and bacteriochlorins) generation porphyrin PSs. On the other hand, the non-porphyrin PSs include cyanine (Wang et al. 2014, b; Jing et al. 2016), methylene blue (Zhao et al. 2014), rose bengal (Tang et al. 2015) and boronated dyes (Adarsh et al. 2010). Nevertheless, the porphyrin PSs have higher clinical acceptance than the non-porphyrin counterparts due to their relatively high biocompatibility, non-toxicity, and high clinically proven safety. Different porphyrin-derived PSs have evolved over many years due to an attempt to improve the properties of original porphyrin. For example, PHOTOFRIN®, the first generation clinically-acceptable porphyrin-derived PS is chemically inhomogeneous with limited absorbance in the infrared (Schuitmaker et al. 1996), and thus could not be used on underlying material. Most common unique properties conferred by modification of the core materials include water solubility (Kikuchi et al. 2011; Kim et al. 2012), optical property improvement, disease-site location (Vincent et al. 2013), prolongation biological circulation half-life (Kim et al. 2012) and therapeutic function (Li et al. 2013; Cheng et al. 2014; Wang et al. 2014, b; Meyers et al. 2015).

Nanomaterials can be synthesized using physical, chemical, and biological means. However, for the purpose of this review, we will focus only on the most commonly employed chemical methods, and centralizing principally on the synthesis of SPIONs, gold nanoparticles, QDs and Lanthanide series nanoparticles, being the commonly reported nanomaterials for the enhancement of PDT.

Synthesis of SPIONs

The main strategy for the synthesis of SPIONs revolves around breaking down the size of the bulk material below a critical size necessary to infer the unique superparamagnetic properties on the nanoparticles. Thus, many factors that promote the production of

smaller-sized nanoparticles, such as increases in stirring rate, pH, concentration of the precursor, and coating materials, are taken into consideration. Typically, SPIONs have been made using various techniques, such as co-precipitation (Lu et al. 2010a), hydrothermal, microemulsion, solvothermal and electrochemical methods. However, for biomedical purposes, SPIONs synthesized via coprecipitation are commonly employed. This may be as a result of its clearer chemistry, cost advantage, and greener procedure compared to other techniques. SPIONs utilized for biomedical applications are of two categories, i.e., magnetite (Fe_3O_4) and maghemite (Fe_2O_3). Both materials exhibit a cubic inverse spinel crystal structure but only iron (II) ion vacancy exists in maghemite. The presence of this vacancy in maghemite makes it less toxic and thus more desirable for biomedical applications. Moreover, maghemite can also exhibit a tetragonal configuration under certain thermal conditions (Kazeminezhad and Mosivand 2014). Under coprecipitation, magnetite nanoparticles are produced first, while maghemite can be subsequently obtained if desired under suitable oxidizing conditions. Stereotypically, magnetite nanoparticles are produced by precipitating stoichiometric molar solutions of iron (II) and iron (III) ions in an alkaline medium in the presence of an inert gas such as nitrogen or argon at a molar ratio of 0.5. The inert gas ensures prevention of oxidation of magnetite to either hematite or maghemite. However, nowadays, the use of inert gases may be less embraced as new methods such as green techniques that generate in situ reducing capping agents capable of preventing oxidation are emerging (Lu et al. 2010b). Pristine SPIONs aggregate in aqueous solution. Thus, to make SPIONs suitable for biomedical applications, they need to be stabilized in water. This is achieved by coating their surfaces with hydrophilic polymers, such as dextran and polyethylene glycol. The coating process may involve encapsulation or covalent or electrostatic linkage.

Synthesis of superparamagnetic magnetite nanoparticles

Synthesis of superparamagnetic magnetite nanoparticles can be described under two categories, i.e., low- and high-temperature syntheses. The low-temperature synthesis involves synthesis with temperature ranging between room temperature and 100 °C under normal atmospheric pressure, whereas the high-temperature synthesis involves synthesis which requires temperature above boiling point of water and pressure greater than normal atmospheric pressure. Coprecipitation and microemulsion syntheses fall under the low-temperature category whereas hydrothermal and solvothermal fall under high-temperature synthesis.

Coprecipitation method

This involves precipitation of magnetite nanoparticles (Figs. 1, 2) at temperatures below the boiling point of water: 40 °C (Mürbe et al. 2008), 60 °C (Lu et al. 2010a), 70 °C (Daou et al. 2006), 80 °C and 90 °C (Thapa et al. 2004), usually in an alkaline medium in the presence or absence of an inert gas such as nitrogen or argon. The magnetite nanoparticles are produced from a 1:2 M ratio of iron (II) and iron (III) ions which can be obtained from the direct addition of iron (II) and iron (III) salts (Wagstaff et al. 2012; Tajabadi et al. 2013), partial reduction of ferric salts by suitable reductants (Qu et al. 1999; Lu et al. 2010a) or oxidation of ferrous salts by suitable oxidizing agents (Mürbe et al. 2008; Shete et al. 2014).

Microemulsion method

This involves coprecipitation of ferrous and ferric ions within the matrix of two immiscible liquids, such as oil and water. This is one of the easier ways that smaller magnetite nanoparticles can be obtained, since reactants are confined within a limited small space so that coprecipitation occurs within the microdroplets formed as a result of the immiscibility of the organic and aqeous phases (Nassar and Husein 2006; Chin and Yaacob 2007; Okoli et al. 2011, 2012).

Hydrothermal synthesis

This is also aqueous-based coprecipitation, but occurs at a higher temperature and pressure than the boiling point of water and normal atmospheric pressure (Wu et al. 2008; Ge et al. 2009; Haw et al. 2010). Typically, it involves heating the aqueous mixture of ferrous and ferric ions at a molar ratio of 1:2 in a sealed container (usually a Teflon stainless steel autoclave) at a temperature above 100° C. Crystalline monodispersed magnetite nanoparticles may be obtained using this method. The higher temperature and pressure seem to promote higher crystanillity and monodispersity.

Solvothermal synthesis

This is similar to hydrothermal synthesis but employs high-boiling point polar or non-polar organic solvents instead of water. For example, Hou et al. (2003) synthesized magnetite nanoparticles by heating the mixture of Iron (III) acetyl acetonate, hydrazine (b.p. 114 °C) and ethylene glycol (b.p. 197.3 °C) in a teflon stainless steel autoclave at 180 °C.

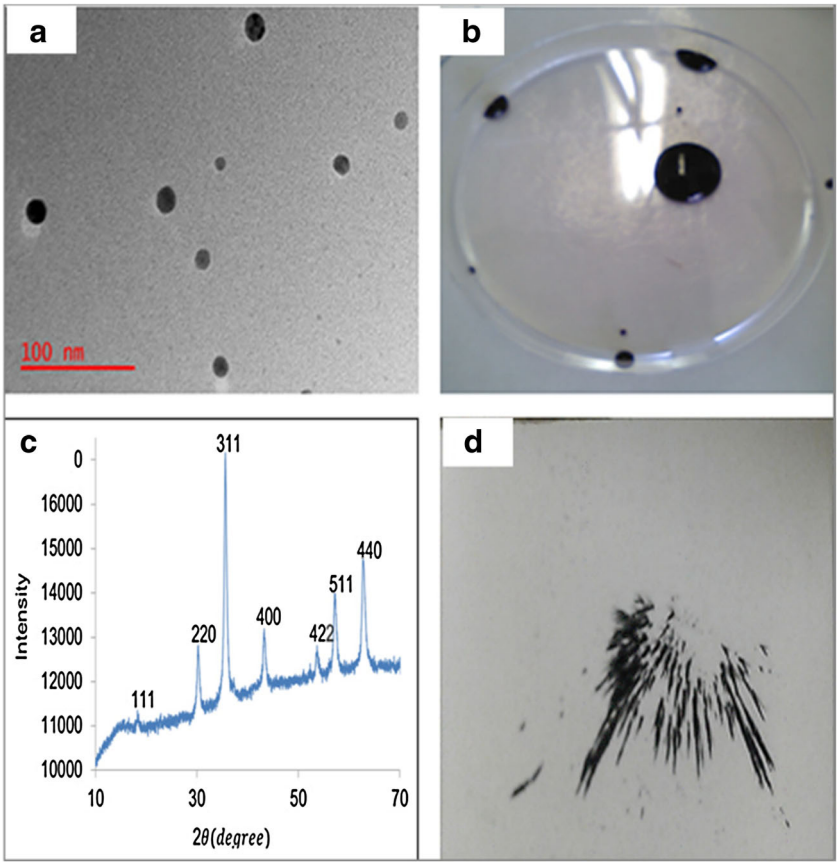


Fig. 1 Digital images and some physical characterization of magnetite SPIONs synthesized by coprecipitation. **a** TEM Image; **b** aqueous SPIONs; **c** XRD spectrum; **d** dried solid SPIONs in the presence of an external magnetic field

High-temperature reflux synthesis

Sun et al. (2004a) synthesized crystalline monodispersed magnetite nanoparticles by refluxing a mixture of Iron (III) acetyl acetonate, 1,2-hexadecanediol, phenyl ether, oleic acid and oleylamine at 265 and 300 °C after initial heating of the reactants to 200 °C. This is similar to the solvothermal technique but the experimental setup is carried out in a reflux system rather than in an autoclave. High-temperature reflux synthesis seems to produce highly monodispersed, uniformly shaped, narrow distribution nanomaterials (Saville et al. 2014).

Aerosol assisted chemical vapor deposition

This involves coprecipitation of magnetite under high-temperature thermal decomposition of ferrous salt solution in the presence of regulated constant flow of a given volume air/argon mixture, usually at temperature above 420 °C. The air is responsible for the partial oxidation of ferrous ions while the argon keeps the synthesis environment inert. The setup is such that the magnetite can be collected in methanol and be separated from other components by a permanent magnet (Monárrez-Cordero et al. 2014).

Electrochemical synthesis

This involves synthesis of magnetite from an iron salt solution using an electrochemical setup. Typically, iron is made the anode while the electrolyte consists of mixture of salt and stabilizer. This method has been used by many authors (Cabrera et al. 2008; Starowicz et al. 2011; Rodríguez-López et al. 2012; Kazeminezhad and Mosivand 2014; Yu et al. 2014) to synthesize magnetite nanoparticles of well-defined characteristics. Moreover, it has been reported that the distance between the anode and cathode as well as optimized low potential favors the formation of magnetite nanoparticles without metallic iron impurity (Cabrera et al. 2008; Starowicz et al. 2011; Rodríguez-López et al. 2012).

Synthesis of superparamagnetic maghemite nanoparticles

Maghemite nanoparticles are typically synthesized by oxidizing magnetite nanoparticles (Bee et al. 1995; Jolivet et al. 2002; Sun et al. 2004b; Mürbe et al. 2008) either in the presence of air at 100 °C (Sun et al. 2004b) or 300 °C (Mürbe et al. 2008) or another suitable oxidizing agent, such as nitric acid (Wagstaff et al. 2012) or ferric nitrate (Bee et al. 1995) at 90 °C after washing the magnetite with nitric acid. This is usually

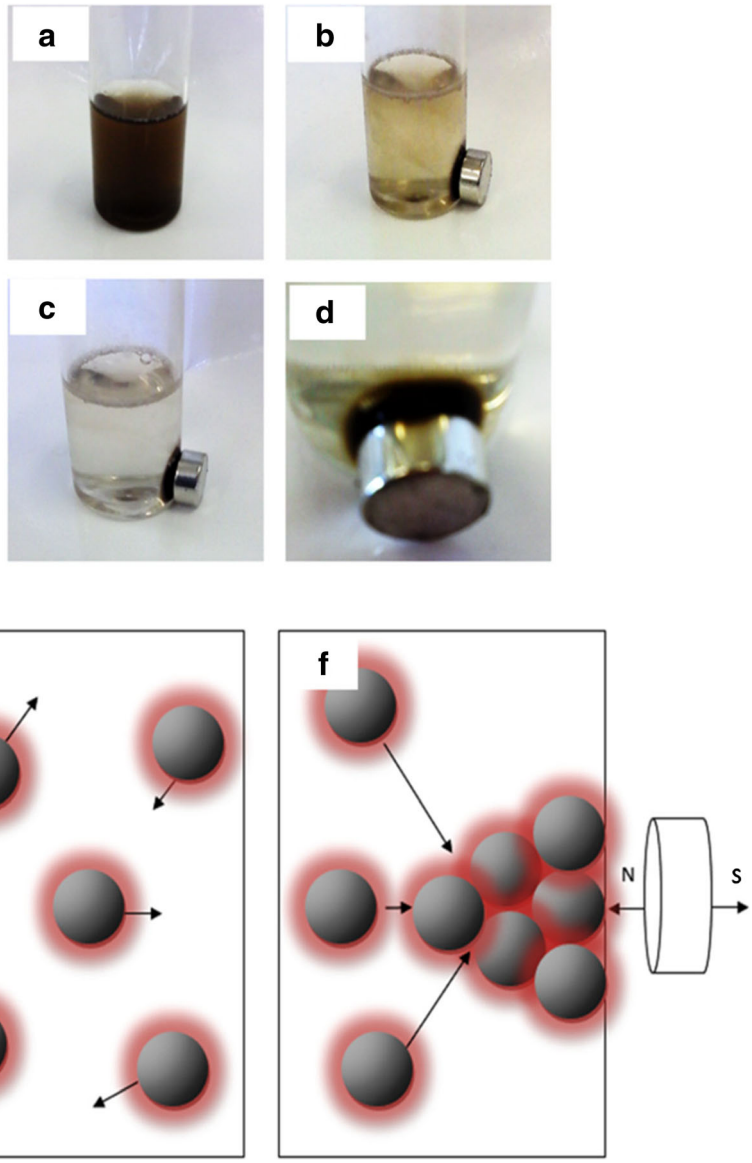


Fig. 2 Digital images of aqueous magnetite SPIONs' response to external magnetic field with time. **a** 0 min; **b** 5 min; **c** 10 min; **d** enlargement of (**c**); **e** modeling structure of (**a**); **f** modeling structure of (**b**)

accompanied by a change of color from a black magnetite nanoparticle solution to a light brown (Kazeminezhad and Mosivand 2014) or reddish brown color of maghemite nanoparticles (Sun et al. 2004b; Kazeminezhad and Mosivand 2014) depending on the synthesis conditions. Moreover, sintering of magnetite nanoparticles at 200 °C and 650 °C has also been reported for the synthesis of pure maghemite nanoparticles of different structures (Kazeminezhad and Mosivand 2014).

Surface modification of SPIONs

Many biocompatible polymers, such as dextran (Saraswathy et al. 2014), polyethylene glycol (Zhang et al. 2002; Silva et al. 2016), polyvinyl pyrrolidone (Arsalani et al. 2010), liposomes (Vincent et al. 2013), dendrimers (Tajabadi et al. 2013), copolymers, such as poly(aspartate)-graft-poly(ethylene glycol)-dodecylamine- hydrazone-(adriamycin-levulinic acid) (Huang et al. 2013), polyethylene glycol-polylactic acid (Zhang and Xie 2011) or poly (3-(trimethoxysilyl) propyl methacrylate-r-PEG methyl ether methacrylate –r-N-acryloxysuccinimide) (Lee et al. 2007), and protein (Lee et al. 2006), as well as functionalized inorganic gold (Liu et al. 2008; Wagstaff et al. 2012; Azhdarzadeh et al. 2016) and a metalloid, such as silica (Tadić et al. 2012), has been reported to stabilize SPIONs in aqueous solution. In addition, coatings with organic polymers, monomers, such as gluconic acid (Lu et al. 2010a), citric acid (Klein et al. 2012) or mercaptopropionic acid (Lee and Woo 2006), have also been reported. Modification of a SPION's surface is usually achieved by direct addition of the coating agent during or after synthesis or by ligand exchange. The latter involves the

interchange of a hydrophobic ligand on the surface of the SPION with a hydrophilic ligand in order to make the SPION water-soluble (Zhou et al. 2014; Silva et al. 2016).

Synthesis of gold nanoparticles

Gold nanoparticles have a long history in biomedical applications basically as passivation, drug delivery, imaging and photothermal agents. They have different characteristic shapes, such as spherical, rod and cages with tunable sizes (Huang and El-sayed 2011). However, for the purpose of PDT, spherical gold nanoparticles are used on their own or as part of multifunctional nanomaterial hybrid system for drug delivery purposes. The spherical gold can be obtained using simple established laboratory procedures, such as sodium borohydride (Shervani and Yamamoto 2011), citrate (Huang and El-sayed 2011; Verissimo et al. 2016; Zhao et al. 2016), amino acid (Katti et al. 2009; Vijayakumar and Ganesan 2012; Wang et al. 2016), UV-irradiation (Cai and Yao 2013), gamma-ray (Hien et al. 2012) and carbohydrate (Engelbrekt et al. 2009; Pienpinijtham et al. 2011; Shervani and Yamamoto 2011; Chairam et al. 2015) reduction methods. Stereotypically, the reaction undergoes many color change phases depicting different sizes and electronic transition transformations with time (Shervani and Yamamoto 2011). Classically, the color changes from yellow to blue to purple to wine red color (Hussain et al. 2009; Zhao et al. 2016). This mechanistically suggests that, at first, the reaction was very fast and many small nanoscale gold nanoparticles were produced. However, these nanoparticles are very unstable due to their high surface energy. Thus, they aggregate in order to minimize this surface energy. This results in the shifting of the surface plasmon resonance (SPR) signal to higher wavelength and corresponding change in the color of the medium from yellow to blue (Fig. 3). Moreover, as the reaction proceeds, the aggregate redissolves in the solution forming smaller particles which lower the SPR wavelength. This causes a change in the color of the solution from blue to purple and finally to red (Fig. 3) or even yellow-brown (Pal 2004). This approach is particularly attractive because specific size distribution can be easily controlled by evolution of each color.

Citrate-reduction method

This typically involves reduction of the gold precursor salt into its nanoscale dimension by citrate ions at the boiling temperature of water. Many authors have used this method to obtain gold nanoparticles of variable sizes (Wang et al. 2012; Zhang et al. 2012; Verissimo et al. 2016; Zhao et al. 2016). Also, the citrate ions can serve as both reducing and capping agents, making this approach more cost-effective than some techniques (e.g., sodium borohydride) which require stabilizing agents in their syntheses. The mechanism of reduction of gold salt to its nanoparticle scale by citrate ion could follow the following pathway: oxidation of citrate ion by gold (III) ion via acceptance of electrons from the former which thus reduces it to its zero oxidation state. After reduction, excess citrate ions surround the gold nanoparticles preventing their aggregation. However, it has been reported that citrate-capped gold nanoparticles are prone to aggregation in the presence of high ionic strength (40–100 mM NaCl) (Wang et al. 2010).

Carbohydrate-reduction method

This involves utilization of sugars, such as glucose (Engelbrekt et al. 2009; Shervani and Yamamoto 2011), starch (Pienpinijtham et al. 2011), dextran (Wang et al. 2010) and some naturally occurring gum (Tagad et al. 2014), as reductants for gold nanoparticle production. This typically takes place in the presence of an alkaline promoter or high temperature or both (Pienpinijtham et al. 2011), as many of these sugars inherently could not feasibly reduce at ordinary room temperature or in an acidic or neutral media. For example, in the case of glucose, the reducing aldehyde moiety is only available in the low-population linear form and not in any of the cyclic forms. The use of carbohydrate reducing agents for the synthesis of gold nanoparticles has several advantages over other methods. These include cost-effectiveness, availability, non-toxicity and biocompatibility. Other advantages include the ability of some of these carbohydrates to serve as both reducing as well as stabilizing agents. Furthermore, reducing monosaccharides (e.g., glucose) could generate an in situ acidic stabilizing agent which stabilizes the gold nanoparticles. The proposed mechanisms of reduction of gold (III) salt by different forms of carbohydrates are shown in Scheme 1. The disaccharides, trisaccharides, oligomers and polymers tend to undergo alkaline hydrolysis to produce their respective reducing monomers which function as an active reducing entity. After reduction, the excess polymer or the oxidation products of the monomers tend to stabilize the gold nanoparticles.

Surface modification of gold nanoparticles

Pristine gold nanoparticles may not be stable for very long and thus require stabilizing agents to prevent aggregation. Like many nanoparticles, gold nanoparticles are well stabilized using polymers. However, for the purpose of biomedical applications, non-toxic biocompatible polymers are required. To this end, many biocompatible polymers, such as polyethylene glycol (Penon et al. 2015), dextran (Wang et al. 2010; Cai and Yao 2013), polylysine (Wang et al. 2016) and starch (Hussain et al. 2009; Katti et al. 2009), have been reported to stabilize gold nanoparticles in aqueous solution. Furthermore, coating

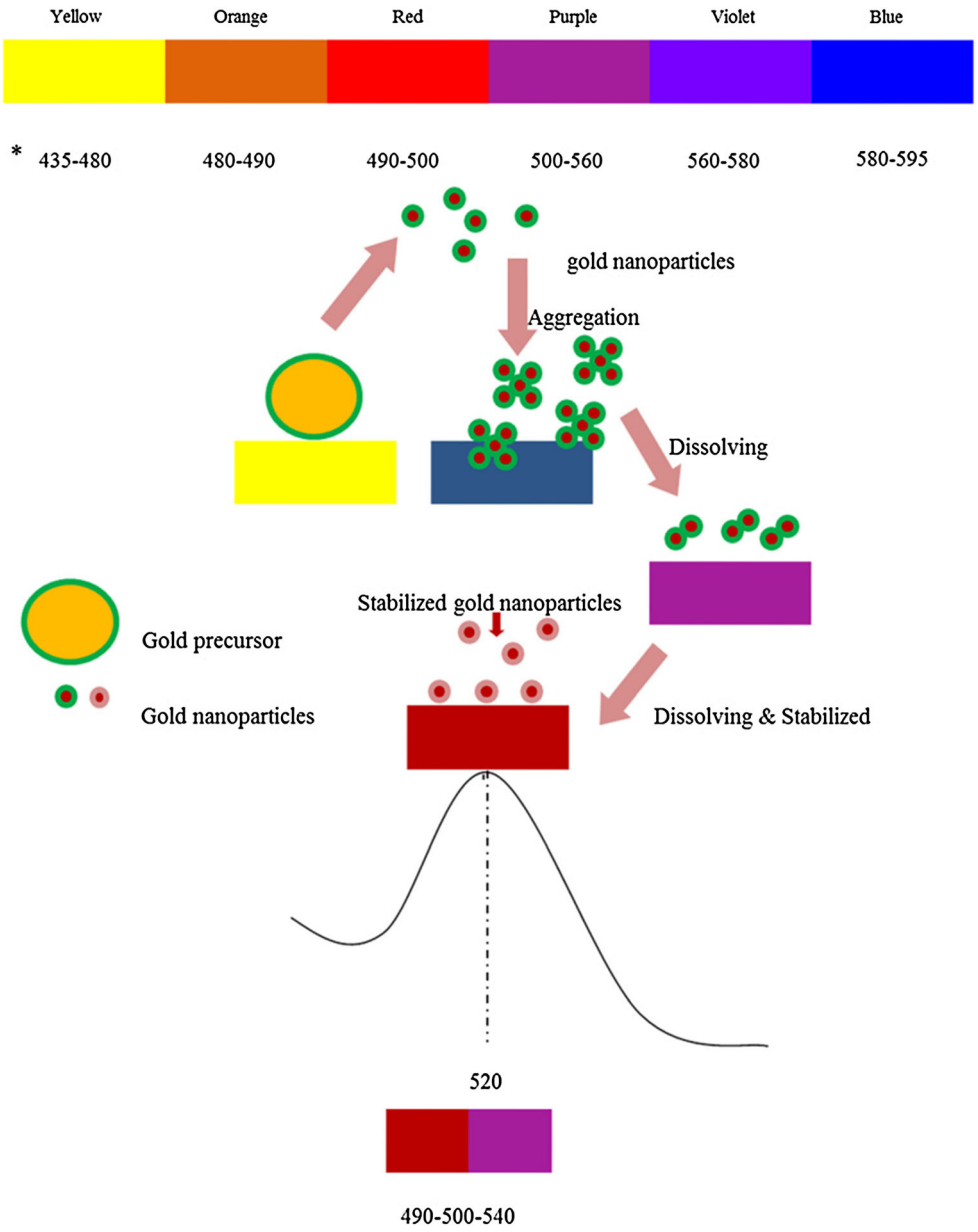


Fig. 3 Possible synthesis pathway for the synthesis of red-colored gold nanoparticles (SPR 520 nm); *Absorbed wavelength range

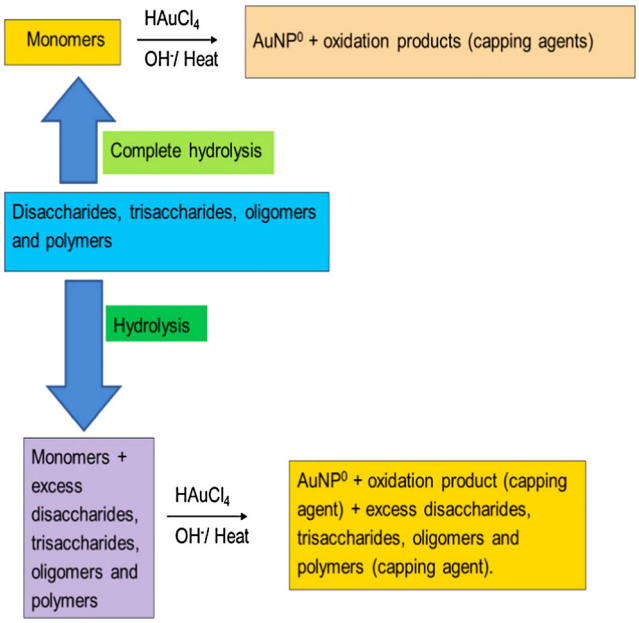
the surface of gold nanoparticles with silica (Li et al. 2015a) has also been reported.

Synthesis of quantum dots

Synthetic methods for QDs are aimed at controlling the crystalline structure, mono-dispersion and narrow size distribution for various applications. The formation of QDs has been researched over 40 years with many methods being reported, including micro-emulsion, pyrolysis, the use of microwaves, and organic (Mohan et al. 2014) and aqueous synthetic methods (Dhar 2014). Synthetic methods use physicochemical parameters, growth time and temperature to control the size and shape of the QDs. Through the selection of precursors, solvents, coordinating agents and the purity of the coordinating solvent, QDs can be tailored to the required size and shape (Bera et al. 2010).

Organic synthesis of quantum dots

The organometallic approach for the synthesis of QDs is one of the most widely used methods. It produces high-quality, nearly mono-dispersed QDs and involves the use hydrophobic ligands such as trioctylphosphine (TOP), tri-n-octylphosphine oxide (TOPO) or hexadecylamine (HDA) (Oluwafemi et al. 2016). High temperatures of ~ 220 °C and above are commonly used to boil the organic ligands to homogenize the



Scheme 1 Possible mechanism pathway for the synthesis of gold nanoparticles using carbohydrate reductants

mixtures. High temperatures are essential to decompose the precursors into monomers that form the QDs (Fontes et al. 2012). Organic synthesis uses inert gases (argon and nitrogen are commonly used) and hot injection of the metal precursors. This synthetic method renders the QDs hydrophobic as the functional groups (i.e. amines, phosphines and phosphine oxides) of the ligands attach their terminal ends to the QDs surface with their ligand alkyl chains directed away from the surface. Hydrophobic QDs synthesized using organic methods are reported to produce high quantum yields and luminescent materials. Quantum dots synthesized via organo-metallic methods have limited applications in biomedical fields due to their hydrophobicity. However, in order to be suitable for biomedical applications, they are converted to hydrophilic materials via organic-water phase transfer strategy. This can be achieved by replacing the hydrophobic ligands with hydrophilic ligands such as glutathione (GSH), thioglycolic acid (TGA), and mercaptosucinnic acid (MSA) via ligand exchange approach. Alternatively, the surface of the hydrophobic core may be coated with a water soluble shell material (Bera et al. 2010). On the other hand, they can be synthesized directly in aqueous media.

Aqueous synthesis

Preparation of QDs directly in water increases their biocompatibility and stability. Aquatic synthesis of QDs produces good reproducibility, low toxicity and environmentally friendly materials. General features of aqueous synthesis are direct water-solubility and facile preparation at low cost (Wegner and Hildebrandt 2015). These QDs emanate from precursors consisting of heavy metal salts that are easily dissolved in water such as chlorides, nitrates and acetates. Capping agents often used for the synthesis of water soluble QDs are small organic molecules such as those containing mercapto-acid (Dhar 2014), mercapto-amine (Zhou et al. 2011) and mercapto-amine-carboxylic acid functional groups (Wei et al. 2014).

Surface modification of quantum dots

Modification of the surface of QDs allows their use in applications where they ordinarily would not be utilized. QDs produced via organic synthetic methods are insoluble in aqueous media and therefore not applicable in biological systems. For biological applications, it is therefore necessary to modify the surface to provide the desired specific bio-recognizable or targeting surface (Delehanty et al. 2009). A variety of surface modification techniques have been reported with the intention of achieving surfaces that are stable in biological media without altering the photo-physical properties of the QDs. These include encapsulation via hydrophobic interaction and ligand exchange - Encapsulation approach often includes coating with amphiphilic molecules that contain functional groups such as amines ($-NH_2$), carboxylic acid (-COOH), hydroxyl (-OH) and thiols (-SH). These molecules contain both hydrophobic and hydrophilic terminals. The hydrophobic domain encapsulates the hydrophobic cavity of the QDs while hydrophilic end enables the dispersion of QDs in aqueous solution (Palui et al. 2014). The encapsulation method is frequently used because it addresses the problems of decrease in luminescence quantum yields, aggregation and precipitation during surface modification. On the other hand, ligand exchange involves the addition of native ligands such as carboxylate- or- amine terminated thiols in excess in exchange for the hydrophobic surface of the QDs. However, this method can lead to surface defects which have significant effects on the optical properties of the QDs. Furthermore, ligand exchange can extend the functional groups introduced to the surface of the nanocrystals (Sperling and Parak 2010; Jin et al. 2011). As a result, QDs size may be increased to sizes that limit their use for biological applications. In terms of solubilization, QDs are often functionalized to perform the required application via bio-conjugation such as attachment to peptides, antibodies, DNA and albumin (Zhang et al. 2016). Advantage of this approach is that the conjugates often have greater luminescence and stability when compared to unconjugated QDs. Additionally; bio-conjugation enables the use of QDs in therapeutic treatments such as gene therapy and PDT.

Lanthanide series nanoparticles – synthesis and surface modification

Lanthanide series are rare-earth elements having atomic number ranging from 57 to 71. Their ions are exceptional UV, visible and near infrared light emitters when irradiated with near infrared (Up-conversion) (Hemmer et al. 2013; Zeng et al. 2013; Yang et al. 2015) or X-ray (Down-conversion) (Chen et al. 2015) light of appropriate wavelength. Thus, they have found major use in both up and down-conversion optical applications such as visible or UV up-conversion luminescence PDT (Chen et al. 2015) and X-ray down-conversion visible luminescence PDT (Chen et al. 2015). This urpose is usually achieved by doping with suitable host compounds such as yttrium oxide (Hemmer et al. 2013), chloride (Guo et al. 2007) or sodium gadolinium fluoride (Yang et al. 2015). This can be achieved by microemulsion (Guo et al. 2007) or high temperature reflux (Zeng et al. 2013) or thermal decomposition of the precursor salts (Wang et al. 2011) usually in the presence of a suitable organic stabilizing agent such as oleic acid (Wang et al. 2011) or cetyl trimethylammonium bromide (CTAB) (Guo et al. 2007). However, for biomedical purposes, ligand exchange may be employed using carbohydrate such as α-cyclodextrin (Tian et al. 2013) or polymer such as polyethylene glycol (Zeng et al. 2013; Yang et al. 2015) to prevent toxicity, ensure aqueous stability and prolong circulation half-life. The core-shell architecture of up- and down-conversion lanthanide series nanoparticles embedded in their host matrix used for the purpose of enhancement of PDT is schematically shown in Fig. 4.

Typically, the nanoparticle structure consists of the core made of lanthanide ion embedded within its host matrix and a shell consisting of functionalized PS. The whole structure may be embedded in a mesoporous material such as meso-silica (Chen et al. 2015) or within a polymer matrix (Zeng et al. 2013). It has been noted that the distance between the core and the PS should be optimized for effective fluorescence resonance energy transfer (FRET) from the core to the PS (Wang et al. 2011).

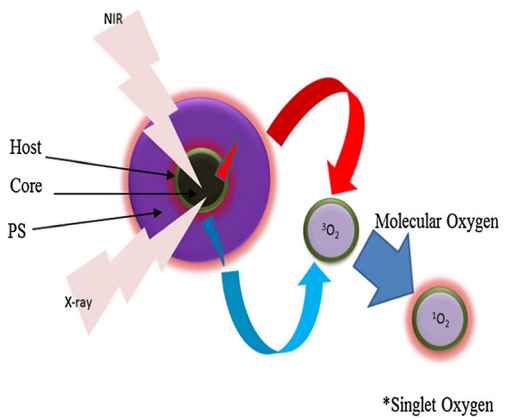


Fig. 4 Schematic diagram of the singlet oxygen generation potential of the up and down-conversion of the core-shell lanthanide series–PS conjugate

Characterization of nanomaterials for biological application

Characterization of nanomaterials is essential to determine their safety and efficacy. Nanomaterials are characterized for the elucidation of their inherent physicochemical parameters such as composition, size, shape, stability, solubility, surface properties, molecular weight, identity, purity and optical properties such as light absorption and emission which are of paramount importance for physiological interactions. Characterization techniques that are available for the measurement of the physical and chemical properties of nanomaterials. These include ultraviolet-visible spectrophotometry (Dong et al. 2016), photoluminescence spectroscopy (Mohan et al. 2014; Zhang et al. 2016), scanning electron microscopy (SEM) (Iram et al. 2010; Goswami et al. 2016), transmission electron microscopy (TEM) (Saville et al. 2014; Jing et al. 2016; Oluwafemi et al. 2016), energy dispersive X-ray spectroscopy (EDX) (Shervani and Yamamoto 2011), X-ray photoelectron spectroscopy (XPS) (Azhdarzadeh et al. 2016; Dong et al. 2016), dynamic light scattering (DLS) (Zamora-Mora et al. 2014), zeta potential (Iram et al. 2010), inductively coupled plasma optical emission spectroscopy (ICP/OES) (Saville et al. 2014), vibrating sample magnetometry (Shen et al. 2014) and powder X-ray diffraction (XRD) (Ngenefeme et al. 2013). However, determination of the core nanocrystallite particle size distributions, hydrodynamic size distribution, shape morphology and crystallinity are usually done using correlative data from SEM, TEM, DLS, HRTEM, SAED and XRD (Lu et al. 2010b; Behdadfar et al. 2012; Shete et al. 2014). Surface chemistry such as surface chemical functional group composition, specific surface area and surface reactions are often characterized using Fourier transform infrared spectroscopy (FTIR) (Behdadfar et al. 2012; Shen et al. 2014), Brunauer- Emmett-Teller techniques (BET) surface area analysis (Aphesteguy et al. 2015) and surface enhanced Raman spectroscopy (Bera et al. 2010; Han et al. 2012) respectively. In terms of surface charges and elucidation of the oxidation states of metallic composition, zeta potential (Ngenefeme et al. 2013) and X-ray photoelectron spectroscopy (XPS) (Azhdarzadeh et al. 2016; Dong et al. 2016) respectively are especially useful. For the optical absorption and fluorescence probing, ultraviolet-visible spectrophotometry (Shervani and Yamamoto 2011) and fluorospectrophotometry (Mandal et al. 2013) are respectively the most commonly employed. Moreover, elemental composition and quantification determinations are usually done using EDX (Shervani and Yamamoto 2011) and ICP/OES (Saville et al. 2014) respectively.

Fate of nanomaterials for biomedical applications

There is a long-standing and on-going debate concerning the toxicity of nanomaterials when employed for biomedical applications. However, reports have proven non-toxicity of some nanomaterials both in vitro and in vivo. Thus, for a nanomaterial to be acceptable for biomedical applications, its biocompatibility as well as cytotoxicity properties must fulfill biomedical safety requirements. Many pristine nanoparticles especially noble metals, metal oxides and QDs aggregate in aqueous solution due to their hydrophobic character. Aggregation within biological fluid raises a concern since aggregated nanomaterials can cause embolism in blood vessels (Kim et al. 2012). Naked nanoparticles can also react readily with cellular composition inducing certain toxicity. As a result, these nanomaterials are usually covered with biocompatible hydrophilic materials such as dextran (Wang et al. 2010; Cai and Yao 2013), liposomes (Vincent et al. 2013; You et al. 2014), dendrimers (Daou et al. 2009; Tajabadi et al. 2013) and polyethylene glycol (Ichikawa et al. 2005; Penon et al. 2015) which infer on them stability against aggregation and help to prevent toxicity. Nanomaterials may be administered into the human body via oral, injection and intravenous routes (Cortajarena et al. 2014). Nonetheless, nanomaterials need to overcome certain barriers such as protein interaction, phagocytic invasion and cellular resistance before they can become efficient for biomedical use. Again the surface charge, shape and nature of coating materials (Cortajarena et al. 2014), in addition to size (Weinstein et al. 2010; Kim et al. 2012) play essential roles in this regard. Neutral nanomaterials may be required to avoid protein interaction while an intermediate optimum size profile may be needed to avoid phagocytic elimination (Weinstein et al. 2010). Furthermore, cellular resistance against internalization may be prevented using positively charged nanomaterials (Cortajarena et al. 2014). As a result, the evaluation of the pharmacokinetic parameters such as absorption and internalization into cells, circulation half-life as well as elimination mechanism from the body is crucial for the determination of the fate of nanomaterials within the biomedical environment.

Photodynamic therapy (PDT)

Principle, mechanism and clinical procedure

PDT is a non-invasive cancer treatment technique (Allison and Moghissi 2013) that entails generation of in situ reactive oxygen species for the destruction of cancer cells. It involves activation of a prodrug (photosensitizer) with a non-toxic light (Master et al. 2013) of a suitable wavelength (from visible to near infrared (Gao et al. 2012; Li et al. 2013). The prodrugs are usually fluorescent materials that have the capability to undergo transition from their excited singlet state to corresponding triplet state population (TSP) via photochemical intersystem reactions. The TSP produces reactive oxygen species via Type I and Type II reactions which involve transfer of electrons and energy respectively to molecular oxygen (Chiaviello et al. 2011). In most cases, the Type II reaction involving generation of singlet oxygen predominates (Ethirajan et al. 2011; Allison and Moghissi 2013; Li et al. 2015a) especially in an oxygen-rich environment. Under low tissue oxygenation or high concentration of photosensitizer, the anoxic and hypoxic conditions arise and the Type I reaction occurs leading to the generation of other reactive oxygen species such as superoxide and hydroxyl radicals (Ethirajan et al. 2011) (Fig. 5).

The clinical procedure of PDT involves intravenous administration of the prodrug, followed by a waiting time to allow the drug to circulate around the body in the absence of light. Following this the tumor site is irradiated with light of appropriate wavelength for a specific time. Consequently, the tumor becomes reduces in size and eventually disappears with time (Hirohara et al. 2015). Reports have shown that reactive oxygen species destroy cancer cells via apoptosis and necrosis (Piette et al. 2003; Samaroo et al. 2007; Gariboldi et al. 2009; Chiaviello et al. 2011; Master et al. 2013; Hirohara et al. 2015).

Apoptosis is a form of programmed cell death that can be controlled via a natural energy-dependent biochemical pathway. Its effect has been associated with mitochondrial damage (Yan et al. 2010). However, apoptosis being a naturally-controlled process may be reversible under certain conditions. On the other hand, necrosis is an uncontrollable process and thus could be regarded as more devastating than apoptosis. It damages the cell membrane causing the release of its contents into the surrounding environment. As a result, the process could be predictably irreversible. Necrosis effect has been associated with uncontrolable generation of the reactive oxygen species and impaired ion channel within tissue environment. This generally leads to the cessation of the normal biochemical activities such as angiogenesis (Acharya and Sahoo 2011) of the tumor. Both apoptosis and necrosis can be detected using various biological staining assays coupled with microscopic techniques (Yan et al. 2010; Hirohara et al. 2015; Meyers et al. 2015).

Importantly, for effective PDT, certain parameters are essential. These include the amount of energy per unit area (fluence or dose), power (fluence rate or intensity) (Chiaviello et al. 2011) and wavelength of the irradiating light (Postiglione et al. 2011), tissue oxygen concentration (Ethirajan et al. 2011), singlet oxygen generation potential of the photosensitizer, optical absorptivity of the photosensitizer, photobleaching resistance of the photosensitizer, as well as time of irradiation, area of irradiation and the prodrug

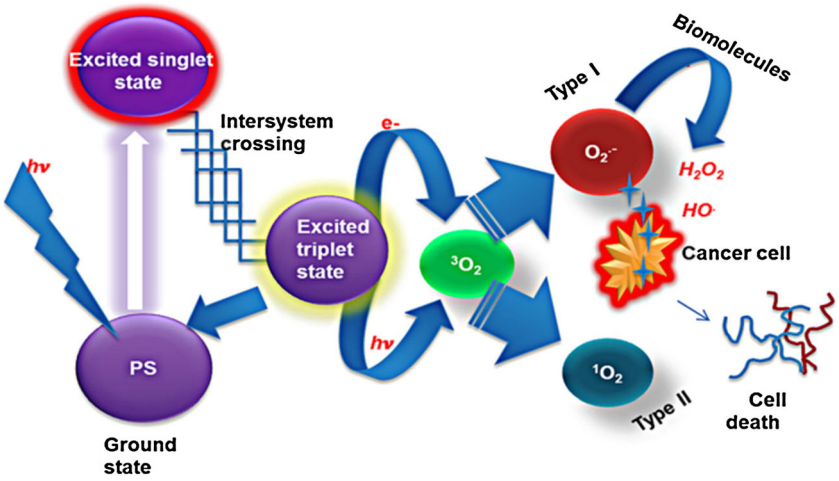


Fig. 5 Mechanism of photodynamic therapy. PS = Photosensitizer

incubation-light irradiation time interval (Chiaviello et al. 2011). The relationship between the light dosimetry parameters and time of irradiation is shown in Fig. 6.

Advantages, limitation and improvement of PDT

PDT, being a non-invasive technique, has several advantages over the conventional treatments such as chemotherapy, ionizing radiotherapy and surgery. These include the use of non-toxic light and biocompatible prodrug, simple and programmable operational time procedure, cosmetic advantage and patient's psychological peace of mind as opposed to possible depression that may be experienced after surgical operation. It

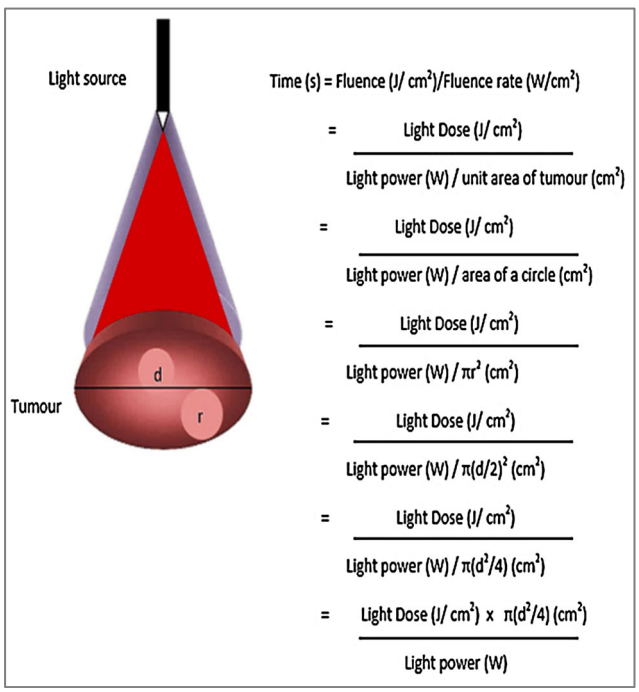


Fig. 6 Relationship between the light dose, power, tumor unit area and time of irradiation

can also be used to treat certain non-cancerous diseases such as bacterial infections (Tegos et al. 2006; Yan et al. 2010; Park et al. 2012; Sperandio et al. 2013) and age-related eye disorder such as macular degeneration (Postiglione et al. 2011).

However, despite all these advantages, PDT has many challenges. These include post-therapeutic photosensitivity, optical absorption limitation, aggregation and non-specific localization of some photosensitizers. The first clinically acceptable photosensitizer, PHOTOFRIN® is an oligomer mixture of hematoporphyrin. Porphyrin PS has long history of biosafety as many are found directly in nature. However, PHOTOFRIN® has weak absorption at the longer therapeutic wavelengths and thus has only been used to treat superficial tumor cases. Moreover, the need to treat deep-seated tumors has led to the development of the second-generation porphyrin PSs such as chlorins and bacteriochlorins. These latter PSs absorb light of longer wavelengths within the biological therapeutic window than PHOTOFRIN®. The second generation porphyrin PSs also have faster clearance indices compared to PHOTOFRIN® and thus reduce the duration of patient photosensitivity. Nevertheless, all porphyrin PSs show non-specific therapeutic effect leading to the demand for the development of third generation porphyrin prodrugs. These materials involve attachment of porphyrin prodrugs to nanomaterials functionalized with cancer-surface targeting (CST) agents such as antibody, reducing carbohydrate and folate or capable of being driven by an external magnetic field such as superparamagnetic iron oxide nanoparticles (SPIONs). The CST agents specifically bind to their receptors overexpressed on the surface of tumor. This avoids non-specific reactions within the physiological fluid matrix. Similarly, the use of external magnetic field-driven SPIONs helps to ensure the prodrug is actually delivered into tumor sites. The advantages of making porphyrin tumor-specific are enormous. These include safety of normal cells within the vicinity of the irradiated tumor environment, reduced photosensitivity time, very high therapeutic function and reduction

in therapeutic agent's dose. Another factor that affect effective PDT efficiency is the PS aggregation and medium influence. Tang et al. has shown that PS aggregation caused reduction in fluorescence emission and $^1O_2$ generation efficiency (Tang et al. 2005). On the other hand, it can be favorable for the generation of radical species (Severino et al. 2003; Daghastanli et al. 2008). One way of solving aggregation problem is by conjugating the PS to nanoparticles (NPs). Tada et al. 2010, reported that by conjugating PS to NPs, singlet oxygen generation efficiency could be controlled. In addition, the nanoparticles could also protect the PS from environmental influences in the ground, singlet and triplet excited states. This has led to development of many NPs-porphyrin conjugate for improved PDT efficacy (Lemon et al. 2013; Sherwani et al. 2015; Abdurahman et al. 2016; Cao et al. 2017).

Nanomaterials currently employed in PDT

Superparamagnetic iron oxide nanoparticles (SPIONs) - application and current challenges

SPIONs are magnetic iron oxide nanoparticles with a core diameter usually less than 16 nm (Mürbe et al. 2008) and hydrodynamic diameter less than or equal to 300 nm (Corot et al. 2006). For biomedical use, they may be classified based on their routes of administration and hydrodynamic sizes as oral SPIONs (300 nm) (Corot et al. 2006) and intravenous standard SPIONs (50–180 nm), ultrasmall (10–50 nm) and very small (< 10 nm) (Weinstein et al. 2010) The SPIONs with sizes between 10 and 180 nm may also be injectable (Cortajarena et al. 2014). They are generally employed as excellent magnetic resonance imaging contrast agent for cancer diagnosis and currently being exploited for their potential as a whole therapeutic agent in magnetic hyperthermia and drug delivery agent in other disease treatment strategies such as chemotherapy (Wagstaff et al. 2012) and PDT (Wang et al. 2014, b). In PDT, SPIONs have been successfully used to deliver both porphyrin (Li et al. 2013) and non-porphyrin prodrugs into their tumor target sites (Zeng et al. 2013). The success of this strategy has led to the development of multi-functional SPIONs–PS conjugate systems capable of performing a wide array of specific functions as one entity. For example, Zeng and co-workers developed a multicomponent prodrug system consisting of SPIONs, up-conversion nanoparticles and phthalocyanine PS (Zeng et al. 2013). However, despite this success, SPIONs–prodrug conjugation has many challenges. These include inefficient loading of the targeting agent and prodrug on SPIONs, aggregation (water solubility issue) and hydrodynamic size expansion. In order to resolve these drawbacks, a new synthesis and conjugation approach may have to be developed. Also, optimizing encapsulation of SPIONs–prodrug conjugate into polymers, such as polyethylene glycol, liposomes or dendrimers, should be fully exploited.

Gold nanoparticles: application and challenges

Not much has been reported about gold nanoparticles in PDT experiments other than using them as a passivating agent of SPIONs (Wagstaff et al. 2012) and carriers of anticancer drugs and PS (Jang et al. 2011; Li et al. 2015b). However, a few challenges that may be encountered might be the aggregation of gold nanoparticles in physiological media leading to clearance by the body's immune system before reaching the target site. Nonetheless, aggregation may be prevented by using suitable biocompatible materials capable of preventing protein adsorption and escaping the invasion of the phagocytic system. Another challenge is the absorption of light by gold nanoparticles. Gold nanoparticles, being plasmonic in nature (Huang and El-sayed 2011), are capable of absorbing visible and near-infrared light and thus may reduce the amount of light needed for the PS to achieve a complete therapeutic efficacy. As a result, it is necessary to tune the surface plasmon resonance peak of the gold nanoparticles far from the absorption peaks of the PS in order to avoid interference which could lead to a reduction in therapeutic function. Also, it is of paramount importance to use gold nanoparticles of uniform morphology (size and shape), as any deviation from this may lead to different light effects which can cause unpredictable and distorted therapeutic functions.

Quantum dots: application and current challenges

Quantum dots (QDs) are a specialized type of zero-dimensional nanomaterials with unique quantum confinement effect characteristics. Thus, they exhibit unique optical and optoelectronic properties. QDs have an excellent wide range of light absorptions with unique narrower emissions. They have excellent photobleaching resistance, conjugable surfaces and tunable size properties. Their tunable sizes can produce emissions in the near-infrared region making deep-seated optical imaging easier. The large surface area, high brightness and flexible surface of QDs permit their use in the development of excellent drug delivery systems. As a result, QDs have been used extensively in many biological applications, such as biosensors (Wegner and Hildebrandt 2015), cell labeling (Chang et al. 2008), cellular imaging (Biju et al. 2010) and cancer diagnostics (Malik et al. 2013). With respect to PDT, QDs can simultaneously function as diagnostic as well as therapeutic tools. Due to their unique narrow emission light properties (between visible and near-infrared), they can be used alongside cancer-surface targeting moieties such

as antibodies or peptides to track down the site of tumor occurrence in the body. Binding of the QDs to the tumor receptors is dependent on the type of moiety used to functionalize the QDs. The moieties dictate the direction toward the location of the tumor and bind to the respective receptors over-expressed on the tumor surface, while the QDs give the signal by light emission after light irradiation within the tumor vasculature. In terms of the therapeutic function, QDs can be used as FRET agents helping a neighboring conjugated PS under two-photon irradiation (Fowley et al. 2012) or up- and down-conversion mechanisms (Dong et al. 2016) to carry out the therapeutic function at a wavelength where normally the prodrug does not absorb light. This enables a native visible light-absorbing PS to function well under near-infrared light irradiation without having to modify its structure. However, despite these advantages, the use of QDs in PDT has faced some challenges. For example, the use of a toxic heavy metal such as cadmium as part of the core or shell structure of QDs has been a long-term concern. Thus, there is a need to develop cadmium-free QDs (Mandal et al. 2013), probably focusing on a less toxic or more biocompatible metal base of comparable or better optical properties. Also, poor loading efficiency of both cancer-targeting agents and PSs on the QDs is another difficulty. To resolve this, new strategies must be developed to optimize the loading capability of these materials on QDs. Another challenge is the solubilization of hydrophobic QDs in aqueous solution.. Thus, there may be a need to improve the existing solubilization techniques involving conversion of hydrophobic QDs to aqueous QDs.

Up- and down-conversion nanoparticles—application and challenges

The development of up- and down-conversion nanoparticles arises as a result of on-going efforts in resolving the inability of some primary PSs from treating deep-seated tumors due to their inability to absorb near-infrared light (Chen et al. 2015; Yang et al. 2015). Up-conversion PDT involves excitation of nanomaterials such as lanthanide series nanoparticles by near infrared light of appropriate wavelength leading to an emission of light that is capable of exciting an inherent visible light-absorbing PS. By this, the PS does not need to absorb within the therapeutic window before it can be used to treat deep-seated tumors. Another advantage of this approach is the cost effectiveness. There may not be any need for manipulation of PS's structure in order to make it absorb in the near infrared region. This is very important as manipulating PS structure may involve expensive chemicals which in addition may also be toxic to both humans and the environment. For example, efficient conversion of a free base porphyrin to its corresponding chlorin or bacteriochlorins may require the use of osmium tetroxide and hydrogen sulfide (Mccarthy et al. 2009), both of which are toxic to both humans and the environment. On the other hand, the down-conversion PDT involves excitation of nanomaterials such as lanthanide series nanoparticles by X-rays of appropriate wavelength capable of exciting an inherent visible light-absorbing PS by its UV or visible light emission (Chen et al. 2015). The use of X-ray light has been argued to be suitable for the excitement of PSs for the purpose of treating deep-seated tumors in the presence of a scintillation nanoparticles (Tang et al. 2015), since X-rays are currently being used clinically for imaging body parts localized deep inside the body. The advantage of this approach, like up-conversion, is that the structure of the PS is not destroyed. However, despite this advantage, a concern about the safety of lanthanide series nanoparticles and toxicity emanating from prolonged exposure to X-rays may limit the future acceptability of this interesting PDT approach.

Perspective and conclusions

The need for a better class of therapeutic agents for difficult-to-control diseases such as cancer is frequently expressed. The combination of existing approaches, such as chemotherapy, radiotherapy and surgery, is well established. PDT, among existing cancer treatment methodology, has attracted attention over the last few years due to its relatively non-invasive, patient-friendly clinical procedure, and ability to complete the unfinished therapeutic work of some conventional therapies, such as chemotherapy and surgery. Nevertheless, the untargeted accumulation of PSs in the body has limited the application of PDT. The use of functionalized nanomaterials has raised hope for the resolution of this limitation. Nanomaterials such as functionalized SPIONs, QDs, gold nanoparticles and up- and down-conversion Lanthanide series nanoparticles have been used with excellent effects. However, further work is necessary to reduce or eliminate the toxic side effects of these treatments.

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Compliance with ethical standards

Conflict of interest Olayemi J. Fakayode declares that he has no conflict of interest. Ncediwe Tsolekile declares that she has no conflict of interest. Sandile P. Songca declares that he has no conflict of interest. Oluwatobi S. Oluwafemi declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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