Use of nanostructured materials in drug delivery

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20.1 Introduction

The current human population in the world is 7492 billion. According to the World Health Organization [1], 56.4 million deaths worldwide occurred in 2015. The top ten leading causes of death were ischemic heart disease (8.76 million deaths), stroke (6.24 million), lower respiratory infections (3.19 million), chronic obstructive pulmonary disease (3.17 million), lung, trachea, and bronchus cancers (1.69 million), diabetes mellitus (1.59 million), Alzheimer's disease and other dementias (1.54 million), diarrheal diseases (1.39), tuberculosis (1.37 million), and road injury (1.34 million). Cancer ranks fifth place as a cause of death worldwide.

According to the GLOBOCAN 21012 report from the International Agency for Research on Cancer from the World Health Organization [2], the most frequently occurring cancers in men were lung (1.2 million), prostate (1.1 million), colorectum (0.75 million), stomach (0.63 million), and liver (0.55 million), while the top five fatal cancers were lung (1.1 million), liver (0.52 million), stomach (0.47 million), colorectum (0.37 million), and prostate (0.3 million). In the case of women, the most frequently occurring cancers were breast (1.67 million), colorectum (0.61 million), lung (0.58 million), cervix uteri (0.53 million), and stomach (0.32 million), while the top five fatal cancers were breast (0.52 million), lung (0.49 million), colorectum (0.32 million), cervix uteri (0.26 million), and stomach (0.25 million). It is projected that there will be 12 million cancer deaths by 2030 [3]. In addition, the economic impact of cancer worldwide in 2008 was estimated to be $895 billion [4]. The aforementioned data reveal that cancer is a serious health concern with a high economic cost, requiring new strategies to defeat it.

One of the most common treatments used in cancer is chemotherapy. Even though it has good results, its use has profound effects on the whole body, affecting both normal and cancer cells, with many undesirable secondary effects. Moreover, not all patients respond similarly to treatments because of genetic differences. One such example, single nucleotide polymorphism (SNP) is expressed in the enzymes involved in drug metabolism and can affect things such as affinity constants for their target drugs and rates of drug metabolism. Consequently, there

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is alteration of the effective half-lives and elimination rates of drugs in the body. Therefore, there is a dire necessity to develop new approaches to recognize and deliver drugs in target sites for the specific, effective killing of cancer cells. One of these tools is the use of nanoparticles (NPs) for drug delivery. The first objective of a delivery system is to control the release of therapeutic agents at the desired anatomical site, at a suitable concentration, and for a desired duration. The delivery system usually consists of a carrier, which often attaches or adsorbs the drug, and then releases it upon a change of the external environment. Several formulation approaches have been explored for the development of drug delivery systems. Nanoparticles can be used for drug delivery in a number of illnesses besides cancer, including Alzheimer's disease, diabetes, and bacterial, fungal or parasitic infections, among others.

Recently, new NP-based devices have been developed for simultaneous disease diagnosis and therapeutic drug delivery in an approach called theragnosis (or theranostics) [5,6]. However, immune phagocytic cells can uptake these drug carrying NPs, preventing the drugs from reaching therapeutic concentrations, resulting in unspecific distribution of drugs in the body, inhibiting efficient transit through blood vessels, interfering with the intracellular internalization mechanism, and leading to multidrug resistance [7].

This text describes the main NP types currently used for developing engineered nanoparticles for specific, efficient drug delivery, including chitosan, dendrimers, liposomes, carbon nanotubes, hydroxyapatite nanoparticles (nHAps), semiconductor QDs, metallic QDs, ferromagnetic QDs, and Au NPs. Cytotoxicity and the use of some of these NPs in photodynamic therapy will be described as well. There are excellent manuscripts describing NPs used as drug delivery systems or fundamentals in drug delivery that readers should also consult [8–12].

20.2 Chitosan nanoparticles

Chitosan is a polycationic polymer constituted by randomly alternating units of D-glucosamine and N-acetyl-D-glucosamine bound via β-1,4-glycosidic bonds. It is produced by deacetylation of chitin (which is the second most abundant natural polymer after cellulose, and commonly found in fungi cell walls, and crustaceans' exoskeletons). When the content of N-acetyl-D-glucosamine residues is lower than 50%, then it is called chitosan. If the content is higher than 50% it is called chitin [13]. Chitosan has great thermal and chemical stability, is biocompatible and biodegradable, has mucosal adhesion properties, is non-toxic, and is approved for use in humans [14,15]. It is a linear polymer containing a number of free amino-groups that are positively charged at an acidic pH, conferring an advantage for crosslinking with different molecules. Chitosan's polymer chain length and degree of acetylation affect its solubility, viscosity, and degradation rate. At a low degree of acetylation and neutral pH, chitosan's solubility is reduced due to the presence of strong hydrogen bonds between polymer chains, conferring stability [14].

20.2.1 Preparation methods of chitosan NPs

There are several methods for producing chitosan nanoparticles [14–22]. They include the ionotropic gelation method, polyelectrolyte complex method, and microemulsion, among others.

Ionotropic gelation method. This method is the combination of tripolyphosphate (TPP) and chitosan in aqueous solution at room temperature to auto-assemble NPs through electrostatic forces and ionic crosslinking. The result is a milky solution, indicating formation of chitosan NPs. The optimal weight ratio of chitosan/TPP to obtain high yields of nanoparticles must be in the range between 3/1 and 6/1 [16]. Chitosan NPs' size and zeta potential are directly affected by pH; thus, an average size of 100 nm is obtained at acidic pH, while bigger NPs (800 nm in average) are obtained at neutral or alkaline pH. On the contrary, the positive zeta potential at acidic pH decreases when pH is raised to neutral or alkaline values [17]. Other ionic species that can be used include sodium citrate and sodium sulfate [22].

Microemulsion method. This method involves the formation of reverse micelles, which are generated by the incubation of oil, a surfactant, and water mixed with organic solvents (including benzene, chloroform, diethyl ether, n-hexane, among others). Suitable oils in this process are mineral oil and vegetable oil, while a common detergent used is sorbitan trioleate. If chitosan in aqueous solution is added (generally as an acidic solution), then an emulsion will form, containing NPs in the hydrophilic core of reverse micelles. The NPs are lower than 100 nm in size and can be covalent cross-linked with compounds containing aldehyde groups (glutaraldehyde for example), then loaded with selected cargos during synthesis [16–21].

Emulsification method. This method involves the addition of an organic solvent to an aqueous solution of chitosan in water, along with a stabilizing agent, and mixing. After the emulsion forms, the mixture is diluted with water in order to precipitate chitosan and trigger nanoparticle formation. Alternatively, the mixture is left to evaporate when using a volatile organic solvent, and then NPs can be washed by filtration. With this method, hydrophobic drugs can be loaded into microparticles and NPs [22,23].

Covalent cross-linking of chitosan NPs. This method is used to improve their properties. In this case, chitosan NPs are produced in the presence of a cross-linking agent (such as glutaraldehyde, polyethylene glycol (PEG), dicarboxylic acids, different acyl compounds, and carbohydrates, such as dextrin [20]). The covalent coupling of molecules occurs in either the hydroxyl or amine groups of chitosan; amine groups are more reactive than hydroxyl groups [20]. Attachment is achieved through interaction with reactive groups present in monomers of polymeric compounds (such as acrylics, ethylene glycol, thiol-harboring molecules, acrylamide, etc.), or through activating compounds like 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC).

Another way to confer a number of different properties to chitosan-derived NPs is mixing them with other compounds. Several natural polymers have been used to synthesize complex chitosan NPs, including alginate, carrageenan, cashew gum, gum arabic, carboxymethyl cellulose, Gellan gum, gum kondagogu, hyaluronic acid, Konjac glucomannan, Xanthan gum, and pectin, among others [24]. Alginates are unbranched

linear polymers containing blocks units of D-mannuronic acid linked through β-1-4 linkages and blocks of guluronic acid bound through β-1-4 chemical bonds, which are isolated from brown algae [25]. Carrageenan is the general term to describe a family of sulfated high molecular weight polysaccharides isolated from seaweeds (red algae). They are composed of repeating blocks of galactose and 3,6-anhydro-D-galactose joined through alternating α-1,3 and β-1,4-glycosidic linkages [26]. Cashew gum is a polysaccharide extracted from *Anacardium occidentale.* It is mainly composed of units of β-D-galactopyranose (galactan). Other residues found are α-D-glucopyranose, α-l-arabinofuranose, α-l-rhamnopyranose and β-D-glucuronic acid, bound through different linkages to the galactan core [27]. Gum arabic is a complex polysaccharide exuded by *Acacia senegal* and *A. seyal* species. Its main chain is composed of β -D-galactopyranoside units bound through 1,3-linkages. The side chains are composed of two to five β -D-galactopyranoside units bound through 1,3-linkages as well, which are linked to the main chain through 1,6 chemical bonds. In addition, both chains contain residues of α-l-arabinofuranosyl, β-D-glucuronopyranosyl, 4-O-methyl-β-D-glucuronopyranosyl, and α-l-rhamnopyranosyl [28]. Carboxymethyl cellulose is a modified form of cellulose, a linear polymer composed of units of D-glucopyranose bound through β-1,4 linkages, which is produced by the reaction of chloroacetic acid with cellulose in alkali [29]. Gellan gum is an exopolysaccharide produced by *Pseudomonas elodea*. It is composed of a repetitive unit formed by residues of β-1,3-D-glucose, β-1,4-D-glucuronic acid, β-1,3-D-glucose, and α-1,4-L-rhamnose. The first glucose of this unit has two additional groups: an acetyl group and a glyceryl group linked by ester groups at positions 2 and 5, respectively [30]. Gum kondagogu is a polysaccharide isolated from the exudate produced by *Cochlospermum gossypium.* It is mainly composed of arabinose, galactose, glucose, glucuronic acid, galacturonic acid, mannose, and rhamnose. These molecules are linked through the following chemical bonds: 1,2-β-D-Gal p, 1,6-β-D-Gal p, 1,4-β-D-Glc p A, 4-O-Me-α-D-Glc p A, 1,2- α-L-Rhamnose, 1,4-α-D-Gal p A [31]. Hyaluronic acid is the main structural component of the extracellular matrix in vertebrates. It is a linear polymer of alternating units of acetyl-D-glucosamine and D-glucuronic acid linked through β-1,3 and β-1,4-glycosidic chemical bonds [32]. Konjac glucomannan is a polysaccharide isolated from the tuber of the plant *Amorphophallus konjac* K. Koch. This compound has a linear main chain composed of D-glucose and D-mannose linked through β-1,4-glycosidic chemical bonds, with short branches composed of β-1,6-glucosyl residues [33]. Xanthan gum is a polysaccharide produced by the bacteria *Xanthomonas campestris*. This molecule has a main chain of D-glucose molecules linked through β-1,4-glycosidic bonds. In addition, a small branch composed of mannose-β-1,4-glucuronic acid-β-1,2-mannose, is linked through a β-1,3-glycosidic bond to the main chain in alternating glucose residues through a mannose residue, which has an acetyl group at position O-6. The terminal mannose of the branch has a pyruvic acid molecule linked via ceto group to positions 4 and 6 [34]. Pectin is a complex polysaccharide that contains three domains: homogalacturonan, rhamnogalacturonan domain I, and rhamnogalacturonan domain II. The first one is composed of D-galacturonic acid linked through α-1,4 chemical bonds. These residues can be modified by the partial esterification with methyl and/or acetyl groups. The second

domain, rhamnogalacturonic acid domain I, is composed of repeating units of disaccharide 1,4-α-D-galacturonic acid-1,2-α-1-rhamnose. Approximately 20% to 80% of rhamnose molecules are replaced by arabinose of galactose. Moreover, several residues can be found as terminal residues of side chains, including fucose, glucopyranose, and 4-O-methyl-glucopyranose. Rhamonogalacturonan domain II is composed of a small backbone formed by D-galacturonic acid linked through α-1,4 chemical bonds, and lateral chains composed of α-L-rhamnose, α-D-galacturonic acid, α-D-galactose or β-D-galactose, α-L-arabinose, α-L-fucose, and (3R)-4-(hydroxymethyl) tetrahydro-2,3,4-furantriol (β-D-apiofuranose), among others [35].

20.2.2 Uses of chitosan NPs in drug delivery

There are many examples of different technological developments using chitosan-derived nanoparticles in biomedicine. While many laboratories are involved in the identification of biomarkers for diseases, others develop new devices for drug delivery. Our laboratory is one of those identifying protein molecular biomarkers using tissue sections of brains with Alzheimer's disease, and discovering biomarkers using breast cancer cell lines. Multidimensional Protein Identification Technology (MudPIT) and quantitative mass spectrometry using iTRAQ labeling and tandem mass spectrometry have been used in both cases [36,37]. The scientific community has great expectations that these biomarkers could be useful in identification of disease-altered cells for specific drug targeting and delivery. There are many examples of the use of chitosan-based nanoparticles for drug delivery, including peptides [38–42], vaccines [21,43–45], drugs [46–49], siRNAs [50–52], that readers are invited to read about in the available literature.

20.2.3 Conclusions

Chitosan is a material with excellent potential for development of nanodevice-based drug delivery systems. Their characteristics can be improved using myriad other compounds, including natural or synthetic polymers, small molecules, proteins, etc., to obtain chitosan-derived nanoparticles.

20.3 Dendrimers nanocarriers

Dendrimers are controlled hyperbranched three-dimensional globular polymeric nanostructures [53]. They contain a core wherein several chemical species can be encapsulated. Their building blocks consist of repeating units that provide space to accommodate small molecules, and their multivalent surface displays multiple peripheral functional groups for the attachment of different molecules [54]. Materials like 4-dimethylaminopyridine, 2,2-bis(hydroxymethyl)propanoic acid, ethylene diamide, methyl acrylate, propyl amine, ethylene imine, D,L-lactide-co-caprolactone, and others are employed as monomers for building blocks. Properties of dendrimers, such as architecture, biocompatibility, retention, specificity, and functionality [53] are

valuable characteristics for a number of applications like catalyst [55,56], carriers for contrast agents [57], gene carriers [58,59], drug delivery systems [60–62], etc. Use of dendrimers as delivery vehicles requires negative or neutral-charged particles to secure biocompatibility, controlled architecture to facilitate pharmacokinetics, enough space between building blocks to internalize therapeutic agents, and functionalization in order to increase solubility, and for attaching drugs to their surface for specific medical treatments [63].

20.3.1 Synthesis of dendrimers

The synthesis of dendrimers is carried out through a repetitive two-step reaction sequence which includes a generation growth and an activation step. There are two strategies commonly used in the preparation of dendrimers, the divergent approach [64,65] and the convergent approach [66]. In the divergent approach, material grows by generations, i.e., layer-by-layer from the focal core, and builds up towards the periphery by coupling building blocks to create new reactive functional groups on the surface [54]. The core reacts with two or more protecting branching sites, followed by removal of the protecting groups leading to the first generation (G1) dendrimers [67]. It is a controllable reaction due to the protection of other functional groups on building blocks. Thereby, the next generation grows from modification of newly attached surface functionalities, a process that is repeated until the desired number of generations is obtained [68]. On the other side, when the convergent approach is used, the chemical reaction begins at functional groups on the dendrimer surface and proceeds to the core, linking surface units together with more monomers and allowing for intermediate purification resulting in a nearly perfect dendritic structure [54,67].

20.3.2 Incorporation of drugs into dendrimers

Drugs can be incorporated into dendrimers using different strategies. When they are encapsulated into void spaces of dendrimers, nanoscale dendrimers are made. If drugs are associated with surface groups, then dendrimers are used as nanoscaffolds. When both strategies are used, then we have a mixed approach of incorporation. Drugs are incorporated into dendrimers through hydrogen bonds, van der Waals bonds, and electrostatic attraction between opposite charges on dendrimers and drugs [69].

Noncovalent encapsulation of drugs in dendrimers. This approach maintains unimolecular “dendrimer boxes” for the noncovalent encapsulation of drugs; structure is maintained at all concentrations due to the covalently connected hydrophobic segments. However, it could be difficult to release the drug or it could be an accelerated release [70].

Covalent encapsulation of drugs in dendrimers. This method exploits the well-defined multivalency of dendrimer periphery for covalent attachment of drug molecules by varying the generation number of the dendrimer and incorporating degradable linkages between the drug and dendrimer [70]. It offers an electrostatic complexation of drugs to dendrimers for controlling drug release [69].

Chemical conjugation. This procedure uses physical interaction between dendrimers and drugs to keep them unaltered, and with a less challenging regulatory pathway, establishing control over the release kinetics but allowing limited drug loading [68].

20.3.3 Applications of dendrimers as drug delivery systems

20.3.3.1 Cancer therapy

Ma et al. [71] efficiently synthesized pegylated thermoresponsive aliphatic polyester G5 dendrimers loaded with doxorubicin (DOX). Cytotoxicity was evaluated in SKOV-3 ovarian cancer cells, where it was demonstrated that dendrimers without drugs are non-toxic, while the material loaded with DOX decreased cell viability. G5 dendrimers showed excellent capacity for drug encapsulation and controlled drug release. Khatri et al. [72] fabricated methotrexate (MTX)-polyamidoamine (PAMAM) dendritic nanoconjugates by conjugation using a dicyclohexylcarbodiimide coupling reaction and studied their effect on MES-SA uterine sarcoma cells. The conjugates were evaluated by ultraviolet spectroscopy and 1H nuclear magnetic resonance spectroscopy confirming the formation of covalent bonds between drug and dendrimer. Cell viability studies indicated that nanoconjugates improved cell killing and therefore, they can be used for targeting cervical cancer when administered intravenously or through local tumor injection. Lv et al. [73] developed folic acid (FA) covalently conjugated PAMAM dendrimers as carrier systems for improvement of water solubility, bioavailability, and tumor specificity of the antitumor drug baicalin (BAI). They tested these dendrimers in folate receptor (FR) positive HeLa cancer cells and in FR negative A549 cells, producing enhanced toxicity and tumor specific therapeutic efficacy against HeLa cells. Thus, they have demonstrated that their fabricated nanocarriers had the potential for specific target delivery of BAI into cancer cells. Kaur et al. [74] prepared folate-conjugated polypropylene imine dendrimers (FA–PPI) as nanocarriers for a controlled MTX release at acidic pH medium. They studied their cytotoxic effect and intracellular uptake in the MCF-7 human breast cancer cell line, demonstrating that at high concentration (10 μg/mL) of nanocarriers, cell viability decreased 85% and preferential cellular uptake of MTX carried by dendrimers was accomplished. Moreover, in vivo studies determined an increase in MTX concentration in liver in comparison with free MTX formulation in Wistar rats.

20.3.3.2 Antimicrobial

Wong et al. [75] synthesized G5 PAMAM dendrimers attached to polymyxin B (PMB), a lipopolysaccharide, which was nanoconjugated with photocaged ciprofloxacin, a broad-spectrum antibiotic, to specifically target Gram (-) bacteria. Their functionality was evaluated with Gram (-) *Escherichia coli* bacteria, and the results demonstrated an enhancement in selectivity and delivery control of the antimicrobial compound to bacteria.

20.3.3.3 Antifungal

Hutnick et al. [76] synthesized PAMAM dendrimers with 13% of their chain ends PEGylated as vehicles for silicon phthalocyanine Pc 4, as a photosensitizer delivery

vehicle, to employ them in photodynamic therapy (PDT) against fungal infections from *Candida albicans* (*C. albicans*). They used *C. albicans* 9652 R cells to study the photosensitizing agent because its resistance to traditional antifungal medications. Cells efficiently internalized these nanoparticles, and when they were irradiated, Pc 4 maintained its ability to generate reactive oxygen species (ROS), which induced oxidative stress resulting in apoptosis.

20.3.3.4 Delivery and imaging

Sharma et al. [77] designed traceable dendrimers with 2′,4′,5′,7′-tetraiodofluorescein (TIF) as a fluorescent label in the core and a desired number of α-lipoic acid (α-LA) molecules at the periphery. Biological experiments were carried out with peripheral J774A.1 and central N9 nervous system macrophages and microglia cells, respectively. They demonstrated that these dendrimers were traceable, fluorescent, and non-cytotoxic, and were internalized within minutes by the microglia, making them promising tools as traceable drug delivery systems.

20.3.3.5 Delivery mechanisms

Manikkath et al. [78] prepared arginine terminated peptide dendrimers conjugated with ketoprofen to probe their transdermal permeation, both passively and with the help of low frequency ultrasound. They used Swiss albino mouse skin to determine permeation of the drug, and they found that the terminated 16^{+} peptide-charged dendrimer plus the sonophoretic treatment enhanced drug permeation compared with passive diffusion of the same dendrimer complex. Also, there were no major toxic reactions in the in vivo model.

20.3.4 Conclusions

Dendrimers from fourth to sixth generations exploit the space between their building blocks to carry drugs and/or fluorescent labels for specific targeting determined by their peripheral functional groups.

20.4 Carbon nanotubes in drug delivery

Carbon nanotubes (CNTs) are currently being widely implemented in various investigations because of their cylindrical, elongated, and hollow structures that make them suitable as drug delivery systems. Carbon nanotubes as drug carriers are presented as an alternative to conventional methods in cancer treatments based on chemotherapy, which presents high toxicity and greater side effects. Carbon nanotubes were reported for the first time in 1952 thanks to Radushkevich and Lukyanovich, who obtained carbon nanotubes of 50 nm in diameter [79–82]. Oberlin et al. reported the synthesis of nanometric-sized carbon fibers [83]. Abrahamson et al. produced carbon nanoparticles using the thermocatalytical technique [84]. It was not until 1991, when Sumio Lijima synthesized carbon nanotubes, that carbon nanotubes achieved scientific relevance [81,82,85].

The family of fullerenes is the third allotropic form of carbon [86]. These materials have the peculiarity that they are molecules exclusively composed of carbon atoms. Fullerenes can be classified into three categories according to their form [81,82]: Fullerene C60 has a spherical shape and is composed of 60 carbon atoms. Graphene sheets have an elongated flat shape. Carbon nanotubes are graphene sheets rolled into a cylinder. These materials are further classified into two types according to the number of layers they contain [84,87], single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). The former are composed of a tubular structure made from a single sheet of graphene and have a diameter between 0.4 nm and 2 nm and a length of 0.2 nm to 5 μm [81,88]. The latter is made of two or more coaxial cylinders, each formed by a single graphene sheet surrounding a hollow core. The outer diameter of MWCNT ranges between 2 and 100 nm, while the inner diameter is in the range of 0.4–2 nm, and its length is from 0.2 nm to several μm [81,89].

20.4.1 Methods of synthesis of carbon nanotubes

There are different synthesis methods for the production of carbon nanotubes, the choice of which is heavily influenced by the desired application. These applications include hard coatings, electronics, and biomedical applications (especially as drug delivery systems) the latter being the most important in recent years. Because carbon nanotubes have an ideal size and shape for the transport and location of drugs, they also are advantageous for reducing of the concentration of the drugs used. The properties of carbon nanotubes depend directly on the synthesis method used. The most common types of synthesis of these materials are the arc discharge method, the laser ablation method, and the chemical vapor deposition method, which uses plasma-enhanced chemical vapor deposition (CVD), thermal CVD, liquid pyrolysis, and solid state pyrolysis [82].

Arc discharge method. This is the simplest and most commonly used method in the synthesis of carbon nanotubes, and it was initially proposed for the production of fullerene C60 [85,90]. An inert atmosphere is necessary during synthesis, as is an electric discharge produced by a current of 50–100 A, with a potential difference of approximately 20 V. This energy is applied to two carbon electrodes: the cathode (carbon white) used as a carbon source, and the anode, which is doped with a catalytic metal (e.g., Fe, Co, Ni) [91–94]. The arc discharge generates a very high temperature which evaporates the surface of one of the carbon electrodes, resulting in a mixture of soot, catalyst residues, and carbon nanotubes. The presence of contaminants is one of the main problems inherent to this technique and requires an additional purification step to obtain the carbon nanotubes [81,82]. Properties of carbon nanotubes, such as types SWNTS and MWNTS [95–97], and size are susceptible to changes in the experimental conditions of the arc discharge technique; these changes might include the type of dopant used as catalyst as well as its concentration, the inert gas used, chamber pressure, temperature and deposition time, electric current and geometry used, and so on [98–100].

Laser ablation method. This is the second most frequently used method for the production of carbon nanotubes. In this method, a high-power laser located outside

the deposition chamber is focused on a carbon source (block of carbon) within the same room through a glass window. The carbon source is located perpendicular to the incident beam. In front of it is a substrate holder where synthesized material is deposited by means of laser pulses striking continuously, providing the energy to generate a plasma through ionization of an inert gas in the chamber. This plasma has the energy necessary to uniformly vaporize the target, generating carbon nanotubes [101,102]. An advantage of this technique is the reduction of deposited carbon soot. With this technique, both SWNTs and MWNTs can be obtained through variations in experimental parameters such as time of synthesis, white distance substrate, deposition temperature, type of laser used, target rotation speed, and chamber pressure [86,103,104].

Chemical vapor deposition (CVD). It is the most widely used method for large-scale production of carbon nanotubes [105]. In this technique a hydrocarbon gas (such as methane, acetylene or carbon monoxide) is used as a source of carbon and a catalyst is prepared, generally through cathode sputtering, in which a transition metal on a substrate reacts to the energy used in the process and catalytically decomposes into metallic nanoparticles. Remarkably, the preparation of the catalyst directly influences the characteristics of the synthesized nanotubes because it affects their type, shape and size. There are four variations of the CVD method: the plasma-enhanced CVD method, the thermal CVD method, the liquid pyrolysis method, and the solid-state pyrolysis method [81,106,97]. In most cases, nanoparticles smaller than three nm produce SWCNTs, and nanoparticles are bigger than three nm produce MWCNTs [81,107,108].

In the different CNT synthesis processes, there is catalytic decomposition of compounds generating a variety of impurities such as metal particles, graphite, amorphous carbon, fullerenes, and other types of materials used during the synthesis process [108,109]. Therefore, it is necessary to remove all impurities present and isolate CNTs for different applications. Due to the different CNT synthesis methods used and various uses for CNTs, many different purification methods have been established. However, the maximum amount of CNTs lost during the process of purification must be considered. The most frequently used methods of CNT purification are discussed in the next section [81,82].

20.4.2 Methods of purification of carbon nanotubes

Air oxidation. In this method, oxygen or CO_2 is added at high temperatures (650–700°C) for 50–60 min, oxidizing the layers of the CNT walls. Then, a thinning process removes remnants of other elements present during synthesis. However, 90% of CNTs are lost in this method [105,106,97].

Acid refluxing. Carbon nanotubes are exposed to a reflux with different acids (including hydrochloric acid, sulfuric acid and nitric acid) in order to remove amorphous carbon impurities and metal catalysts [109,112].

Sonication and filtration based on surfactants. Sonication involves application of ultrasound waves to break non-covalent bonds, consequently separating metal particles and amorphous carbon [105]. The procedure occurs in a solution of sodium dodecyl benzene sulfonate in methanol or ethanol, then a microfiltration process captures CNTs, eliminating contaminants [81,82,112].

The greatest scientific expectation centered upon carbon nanotubes is their possible biomedical application, especially for drug delivery. However, CNTs biomedical applicability is limited by their low solubility in aqueous and non-polar organic solvents; aqueous solubility is essential for use in biological systems [81,82,114–116]. For this reason, CNTs must be chemically modified to achieve this property. Currently, surface functionalization of CNTs is the most promising technique being used. Functionalization reduces the toxicity caused by CNTs' highly hydrophobic surfaces. This advantage is made possible by the addition of different functional groups to the carbon nanotubes' walls, which makes the tubular structures soluble in aqueous solutions and less harmful to cells, and therefore biocompatible [86,117]. There are two methods for functionalization of carbon nanotubes: covalent functionalization and non-covalent functionalization. Covalent functionalization modifies the walls of nanotubes using functional groups containing oxygen (such as carboxylic acid, ketone, alcohol, and ester) followed by an oxidative treatment to remove amorphous carbon, metal catalyst particles, and tubes with smaller-than-required diameters [81,82,118]. Non-covalent functionalization uses different types of non-covalent interactions, including π-stacking, van der Waals forces, and hydrophobic interactions, to functionalize CNTs [82].

20.4.3 Applications of CNTs as drug carriers

NTCs as drug delivery systems have been extensively studied in recent years for their use in cancer therapy [119–124]. Several studies have been carried out exploring the potential for loading carbon nanotubes with different drugs for cancer therapy use [82]. One of them used SWCNTs loaded with Pacliataxel to attack breast cancer cells, finding more efficient tumor suppression as compared to conventional methods [125]. Chen et al. (2008) used single-walled nanotubes (SWCNTs) with Taxoid (a prodrug) against different leukemia cell lines ($L_12_{10}FR$), and found significant suppression of tumor lines [126]. Other drugs that are being currently used with carbon nanotubes in cancer treatments are Doxorubicin and Cisplatin [126–129]. Other compounds used are radionuclides [130] and antioxidant molecules such as quercetin [131]. However, there are several disadvantages to using CNTs as drug carriers that needs to be addressed before clinical use, including lower retention in cancer cells and emerging multidrug resistance [132,133], poor solubility, and inability to cross physiological barriers [82,134].

20.5 Conclusions

Carbon nanotubes can be synthesized in different sizes and shapes, including cylindrical, elongated, and hollow. These characteristics are excellent for using CNTs as drug carriers, because they can reduce the drug dose, and consequently, its side effects. Therefore, CNTs are a great alternative to conventional methods used in cancer treatments based on chemotherapy.

20.6 Hydroxyapatite nanoparticles

Hydroxyapatite (HAp) is a porous calcium phosphate with several key properties including biocompatibility, bioactivity, osteoconductivity, non-toxicity, and non-immunogenicity [135–138]. These characteristics make hydroxyapatite a versatile bioceramic material with multiple biomedical engineering applications, including orthopedic coverings, dental implants, dental reparation, tissue engineering, chemical sensors, imagenology, ion exchange chromatography for the separation of nucleic acids and proteins, decreasing the rate of cancer cell replication (in compound), and as gene and drug delivery systems. HAp crystals have also been conjugated to radioisotopes via acetate or citrate linkers and used as a platform for delivery of beta-emitters in radiation therapy in arthritis [139–158]. Since the 1990s, the biocompatibility and porous structure of HAp particles has been exploited to create implantable systems to deliver hormones [159,160], antibiotics [161], anti-cancer agents [162,163], vaccines [164], and anti-AIDS drugs [165]; these examples employed elements several centimeters in length with micropores in which drugs were stored then delivered following implantation [166–168]. At the beginning of the 2000s, HAp nanoparticles were synthesized and investigated as drug or DNA delivery systems, and they demonstrated enhanced bioavailability, greater efficacy, controlled release time, and predictable therapeutic response. All these characteristics were advantageous as compared to conventional dosage methods because they indicated high specificity for targeted cells or tissues and controlled delivery of drugs [169–172]. HAp is considered a diffusion-controlled device because drug molecules incorporated into its matrix could be released more quickly than the matrix degraded [173].

20.6.1 Synthesis of HAp nanoparticles

In order increase HAp nanoparticles' usefulness as drug carriers, they must be either synthesized as mesoporous structures to facilitate the introduction of drug molecules into their matrix, or functionalized on their surfaces to facilitate the attachment of drugs. Additionally, it is also important to facilitate the potential attachment of a polymer to the nanoparticles' external layer in order to regulate drug release. There are several synthesis methods for HAp nanoparticles. However, in this review, we will focus on those methods used to obtain porous HAp nanoparticles.

Wet chemical precipitation. A solution of ammonium dihydrogenphosphate at pH 11 is added dropwise to a calcium solution at different temperatures then stirred to obtain nanoparticles of different sizes. Then, precipitate is washed with water, and subjected to a hydrothermal treatment at 100–500°C, then freeze-dried to produce HAp powders. This method is frequently chosen because it is easy and highly reproducible [174].

Hydrothermal method using a cationic surfactant as a template. The phosphate source and cetyltrimethylammonium bromide are dissolved in deionized water, and the pH is adjusted to 12. Subsequently, the calcium solution source is added dropwise to a phosphate solution. Then, the suspension is sintered for 24 h at 120–400°C, and

the precipitate is washed with water by filtration. Next, the paste is dried for 24 h at room temperature. Finally, the powder is heated to 550°C for 6 h to remove organic material [175,176].

Polymeric micelle-template method to create hollow HAp nanoparticles. In this method, it is necessary to use two polymers which, at low temperature, form micelles with a core shell structure in the presence of a solvent and a phosphorous source; one of the polymers must have a higher cloud point temperature (CP) than the other. Once that CP temperature is achieved, the first polymer remains insoluble and becomes the condensed core of the new micelles, while the other soluble polymer forms the shell through the hydrophobic interaction of their alkyl chains. Then, Ca^{2+} is added, and HAp forms within the shells, with the cores acting as a template for the hollows of HAp. Templates can be removed with water and ethanol solution at a lower temperature than the critical micellar temperature (CMT) of the first polymer. A polar citric compound can be used to regulate the morphology of HAp nanoparticles modifying the shape of micelles [177].

Microwaved-assisted hydrothermal method. This method is based on two principles: the dipolar mechanism and the electrical conductor mechanism. In the first, a polar molecule, influenced by a very high frequency (0.3–300 GHz), follows the alignment of the field and releases enough heat to drive the reaction. In the second one, electric charge carriers move through the irradiated electrical conductor sample under the influence of the electric field, leading to sample polarization [178]. These induced currents will heat the sample, which is advantageous because of the rapid volumetric heating which, when combined with the hydrothermal method, reduces processing time from days to minutes [179].

20.6.2 Drug loading into hydroxyapatite nanoparticles

Drugs can be added either in liquid or powder form, in which case the drug must be dispersed in the matrix formed by the cement [173].

Liquid phase. A more homogeneous distribution of the drug is obtained, but it gets embedded in the matrix [180]. Exploiting the high affinity interaction between HAp nanoparticles and certain compounds such as polyphosphonates, this only requires determination of the optimal conditions for interaction, concentration of reagents, time and temperature of incubation, and washing time [181].

Powder phase. This procedure is carried out by dissolving the drug in a solvent and subsequently adding a solution of nanoparticles through continuous stirring for 24 h to avoid solvent evaporation. This ensures the nanoparticles' structure will be stable during drug release [180]. In another method, nanoparticles are soaked in a drug solution for three days. This is a slow but effective process. In both cases, the amount of drug incorporated into nanoparticles is 30% in weight [182,183].

Encapsulation. In some cases, it is necessary to add other substances to control drug release, for example, by using biodegradable polymers to obtain polymer encapsulation or polymer-HAp hybrid gels [176,182,183]. The polymer can also contain the drug before being blended with the hydroxyapatite nanomaterial [180].

20.6.3 Applications

20.6.3.1 Drug delivery and bioimaging

For this application, hydroxyapatite nanoparticles are labeled with fluorescent compounds, such as organic dyes, quantum dots, gold nanoclusters, ion dopants, or radioisotopes. Ong et al. [175] employed HAp nanocrystals (40–200 nm) conjugated with radioisotopes by exploiting the high-affinity interaction between HAp and polyphosphonates (which are used for treatment of a variety of diseases or as imaging agents). These have been used for selective treatment to minimize phagocytic uptake of Kupffer cells in the liver after systemic administration into mice. Yang et al. [183] obtained luminescence-functionalized mesoporous nanoscale rod-like HAp doped with Eu^{3+} with 20–40 nm in width and 100–200 nm in length, then employed them as ibuprofen carriers. This resulted in a multifunctional material which could be tracked and monitored during the drug release process through the change in PL emission intensity; this material demonstrated potential application for drug delivery and disease therapy. Zhang et al. [184] synthesized luminescence-functionalized mesoporous strontium hydroxyapatite nanorods with a self-activated luminescence (360–570 nm) that were loaded with ibuprofen, resulting in a multifunctional material which might be tracked and monitored during the drug release process. Chen et al. [179] used the microwave-assisted hydrothermal method to prepare multifunctional Eu^{3+}/Gd^{3+} dual-doped HAp nanorods with photoluminescent and magnetic functions. These nanorods showed high ibuprofen adsorption capacity and sustained drug release, establishing them as a multifunctional drug delivery system with imaging guidance. Li et al. [185] employed the wet chemical method to prepare mesoporous ellipsoidal hollow nanocapsule HAp with the incorporation of an organophosphonic acid through P–O–Ca covalent bonds and an aggregation-induced emission active molecule tetraphenylethene by a one-pot condensation process; these exhibited strong fluorescence and good biocompatibility. The material was loaded with ibuprofen, and the release process could be monitored by observing the change in luminescence intensity. Syamchand et al. [186] synthesized FITC-Ho^{3+}-HAp nanocrystals through the wet chemical method with average diameter and length of 10 nm and 60 nm, respectively; these were coated with polyethyleneimine and conjugated to folic acid for targeting the folate receptor overexpressed in cancer cells, resulting in a material well-suited as a contrast agent for T2 magnetic resonance imaging.

20.6.3.2 Anticancer drugs

Kundu et al. [187] developed a nanosized HAp-based drug delivery system loaded with doxorubicin (DOX), which was examined under different pH conditions (found in the human body). Through experiments using animal models, it was observed to be an efficient, safe, and reliable therapy to treat hepatocellular carcinoma. Venkatasubbu et al. [188] reported the use of hydroxyapatite nanoparticles functionalized with polyethylene glycol (PEG) modified with folic acid and loaded with paclitaxel, which successfully targeted tumor cells expressing folate receptors. These nanoparticles showed initially fast release which then became sustained. Yang et al. [189] synthesized biocompatible and biodegradable HAp nanoparticles with hollow cores and

mesoporous shell structures, which enhanced DOX loading, reduced burst drug release, and provided pH-responsive release. The material demonstrated potential as a transmembrane delivery carrier and for intracellular controlled release in breast cancer cells (BT-20). Gu et al. [190] synthesized mesoporous Fe_3O_4/HAp composite loaded with DOX, demonstrating controlled drug release behavior (which was less than 20% within 20 h, followed by a slow and steady release after more than 100 h). This material could decrease drug times and suffering of cancer patients. Li et al. [191] fabricated redox-responsive mesoporous HAp using the polymeric micelle-template method with lactobionic acid-conjugated collagen as a cap, disulfide bonds as intermediate linkers, HAp as nanoreservoir, and fluorescein isothiocyanate as both model drug and intracellular marker. The HAp nanocomposite had redox-response drug delivery under physiological conditions within liver cancer cells.

20.6.3.3 Drug delivery with enhanced control release

Ye et al. [177] created hollow nanospheres and nanotubes of HAp using polymeric micelles as template. They were functionalized with citrate carboxyl–cationic polyelectrolyte and loaded with vancomycin. The material used for functionalization acted as a gate with pH-response for releasing the drug, mainly at weak pH acidity. Li et al. [192] obtained mesoporous rod-like HAp nanoparticles of 20 nm in diameter and 100 nm in length by the hydrothermal method. They incorporated alendronate into HAp nanoparticle pores as a functionalization agent to load ibuprofen. This method showed high drug storage capacity and a slow drug release rate. Aghaei et al. [193] synthesized a mesoporous MCM-48/HAp composite loaded with ibuprofen that was incubated with MG63 osteosarcoma cell line. Results demonstrated a decrease in cell viability due to the high rate of drug release.

20.6.3.4 Poorly water-soluble drugs

Zhao et al. [194] obtained mesoporous rod-like HAp nanoparticles with 30 nm in diameter and between 100 nm and 300 nm in length using the template hydrothermal method. Nanoparticles were loaded with carvedilol (CAR), which produced immediate release of CAR in simulated gastric fluid and intestinal fluid, demonstrating its potential application as an oral delivery system for poorly water-soluble drugs.

20.6.4 Conclusions

The mesoporous property of hydroxyapatite nanoparticles has been exploited to ensure high drug load capability, no matter the nature of the drug. These nanoparticles also showed an adjustable rate of drug release, depending upon the encapsulation method selected.

20.7 Liposomes as drug delivery system

General interest in liposomes is enormous. The liposomes were initially discovered in the mid-1960s [195], and they can be defined as spherical vesicles with a phospholipid bilayer membrane structure that can encapsulate both hydrophilic and hydrophobic

agents with particle sizes ranging from 30 nm to several micrometers. Liposomes can be formed with one or several concentric bilayers, depending upon the growth conditions and their chemical composition. Liposomes are biologically inert, biocompatible, weakly immunogenic, versatile, and demonstrate low toxicity.

Some advantages of liposomes are the increased efficacy and therapeutic index of drug, the increased stability via encapsulation, the reduction the toxicity of the encapsulated agent, and the site avoidance effect. However, liposomes have some disadvantages too, such as low solubility, a short half-life, leakage and fusion of encapsulated drug/molecules, and high production costs, among others [196].

Main components of liposomes are phospholipids (PLs), cholesterol and other employed lipids [197]. PLs are abundant in all biological membranes. They have several components: (1) fatty acids, (2) a platform or scaffold to which fatty acids are attached, (3) glycerol or sphingomyeline as a backbone, (4) a phosphate group, and (5) an alcohol attached to the phosphate. PLs are amphipathic molecules, and they have both hydrophobic and hydrophilic groups. The two hydrocarbon chains constitute the hydrophobic tails, while the phosphate group and its polar attachment constitute the hydrophilic group [198]. Cholesterol is a common component of liposomes, and its incorporation into the lipid bilayer has a major effect on liposome properties, such as improvement of stability and formation of highly ordered and rigid membranes with characteristics similar to those of the fluid [199]. Moreover, other lipids, such as sphingolipids and synthetic phospholipids are used as a minor component for liposome production.

Liposomes are classified on the basis of structural parameters, method of preparation and composition, and applications. In terms of their structural parameters, liposomes are usually categorized into three main types: small unilamellar vesicles (SUVs), large unilamellar vesicles (LUVs), and multilamellar vesicles (MLVs). SUVs are vesicles with a single bilayer, and their size does not exceed 20 nm, allowing a lower amount of encapsulation of hydrophilic drugs. LUVs consist of a single lamella with a size around 100 nm which has the capacity to store a greater quantity of hydrophilic drugs. MLVs range in size from 100 nm to several micrometers, and they are the most suitable for incorporation of lipophilic molecules, in comparison to hydrophilic compounds [200].

20.7.1 Production of liposomes

Liposomes are mainly produced through spontaneous interaction between phospholipids and water. The emphasis on liposome production is based on their ability to form vesicles of the correct size and structure with the most effective entrapment. Liposomes can be prepared by methods involving several different formation mechanisms, some more complex than others [201,202]. The production of liposomes involves three main steps: drying of lipids from organic solvents, dispersion of lipids in aqueous media, and the subsequent purification of the resulting liposomes. The selection of the appropriate method of liposome preparation depends upon the physicochemical characteristics of the material to be trapped, the environment in which it will be dispersed, and the desired size and shelf life of liposomes [203].

There are different methods for preparing liposomes, including mechanical methods, e.g., film method and ultrasonic method [204], the substitution of the organic solvent [205], the transformation of size by freeze thaw extrusion method [206], and the dehydration-rehydration method [206]. The mechanical method of liposome preparation is a simple thin film hydration method performed in an organic solvent such as chloroform. After the lipid film has been completely hydrated, any residual solvent is then thoroughly removed by drying the film under a stream of nitrogen. Afterwards, the film is hydrated with an aqueous buffer, resulting in the formation of liposomes. Sonication is another mechanical method to produce liposomes, in which the process of ultrasonication is employed; the ultrasonic bath method is more suitable for dilute lipid concentrations of a higher volume and as there is a lower energy input, there is subsequently a lower risk of lipid degradation due to heat. Tip sonication is more suitable for the preparation of SUVs on a small scale [208].

Liposomes can be prepared by the substitution of the organic solvent as well. This method necessitates the exposure of the material to an organic solvent, which will be dispersed into an aqueous phase containing the material to be entrapped within the liposome, leading to the formation of SUVs and MLVs [209]. The ether vaporization method consists of the formation of liposomes when ether solutions of a variety of lipids are injected into warm aqueous solutions [210].

Another way to prepare liposomes is by fusing preformed vesicles, or simply transforming their size, (for example, through the use of filter membranes to reduce liposome size) [211], and the freeze-dried rehydration method where vesicles are formed from performed vesicles [212].

20.7.2 Application of liposomes

Thanks to their great physicochemical characteristics, liposomes have been used for a variety of purposes, including delivery systems for antigens [213], chemotherapeutics [214], imaging, genetic materials [215], and their widespread use in the cosmetic industry [216]. However, the most developed application is the drug delivery system [217], because liposomes have a higher bioavailability and are capable of reducing both drug release in undesired areas and the toxicity of different drugs, nucleic acids, proteins, peptides, and other substances. Therefore, liposomes fulfill the general requirements of drug delivery systems, including transport to the site of action and avoidance of non-diseased host tissues, excellent distribution, and controlled release in order to improve the therapeutic effect of cargos and reduce their adverse side effects.

One of the great advantages of liposome-based drug delivery systems is their ability to deliver higher drug concentrations than other systems while targeting specific cells and organs, [218] thereby reducing damage to non-target cells and/or tissue. Therefore, liposomes protect the body from toxic effects of drugs [219]. Liposome-encapsulated drugs are released slowly. Thus, stable levels of therapeutic drugs are maintained in the bloodstream and the frequency of their administration is decreased [220]. Many products formulated with liposomes are in the clinical market. For example, the FDA has approved administration of doxorubicin delivered with liposomes [221].

Liposomal drug delivery systems are some of the most versatile and studied systems of recent years. Many of these systems are already tested and marketed for application. Additionally, other liposomal formulations are still under study due to their great advantages, highlighting their therapeutic activity with low side effects.

20.7.3 Conclusions

Liposomes have become one the best options available as a drug delivery system due to great advances achieved in the last few decades. Liposome preparation is improved thanks to new techniques used, the ability to define the size of liposomes, and their homogeneity and high stability; moreover, they can be prepared in a very short time. Liposomes can act as carriers for a variety of drugs, peptide hormones, vaccines, proteins, and genetic materials, and as such, have potential therapeutic action. Various types of liposome formulations are in the clinical trial stage for medical use, and others are already in the market for public use. In conclusion, liposomes are revolutionizing drug delivery systems, which are still under continuous development to find new biomedical applications.

20.8 Quantum dots as drug delivery systems

Luminescent semiconductor nanocrystals or quantum dots (QDs), are nearly sphere-shaped inorganic semiconductors whose size is in the range of 1–10 nm. Semiconductor nanocrystals are generally made of groups II and VI (e.g., CdS, CdSe, CdTe) or III and V (e.g., InP and InAs) elements [222]. Quantum confinement effects occur when the size of semiconductor particles is smaller than their exciton Bohr radius [223,224]. In comparison with organic fluorophores, quantum dots exhibit unique photophysical properties, such as narrowness, symmetry, size, composition-tunable emission spectra, broad excitation spectra, intense brightness, photostability, and resistance to photobleaching and chemical degradation [225].

20.8.1 Synthesis of quantum dots

High quality fluorescent QDs have been synthesized using the organometallic precursors and high temperature [226]. A variety of methods have been developed for obtaining high quality QDs in aqueous and organic phases, and these are being reviewed in the literature [227]. Several research groups [226,227] have been trying to develop different synthetic routes by using safe single precursors to obtain high quality QDs. Green chemistry utilizes nontoxic chemicals and renewable materials as an alternative safe, inexpensive, reproducible, versatile route to yield QDs with well-controlled size, shape, and monodisperse size distribution [228]. Size of QDs can be varied by different variables in the process of synthesis, such as concentration of precursors, capping agent, temperature, and time as result of the nucleation and crystal growth of quantum dots [222]. However, the main goal of chemical synthesis is to develop successful routes for depositing capping material to protect or passivate the QD particle surface.

Water-soluble QDs were synthetized using soluble starch as a capping material, where starch hydroxyl groups acted as passivation centers for the stabilization of QDs [229]. Typically, emission of QDs is reported for a variety of semiconductor materials with the same size, but different core sizes and shell thicknesses. These data provide access to a full range of potential emission wavelengths [230], which is essential for different biomedical applications.

20.8.2 Bioconjugation of quantum dots

Bioconjugation of QDs involves linking two or more molecules to create novel complex tools for research, diagnosis, and therapeutics [231]. Water-soluble QDs can be prepared through conjugation techniques with peptides, proteins, oligonucleotides, polymers, and drugs. Conjugation of QDs to biomolecules generates multifunctional QDs that can be used to allow specific interactions with biological systems, due to their high specificity and the affinity of biomolecules for the molecular recognition of their targets.

QDs' hydrodynamic diameter is a critical design parameter in the development of potential diagnostic and therapeutic agents [232]. Due to their smaller size, QDs can be used to deliver drugs to the central nervous system. As a consequence of QDs' potential, several nanopharmaceutical patents have been issued by the U.S. Patent and Trademark Office (U.S. PTO): 6933331 B2, 7005669 B1, 7015498 B2, 7192785 B2, 7235361 B2, 7335345 B2 [233].

20.8.3 Toxicity of quantum dots

The immense majority of research scientific papers report on the toxicity of QDs. The diversity of QD types and their physicochemical properties (e.g., size, shape, surface chemistry, composition, and aggregation) can greatly affect their potential toxicity. It is therefore quite difficult to extrapolate the results of such studies to reach any broad conclusions about the interactions of QDs and biological systems. Knowledge about the potential toxicity of QDs is limited. Many recent studies focus on minimizing or reducing QDs' toxicity. QDs can be conjugated to various molecules, increasing their solubility and stability, reducing their cytotoxicity, and allowing exploitation of the characteristic tumor environment [234]. Toxicity of QDs can be evaluated by using both *in vitro* and in vivo models. Studies of the toxicity of QDs are generally performed using cellular models [235–244], and there are few toxicological reports of QDs using animal models [245,246].

20.8.4 Applications of quantum dots

QDs hold great potential biomedical promise for several applications including molecular tagging, diagnosis of cancer (and other diseases), and therapeutic applications. QDs are also improving sentinel lymph node mapping, drug delivery, imaging, and therapy.

20.8.5 Intracellular delivery of quantum dots

An in-depth understanding of the intracellular dynamics and kinetics of QDs, including their mechanisms of uptake and intracellular delivery, is necessary for

their use in gene therapy, vaccination, and as drug delivery systems. The cellular internalization of QDs is not well known, and QDs' interaction with cells' surfaces can be strongly influenced by particle size, shape, and surface chemistry. Recently, cell-penetrating peptides (CPPs) have attracted great interest for their potential to optimize gene therapy, help develop vaccines, and deliver drugs. CPPs were used to facilitate transport of QDs via CPPs into the cell through a simple and efficient process [247]. Similarly, gH625-QDs were used for the successful recognition of specific targets in cytoplasm [248].

QDs have also been used to demonstrate direct participation of the endoplasmic reticulum (ER) in induction of apoptotic cell death of human umbilical vein endothelial cells (HUVECs) [237]. Zhao et al. demonstrated that QDs in organ, tissue, and cell levels can be observed, and one can analyze the mechanism of their lymphatic uptake and cellular distribution. They used four cell lines from different sources and animal models to demonstrate the biodistribution of QDs [249].

Histopathological studies of testis tissue showed toxic effects of QDs at 40 mg/kg in male Balb/C mice. QDs can pass the blood-testis barrier and cause direct destruction of germinal cells and spermatogenesis [250]. The biodistribution, body weight, hematology, blood biochemistry, and organ histology were determined at a relatively high concentration (25 mg/kg) of InP/ZnS QDs over a period of 84 days (12 weeks) in BALB/c mice [245]. Histopathological and biochemical analyses showed that QDs were biocompatible and non-toxic for rodents. In addition, the bright green emission light of QDs demonstrated that they can be used as contrast agents for bioimaging applications [246]. QDs conjugated to hyaluronic acid have been successfully used as novel drug-delivery carriers for the treatment of liver diseases [251].

20.8.6 Photodynamic therapy

Photodynamic therapy (PDT) is a treatment that uses special photosensitizing chemical agents by light activation for numerous malignant tumors. The mechanism by which tissue is destroyed seems to depend on the presence of activated oxygen molecules. Several photosensitizing agents are currently permitted by the US Food and Drug Administration (FDA) to treat certain cancers. QDs and QD-conjugates can be used as photosensitizers for PDT, although QDs' cytotoxicity may be an obstacle to their clinical application. However, due their nanometer-size, QD-conjugates are water-soluble, highly photo-stable, resistant to metabolic degradation, and biocompatible, and they possess size-tunable emission properties resulting from quantum confinement. QDs may have some advantages and potential physicochemical properties in PDT [252].

20.8.7 Lymphatic system surgical

A sentinel lymph node (SLN) refers to the first lymph node in the armpit on the same side as the cancer cells are most likely to spread from a primary tumor. Therefore, SLN biopsy is an important predictor of metastasis; it is a less invasive way to obtain information about possible cancer spread [253]. QDs were used for mapping the reticuloendothelial system (RES) and locating draining lymph nodes in vivo. QDs were

injected into the tumor to map SLNs in rats. In most cases, injection of quantum dots into the tumor produced rapid migration of QDs' fluorescence into contiguous lymph nodes, visible through the skin [254]. NIR emitting QDs were intradermally injected into the paws of mice to map SLN [255]. NIR light and QDs were injected into the thighs of pigs and demonstrated detection of SLN mapping of the gastrointestinal tract in real time [256]. Bio CFQD nanoparticles based on indium have been used for the detection of SLN mapping in animal models [257].

20.8.8 Drug delivery

Conjugation of biomolecules on the surface of the QDs may be achieved using a variety of methods [231]. Multifunctional QDs can be constructed with a therapeutic agent to inhibit tumor growth and an imaging agent to monitor the drug transport route. Multifunctional QD-based drug delivery systems can be a potential tool for nanomedicine, due to their functionalities for drug loading, targeting, controlled release, and monitoring of pharmacokinetics properties and biodistribution [258]. EpCAM aptamer-guided multifunctional DQs were utilized and may be capable of both cancer therapeutics and imaging [259]. The surface of QDs enables attachment of various ligands and loading of both hydrophilic and hydrophobic therapeutics. Therefore, these QDs can be used as fluorescent labels for tagging conventional drug carriers [258]. Liposomes can potentially be used for drug delivery due to their great flexibility in size, charge, rigidity, permeability, and surface functionality. They are resistant to degradation in the gastrointestinal tract, which makes them ideal candidates for oral delivery [260]. Drug-loaded liposome-QD hybrid vesicles were designed with two types of lipid bilayers. The drug-loaded L-QD-Doxorubicin can be utilized as a theranostic strategy for the simultaneous delivery of therapeutic and diagnostic agents [261]. In vivo QD-Doxorubicin nanoconjugates were used as delivery systems. QD-Doxorubicin also may have a potential for diagnosis and treatment of pulmonary disease, due to their selective uptake into alveolar macrophages [262]. Hybrid nanomaterials, Doxorubicin-Polyrotaxanes-QDs, were synthesized and characterized. These hybrid nanomaterials are capable of being used as new systems for drug-delivery and cancer therapy [263].

20.8.9 Conclusions

QDs have numerous applications in nanomedicine, due their exceptional properties such as high brightness, photostability, and resistance to photobleaching and chemical biodegradation. QDs have potential for development as nanopharmaceutical tools for cancer treatment and innovative designs for drug delivery.

20.9 Magnetic nanoparticles for drug delivery

Nanoparticle (NP)-based biomedical applications have been a subject widely studied by the scientific community in the last few decades. Within the research literature, our attention is captured by studies involving magnetic nanoparticles and their potential

use as drug carriers, mainly due to their size, which makes them prominent candidates for use in oncology treatments. Widder et al. were the first to propose using magnetic micro- and nanoparticles as drug carriers [264–266]; the main idea was that the drug used to fight cancer was encapsulated inside nanoparticles, and that by using external magnetic fields, magnetic NPs were taken to the specific site and subsequently released to combat the cancer in question [267]. This is a very good starting point for application of magnetic NPs, but in order to further develop them, it is necessary to consider the type of magnetic material to be used, the shape and size of the nanoparticles, and the type of drug to be used. Different magnetic nanomaterials have different applications depending on their properties [266,268–270]. The magnetic nanomaterials most widely used as drug carriers are magnetic iron oxides, such as magnetite [Fe_3O_4], maghemite [γFe_2O_3], iron-based metal oxides, iron alloys, and ferromagnetic and superparamagnetic [superparamagnetic iron oxide (SPIO)] [267,271–273].

There have been many recently reported studies of magnetic nanomaterials, which have an endless number of properties and specific characteristics. Of these characteristics, the type and shape of the material used are of fundamental importance, because sometimes it is desirable to use a coating of nanoparticles in order to reduce toxicity levels (which can be present due to materials such as cobalt, chromium, and others) [266]. This is critical for biomedical applications, especially drug carriers, which must work in an appropriate cellular environment [270]. The materials most frequently used as drug carriers (and their main characteristics) are:

Magnetite [Fe_3O_4]: Normally, magnetite is presented as iron oxides, which have very strong ferromagnetic properties. The nanoparticles' sizes are closely related to the synthesis method used, and these range from 3 nm to 20 nm [274,275].

Maghemite [γFe_2O_3]: Maghemite presents the same type of structure as magnetite, but all maghemite's iron atoms are in the Fe (III) oxidation state; this is why maghemite is one of the most widely used materials for biomedical applications, as iron (III) ions are widely found in human body [266]. This makes maghemite an excellent drug carrier. The sizes of magnetite nanoparticles range from 4 nm to 16 nm [274,275].

Iron-based metal oxides: Different metallic iron oxide-based materials have specific properties depending on the type of material used. These materials are $CoFe_2O_4$, $NiFe_2O_4$, and $MnFe_2O_4$. These materials have high toxicity because of their Co, Ni, Mn, Sr, and Ba precursors [266,276].

Superparamagnetic iron oxide (SPIO): These nanoparticles consist of an iron oxide core and a hydrophobic material shell; the core can be Fe_3O_4 or γFe_2O_3. These materials have particle sizes from 2 nm to 3 nm [277].

At present, there are different methods of synthesis for obtaining these types of magnetic nanoparticles [278]. Some of them will be described briefly in the next section.

Coprecipitation method: This method involves the simultaneous precipitation of two metal ions (Fe^{2+} and Fe^{3+}) in an aqueous medium; pH control is very important, because the size of nanoparticles depends directly on the pH value [279,280]. One of the major problems is that each ion has a different pH, generating synthesis issues [281]. These nanoparticles are 5 nm in size [266].

Chemical vapor condensation (CVC): In this method, volatile metal compounds are heated in an inert gas atmosphere, which decompose to form metallic nanoparticles. Particle sizes may vary from 3 nm to 20 nm [266,282,274].

Hydrothermal synthesis techniques: Iron salts are dissolved in an aqueous media in a Teflon vessel, then heated above their boiling point, generating pressure inside the vessel and causing formation of the nanoparticles [279].

Liquid phase reduction: In this case, magnetic or nonmagnetic metal oxides are reduced via reducing agents such as $NaBH_4$ and $LiAlH_4$ [266,283].

Because most of magnetic nanoparticles have high toxicity and a low cell affinity (because they are mostly hydrophobic), the surface of nanoparticles must be coated or functionalized, mostly through use of polymers such as dextran or an inorganic coating, in addition to carboxyl groups, and so on [284–287].

At present, there are several investigations on the use of magnetic nanoparticles as drug carriers. For example, Kievit et al. (2011) synthesized iron oxide nanoparticles conjugated to Doxorubicin, through which it was possible to effectively release the drug substance, obtaining pH values lower than 6.5.[291, 292] Lee et al. (2013) reported the synthesis of iron oxide nanoparticles that were conjugated to gemcitabine through a linker consisting of an enzyme-dependent tetrapeptide bound to an amphiphilic polymer covering the core nanoparticle [290], through which it was possible to deliver the drug to the desired location by reducing the pH to 5.5. Moreover, there are other studies which have used magnetic nanoparticles to transport anticancer drug molecules with high efficiency [273,291].

20.10 Conclusions

Magnetic nanoparticles are an excellent alternative for the control of diseases, especially for fighting cancer, because of magnetic nature of their core, which makes them suitable for accurately targeting diseased cells. They also present a high carrying capacity for drug transport. There are still several problems to overcome, such as toxicity reduction and the need to design nanoparticles with high magnetic field intensity nuclei, in order to facilitate more efficient targeting using external magnetic fields.

20.11 Gold nanoparticles applied to photodynamic therapy for cancer theranostics

Nanoparticles' application in nanotechnology has rapidly developed, opening up new possibilities in research, diagnosis, and treatment of various diseases including cancer. For example, fluorescent nanoparticles can be used as tumor biomarkers and for the detection of multiple genes through in situ fluorescence [292].

Metal-based nanoparticles can be designed as theranostic materials for cancer cells when these nanoparticles are adequately functionalized with ligands targeting tumor biomarkers. Most of them can accumulate in cancer cells, and when these nanoparticles are exposed to an adequate excitation source, they can be detected in diseased tissues [293]. One of the more frequently used metal-based nanoparticles are gold nanoparticles (AuNPs), which are relatively inert and stable in biological systems, leading to biocompatibility and a general lack of toxicity. Moreover, AuNPs show electronic and optical properties that have been exploited in a wide range of biomedical applications [294].

20.11.1 AuNPs applied to drug delivery, diagnostic and cancer therapies

Functionalized AuNPs stand out due to their monolayer tenability. AuNPs can be loaded with some drugs by mechanisms such as covalent and noncovalent conjugation. Furthermore, it is easy to control targeting, stability, and drug release in AuNPs [295]. Cancer-targeting molecules on engineered-surface AuNPs may provide specific delivery of drugs to tumor tissues. Cancer cells are precisely targeted with special receptors in selective chemotherapy. The general strategy for actively targeting tumors is coating AuNPs with special ligands which target surface membrane proteins and biomarkers only expressed or overexpressed in cancer cells. The used functionalized parts include special antibodies, aptamers, and molecules bonding to specific tumor biomarkers [293].

AuNPs also have been proposed for medical diagnostic applications. For example, AuNPs increase the nonradiative relaxation time of protoporphyrin IX (PpIX) when this photosensitizer is in a AuNPs-containing solution. The increase of the nonradiative relaxation time in the PpIX with gold nanoparticles also augments the fluorescence time of PpIX when compared with a PpIX solution [296].

AuNPs have been also used to harm viruses, bacteria, and cancer cells because of their heating effects under laser irradiation, attributable to enhanced absorption induced by localized surface plasmon resonance; this is called photothermal therapy [297]. AuNPs' targeted thermal effects appear to be ideally suited for application in photothermally activated drug delivery and medical therapies, which depend on thermal transport between AuNPs and surrounding liquid [298]. Heat transfer in liquids (including water and oils) is generally poor, and thermal conductivity is important for energy-efficient heat transfer. Consequently, several methods have been used to improve the thermal conductivity of liquids. Fluids containing AuNPs can reasonably be expected to display significantly enhanced thermal conductivity relative to those of pure liquids, which is important for efficient photothermal therapy [299]. Gutiérrez Fuentes et al. showed that thermal diffusivity of PpIX mixed with gold nanoparticles increases with the AuNPs' concentration [298].

Photodynamic therapy, a relatively recent technique to combat certain types of cancers, has been successfully applied to skin cancer. In photodynamic therapy, porphyrins are used as photosensitizers for treatment of cancerous tumors; among these porphyrins, protoporphyrin IX (PpIX) is highlighted. PpIX is induced by δ-aminolevulinic acid (ALA) and accumulates in high concentrations in cancer cells, and low concentrations in normal cells.

20.11.2 AuNPs in photodynamic therapy

20.11.2.1 Fundamentals of photodynamic therapy

Photodynamic therapy (PDT) is a medical technology that utilizes lasers and the simultaneous presence of a photosensitizing substance, light of an appropriate wavelength, and the presence of oxygen in tumor tissue. The interaction of these three components is explained by Jablonski's diagram (Fig. 20.1). The photosensitizer in its electronic basal state is in a singlet state (PS_0), and upon having absorbed light of

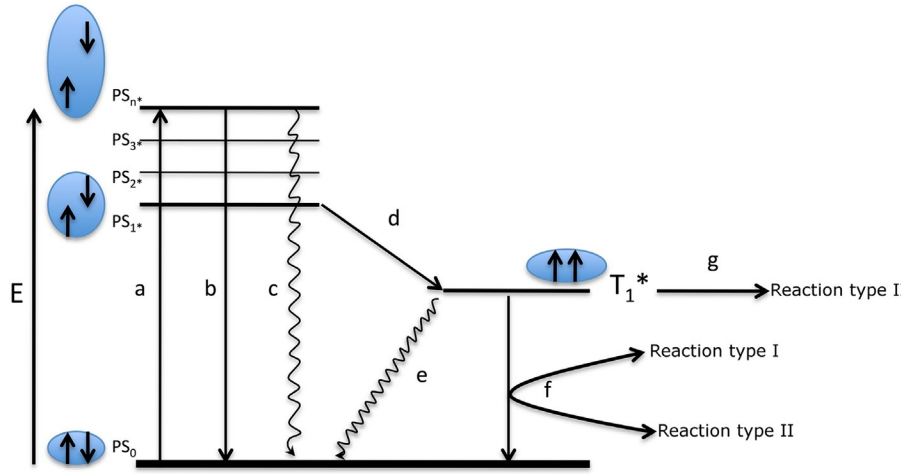

Fig. 20.1 Photophysical basic process of PDT. After irradiate the photosensitizer, this absorbs a photon, then the Ps goes from a basal state (PS_0) to an electrically excited state (PS_1, PS_2, PS_3, or PS_n) (a). If the electron is in PS_1, it can return to its basal state by fluorescence emission (F) (b), and this is used to realize Photodynamic Diagnosis (PDD) or heat liberation by internal conversion (c) or may have an electronic rearrangement and perform an intersystem crossing (ISC) (d) in order to generate the excited triplet state (T_1). The triplet state (T_1) can return to its basal state (PS_0) emitting a photon and generating phosphorescence (Phos) (e), or it can transfer its energy or charge to generate singlet oxygen (type II reaction) or reactive oxygen species (reaction type I), (f) or reacts directly with biomolecules (reaction type III), these reactions lead to action photodynamic (PDT) [305].

an appropriate wavelength (Abs) it reaches a first excited singlet state of short-life (PS_1 or PS_2). Suppose that the excitation is in an electronic level, PS_2. A nonradiative crossing from PS_1 to PS_2 is generally the dominant mechanism needed to achieve the treatment objective. This crossing between two electronic states of the same spin multiplicity is called internal conversion (IC). This IC process is then followed by a rapid vibrational relaxation in which the excess vibrational energy is dissipated as heat. The photosensitizer in S_1 can return to its basal state (PS_0), emitting the absorbed energy as fluorescence (F), useful in the diagnosis of the photodynamic therapy, and it is known as photodynamic diagnosis (PDD), or internal conversion (IC). Alternatively, the photosensitizer (PS_1) can switch to a first triplet excited state (T_1) through a process known as intersystem crossing (ISC). This is a forbidden transition (spin forbidden); however, a good photosensitizer achieves a high yield of triplet state. T_1 state has a half-life long enough to take part in chemical reactions; therefore, the photosensitizer in this energetic state mostly mediates the photodynamic action. The photosensitizer in its triplet (T_1) state can perform an electron or hydrogen transfer to neighboring molecules (water, biomolecules, or oxygen), and after this redox reaction, the radical resultant can lead to the production of peroxyl radicals and trigger other reactions, resulting in the generation of free radicals and peroxides. If it is the oxygen which receives the electronic transfer, it directly forms a superoxide (O^{2-}); this process is

called reaction Type I. When the molecular energy transfer occurs directly between the photosensitizer in its triplet state and basal state molecular oxygen, forming highly reactive singlet oxygen ($^1O_2$), the reaction is called Type II [300–302], and finally the Ps in triplet status reacts directly with biomolecules through an oxygen-independent pathway. These three reactions lead photodynamics and can trigger cascades of biochemistry, biophysical, immunological, and physiological reactions, finally resulting in destruction of the irradiated tumor [300]. Also the photosensitizer in its triplet state (T_1) can return to its basal state (S_0), emitting a photon and generating phosphorescence (Phos) [300–302]. Lastly, the photosensitizer is degraded by light. This process is known as photobleaching [304]. There are key parameters that determine the ability of a photosensitizing compound. These are the yield or production of singlet oxygen (Φ_Δ), which is the probability that a photosensitizer, having absorbed a quantum of light, is converted to the triplet state, and then transfers its excess energy to molecular oxygen, resulting in the formation of singlet oxygen. The yield of the triplet state (Φ_T) is the probability that a photosensitizer, after absorbing a quantum of light, converts to the triplet state [304].

20.11.2.2 Photosensitizers for photodynamic therapy

A photosensitizer (Ps) is a molecule formed by one or more light-sensitive π electron-rich macrocycles, used in photodynamic therapy and other processes. When it comes to choosing an ideal photosensitizer, it is desirable that it displays selective accumulation in diseased tissues, generates cytotoxic chemical species, and induces the biological effect. There is no ideal Ps; however, there are nine required characteristics a photosensitizer should present to be used in photodynamic therapy [306], and as a consequence, they have been classified based on these physical and chemical properties [307–312].

Physicochemical characteristics of photosensitizers: (1) purity, chemical stability, and photostability, which aid or allow extension of the photoirradiation time; (2) solubility in water, where amphiphilicity ensures both transport in blood without precipitation or aggregation, and effective penetration through the lipid bilayer; (3) high capacity for quantum generation of $^1O_2$ (φ_Δ) with the objective of generating singlet oxygen; (4) high molar absorption coefficient (ε) at wavelengths of 600–850 nm in the red light region, which can further penetrate tissues and generate triplet states, inducing fluorescence (which is useful in PDD as well).

Biological characteristics of photosensitizers: (1) high selectivity to be retained in tumor tissue; (2) rapid accumulation in tumor cells in organelles different from the nucleus; (3) no cytotoxicity in the dark, for the photosensitizer or its metabolites; (4) no mutagenic effect when irradiated or nonirradiated; (5) rapid elimination from patients catalyzed by photodegradation, metabolism, and excretion.

20.11.2.3 Applications of photodynamic therapy as theranostic

Since Kelly and Snell [306] and Dougherty [307] published the first work on the use of PDT with hematoporphyrin in humans [313,314], hundreds of thousands of patients throughout the world have been treated with PDT to eliminate cancer from different

sites and treat other diseases. PDT has advanced rapidly in the past 40 years, both in clinical applications and in the understanding of the mechanisms involved in this treatment, leading to approval by the FDA and other health agencies worldwide for use in humans. Currently, PDT has been approved for use in clinical treatment of premalignant, malignant intraoperative, and intracavitary lesions, infections by viruses, bacteria, and fungi, and noncancerous lesions (such as macular degeneration), among others in the United States, the European Community (EU), England, Canada, Russia, Japan, China, South Korea, and in Latin America (Mexico, Brazil and Argentina Costa Rica, Guatemala, Honduras, Nicaragua, Panama, Dominican Republic, El Salvador, Trinidad, and Tobago).

The clinical application of PDT for the purpose of theranostics is applied as follows: (1) the photosensitizing drug is administered either topically or systemically; (2) an elapsed time is considered for the selectively accumulation of photosensitizing drug in target cells; (3) a probe with an optical fiber is introduced to apply light at a certain wavelength (for example at 480 nm) and at low power to activate the Ps PpIX and generate fluorescence, and with an optical pickup fiber which allows observation of the exact site of the tumor cells; (4) a new fiber is introduced, which could be located in the same probe from the beginning of the process, into the patient's cavity to bring light to the tumor, and irradiate it at 635 nm (if the Ps is PpIX) to generate the photodynamic effect by the triplet states of the Ps, which will lead to death for cancerous, sick, or infected cells.

Photodynamic therapy alone has potential as a theranostic tool, because via interaction with light, photosensitizers generate radiative (fluorescence and phosphorescence) and nonradiative (heat, reactive oxygen species, and free radicals) products, as detailed in Fig. 20.1. All these processes occur in different proportions, and PDT has the characteristic of being theranostic because it can allow the detection of fluorescence in situ and in vivo, and the induction of cell death. Nevertheless, it is important to consider the quantum yield of the photosensitizer, i.e., the probability that the process of interest will happen when a photon is absorbed. More simply, the yield of fluorescence (φ_F), internal conversion (φ_{IC}), and intersystem crossing (φ_{ISC}) when absorbing a photon can be determined by the following equation [315]:

$$\varphi_F + \varphi_{IC} + \varphi_{ISC} = 1$$

Thus, when a photosensitizer has high capacity to generate fluorescence (φ_F), it has low capacity to generate triplet states (ISC), and vice versa; therefore, photosensitizers are better in one of the two properties useful for theranostics. However, nanoparticles have been useful in supporting PDT in theranostics. When photosensitizers are conjugated or encapsulated by nanoparticles, this process allows an increase in the transport rate, protection of photosensitizers from environment, and targeting to specific cells. Moreover, nanoparticles can carry hydrophobic photosensitizers [316], immobilize them, and function as an antenna, increasing the ability to absorb light and transmit energy, magnifying their properties to produce fluorescence and generation of triplet states principally.

Gold NPs are among the most used because of the following advantages: large surface area, low hydrodynamic mean size, multimodal applications (targeting,

diagnostics, and therapy), scaffolds for additional agents, ease of surface modification, stability, and biocompatibility. However, there are some disadvantages, like high cost for large-scale production, lack of standard protocols for translational medicine, and nonbiodegradability [317].

20.11.2.4 *AuNPs associated to photosensitizers to eliminate cancer*

NPs generally play an important role in cancer therapy because: (1) they can improve radiation-induced damage; (2) they produce heat during exposure to UV rays and near-infrared radiation, so they can destroy cancer cells through thermal ablation; (3) they can improve the administration of drugs, such as anti-cancer drugs that are highly insoluble in water or unstable in the biological environment; (4) they can increase the average lifetime of drugs and image agents through modification of the NPs' surfaces to avoid drug loss through rapid elimination and metabolism rates [308,318].

Gold NPs are used for two main purposes in photodynamic therapy. Firstly, they serve as a platform for delivery of photosensitizers to cells due to their ability to form stable chemical bonds with thiol and amine groups, allowing modification of its surface with different molecules, including photosensitizers. Secondly, they can be used as antenna molecules to improve photosensitizers' light absorption [319].

Russell et al. [313] first proposed the use of gold NPs coupled with photosensitizers, and showed a clear increase in the quantum yield of $^1O_2$, attributed to the metal via higher emitted fluorescence [320]. Other photosensitizers have been used, including porphyrins, chlorines, PpIX-ALA and a number of newly created photosensitizers (see Fig. 20.2). An attractive feature of this approach is that AuNPs are biocompatible and used in therapy. Therefore, approval and clinical application of this system may be easier to achieve [321].

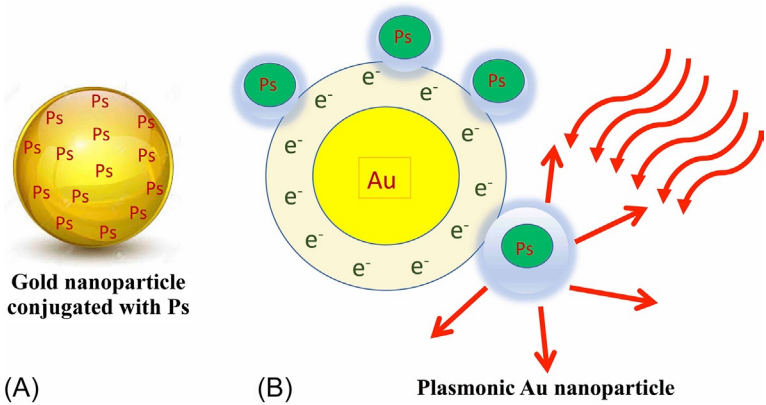

Fig. 20.2 Uses of AuNPs in PDT. (A) Conjugation of AuNPs with PS as transport system, (B) Plasmonic AuNPs. The local electric field caused by conductance electrons potentiates the optical field close to the surface and increases the fluorescence or photoactivity of an attached PS [329].

Cheng et al. [316] developed a set consisting of AuNPs, polyethylene glycol (PEG) and phthalocyanine-4 (Pc-4) for the in vivo administration of drugs for PDT [322]. When the Pc-4 PS is injected in vivo for PDT, it takes one to two days until it accumulates at the tumor site. Using the NP conjugate, this accumulation time is reduced to 2 h [322–324]; this is one of the clearest examples of its potential use.

Cheng et al. [319] evaluated the efficiency of a AuNP conjugate with phthalocyanines in mice and observed a rapid drug delivery system and tumor penetration in just hours. The pharmacokinetics of conjugates in a seven-day trial demonstrated rapid excretion of drug, verified by fluorescence of this drug in the urine. This study suggests that noncovalent delivery through AuNPs offers an attractive approach for anti-cancer drugs to penetrate deeply into the center of tumors [325]. This work shows the potential of PDT as a diagnostic tool using AuNP conjugate with phthalocyanines in mice. In addition, this system showed unique versatility as it facilitated drug administration, quantitative control of the delivery process, and cancer therapy. This whole process is called theranostics. However, in the study of fluorescent images of tumors in mice revealed the location of conjugate not only in the tumor, but also in other areas. These types of delivery systems can be improved (for example with monoclonal antibodies with receptor-ligand specificities for tumor cells). The use of this NP system coupled to photosensitizers as a drug delivery system could be easily controlled and quantified in the future [325].

20.11.2.5 AuNp in photodiagnostic (PDD) for tumor detection

Conventionally, the detection of fluorescence in tumors using photosensitizers has been used for [326] the detection of lesions (premalignant, malignant, infectious, etc.) in vivo, location of lesions in vivo to guide both the application of PDT and surgeries, measurement of the photobleaching of photosensitizers during PDT, and estimation of the efficiency of PDT. Some examples of the clinical applications of diagnostic fluorescence are the detection of micrometastases in ovaries [327] and Barrett's esophagus and bladder carcinoma in situ [328].

To activate photosensitizers using nanoparticles, both materials must be bound to increase the efficiency of the energy transfer from the nanoparticle to the photosensitizer. Resonance energy transfer fluorescence (FRET) is a typical energy transfer mechanism. FRET is the transfer of energy from an initially excited donor (nanoparticle) to an acceptor (photosensitizer). For efficient energy transfer, the donor emission band must overlap with that of the acceptor, and the donor and acceptor must be very near one another (less than 10 nm apart, generally) for the transfer to take place.

Nanoparticles doped to a polymer-conjugated photosensitizer have shown interesting properties. For example, Shen et al. [329] prepared nanoparticles using a reprecipitation method, in which they incorporated polyoxyethylene nonylphenyl ether (CO-520). The polymer conjugate, poly [9,9-dibromohexylfluorene-2, 7-xyleneethylene-1,4- (2,5-dimethoxy) phenylene] (PFEMO), was used as the host matrix to disperse tetraphenylporphyrin (TPP) and an energy donor to improve the excitation properties of two TPP photons.

The doped nanoparticles were stable and had low cytotoxicity in the dark. TPP emission of nanoparticles increased approximately twentyfold by PFEMO under two

excitation photons. Nanoparticles showed significantly greater biophotonic excitation and greater singlet oxygen generation, as well as greater efficiency of photodynamic therapy to eliminate cancer cells [329]. In another manuscript, Zhao et al. [330] demonstrated high biophotonic image capacity and singlet oxygen generation in PDT using gold nanorods. Other works such as that of Bengendahl and Paterson [331] showed the biophotonic activity of porphycene. Gao et al. [332] reported the activity of hypocrelin-loaded gold nanoparticles in photodynamic and photothermal therapy. Other examples can be seen in the works of Li et al. [333] and Vieira et al. [334].

Our group used gold nanoparticles (AuNPs) to eliminate cancer cells because they have proven to be very effective. Cancer cells accumulated 600% more AuNPs than healthy cells. In addition, AuNPs have a high capacity for absorption and dispersion of light. Therefore, our hypothesis in one study was that the effectiveness of photodynamic therapy (PDT) could be improved by the simultaneous use of AuNPs and photosensitizers (PS). The efficacy of photodynamic therapy was determined using AuNPs and protoporphyrin IX (PpIX) induced and not induced by δ-aminolevulinic acid (δ-ALA). Results showed that when cells were exposed to AuNPs and PpIX separately, a PDT efficiency of 20% was obtained [335], while when exposed to the AuNPs-PpIX conjugate, cell death rose to 60% [336].

20.11.3 Future Research

PDT shows potential for future clinical use in theranostics [337]. The development of new Ps-based platforms for drug delivery, with their advantages over current platforms, has been focused on bio-guiding the Ps and increasing its concentration in the target site. Future development will create multifunctional nanocomplexes that confer new properties to Ps and magnify their components through interaction with light [338], and create new photosensitizers coupled with a new generation of NPs that will add more than one property to Ps. Future research will focus on the auto-assembly of nanoparticles (taking into consideration human and intratumoral physiological pH) and upon photosensitizers that take advantage of cell catalytic activities and functional nanoparticles.

20.12 Conclusions

Nanoparticles' application of in biomedical studies has been rapidly developed through nanotechnology research, opening up new opportunities in medical applications including treatments of different types of diseases. Among metal-based nanoparticles, AuNPs are one of the most frequently used because of their optical and electronic properties which have been exploited in biomedical research. Engineering the surfaces of AuNPs may provide specific drug delivery to cancer tumor tissues. AuNPs and some photosensitizers have also been used for diagnostics in tumor tissues because AuNPs increase the nonradiative relaxation time of photosensitizers (as in the case of protoporphyrin IX [PpIX]), which in turn increases the fluorescence time of PpIX as well. Another application of AuNPs lies in photodynamic therapy, in which

photosensitizers such as PpIX are used for treatment of cancerous tumors. PpIX is induced by δ-aminolevulinic acid (ALA) and accumulates in high concentrations in cancer cells and in low concentrations in normal cells. AuNPs are used in PDT to improve light absorption of photosensitizers and also as a platform for delivery of photosensitizers to cells because of their ability to form stable chemical bonds with thiol and amine groups. These groups allow surface modification using different molecules, including photosensitizers. These considerations, coupled with the development of new photosensitizers and new generation nanoparticles, make PDT an excellent candidate for use in clinical applications like theranostics for various diseases, including cancer.

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