Cyclodextrin-Modified Inorganic Materials for the Construction of Nanocarriers

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Abstract

Inorganic nanoparticles, such as gold, silver, quantum dots and magnetic nanoparticles offer a promising way to develop multifunctional nanoparticles for biomedical applications. Such nanoparticles have the potential to combine in a single, stable construct various functionalities, simultaneously providing imaging abilities, thermal therapies and the ability to deliver drugs in a targeted fashion. An approach for providing drug loading abilities to these inorganic nanoparticles consists in the modification of their surface with a coating of cyclodextrins, and thereby endowing the nanoparticles with the potential of functioning as drug nanocarriers. This review presents the advances carried out in the preparation of cyclodextrin-contained gold, silver, quantum dot and magnetic nanoparticles as well as their applications as drug nanocarriers. The nanoparticle surface can be modified incorporating cyclodextrin moieties, 1) *in situ* during the synthesis of the nanoparticles, either using the cyclodextrin as reducing agent or as stabilizer; or 2) in a post-synthetic stage. The cyclodextrin coating contributes to provide biocompatibility to the nanoparticles and to reduce their cytotoxicity. Cyclodextrin-modified nanoparticles display a multivalent presentation of quasi-hydrophobic cavities that enables, not only drug loading in a non-covalent manner, but also the non-covalent assembly of targeting motifs and optical probes. This paper also provides an overview of some of the reported applications including the *in vitro* studies and, to a lesser extent, *in vivo* studies on the drug-loaded nanoparticles behavior.

Keywords

Cyclodextrin, gold nanoparticles, silver nanoparticles, quantum dots, magnetic nanoparticles, drug nanocarriers, multifunctional nanocarriers.

1. Introduction

Nanoparticles (NPs) having inorganic-based cores have found increasing application in many different areas of biomedicine with heavy emphasis on imaging, sensing and drug delivery (Abbasi et al., 2016; Giner-Casares et al., 2016; Rai et al., 2016; Yang et al., 2015). Inorganic NPs have certain advantages over other nanoparticulate systems (Figure 1): 1) Their versatile modification possibilities enable them to act as scaffold for the assembly of well-defined multifunctional structures. Such surface modification may ensure particle stability as well as functionalization with different moieties (i. e. fluorescent dyes, drugs, targeting ligands, etc.) to endow the NPs of sensing, imaging, targeting and therapeutic properties, thereby providing multi-modal treatments (Tonga et al., 2014a, 2014b); 2) A controllable shape, size and large surface to volume ratio that allows for an enhanced drug payload and more effective supramolecular and biological interactions; 3) In addition, optical, electronic, and magnetic properties of inorganic NPs allow them to highlight supramolecular and recognition processes. The remarkable properties of the plasmonic NPs (García, 2011) opened up new directions in the biomedical applications of these materials, that include theranostics and photodynamic and photothermal therapies (Doane and Burda, 2012; Giner-Casares et al., 2016).

As drug nanocarriers, inorganic NPs can provide protection of the drug against degradation in biological conditions and in some cases the design of external-stimuli controlled release methods (Kim et al., 2013; Tonga et al., 2014a). Drugs can be conjugated on the NPs surface via covalent bonds, which requires the chemical modification of the drug and, quite often, some intracellular process to occur or external stimuli (heat, light) for the drug release. In contrast, unmodified drugs can be loaded onto the NPs via noncovalent interactions, thus preserving the therapeutic activity of the drug. Noncovalent drug loading requires the NPs surface modification to endow them with drug hosting capabilities (Montes-García et al., 2014).

Cyclodextrins (CDs) are cyclic oligosaccharide constituted by six (α-CD), seven (β-CD) and eight (γ-CD) D-*gluco*pyranosyl units linked by α-(1→4) bonds forming a torus-shaped structure with a relatively hydrophobic cavity. CDs and their derivatives are well-known to form complexes in aqueous solution by including a large variety of organic molecules of hydrophobic nature and suitable size in the cavity, and thereby increasing both the water solubility and the stability of such molecules. Such guest hosting abilities have found broad pharmaceutical applications (Duchêne et al., 2009; Duchêne and Bochot, 2016, 2011; Loftsson and Duchêne, 2007).

The attachment to metallic NPs of cyclodextrins (CDs), as well as other suitable macrocyclic molecular receptors able to form inclusion complexations with drugs, gives rise to non-porous NPs with host-guest abilities without altering their plasmonic properties. Furthermore, the multivalent presentation of the CD moieties on the surface of the NPs allows for an improvement of the NP-drug complex stability as compared with that for a single CD-drug binding interaction (Mejia-Ariza et al., 2017). The combination of complexing and plasmonic properties of the resulting CD-modified NPs broadens their potential biomedical applications as different modes of action can act simultaneously, including photodynamic and/or photothermal therapies, and chemotherapy. In addition, supramolecular complexation ensures that the drug activity

is kept unaltered, and multivalenty enhances the effective concentration of the drug. Molecules other than drugs such as imaging probes or targeting moieties can be supramolecularly co-attached on the NP surface in a modular fashion, leading to series of different theranostics based on the same CD-modified NPs. Moreover, CDs remarkably improve the water solubility, colloidal stability and biocompatibility of the NPs, and thus remaining in the blood circulation for prolonged times. It has also been suggested that the presence of CDs on the certain NPs may also result in overcoming certain forms of multidrug resistance (Aykaç et al., 2014).

The modification of the NPs surface with CDs is flexible and can be achieved in two different ways. Firstly, CDs can play a role in the preparation of transition-metal and derivatives NPs (Montes-García et al., 2014), and thus CD-decorated NPs can be obtained directly by using CDs as reducing agents during the preparation of NPs as well as for their stabilization and size control. The first case of CD-stabilized particles was reported for a colloidal dispersion of rhodium that is obtained when a water solution of rhodium(III) chloride is refluxed in the presence of native α- or β-CD (Komiyama and Hirai, 1983). As a second strategy CDs can be incorporated onto the NPs through post-synthetic surface modification. In the first reported example of that, the surface modification of gold nanoparticles (AuNPs) with β-CD was achieved by treatment of a colloidal dispersion of AuNPs of a diameter of 11-13 nm with per-6-deoxy-6-mercapto-CD resulting in the coating of the NPs with thiolated CDs, thus giving rise to multisite hosts in aqueous media, able to engage in host−guest interactions with hydrophobic molecules in aqueous solution (Liu et al., 2000, 1999).

Herein, we review the advances carried out in the preparation of CD-contained gold, silver, quantum dot and magnetic nanoparticles as well as their applications as drug nanocarriers. The emphasis has been put on the use of the CDs to endow metal NPs with the ability to encapsulate and deliver drugs. Other relevant biomedical applications such as the development of biosensors for diagnostics are out of the scope of this review.

2. Gold Nanoparticles

2.1 Synthetic strategies

Most of the CD-modified AuNPs prepared for their use as drug nanocarriers are synthesized following two main protocols (Figure 1). Both protocols involve the attachment of CD on the AuNPs surface via Au-S bond. When the Brust–Schiffrin method is applied, CD-coated AuNPs are formed *in situ* by reducing $HAuCl_4$ with $NaBH_4$ in the presence of *per*-6-deoxy-6-mercapto-CD (Liu et al., 2000) or mono-6-deoxy-6-mercapto-CD (Liu et al., 2004), obtaining AuNP@SαCD-I, AuNP@SβCD-I, AuNP@SγCD-I and AuNP@monoSβCD-I, respectively. This method (method I and the resulting NPs are denoted as I) normally provides particles of 2-6 nm diameter. An alternative two-step procedure (method II and the resulting NPs are denoted as II) consists in the synthesis of citrate-stabilized AuNPs by Turkevich-Frens method (Enustun and Turkevich, 1963; Frens, 1973; Kimling et al., 2006; Turkevich, 1985a, 1985b; Turkevich et al., 1951) followed by introduction of the CD as per-6-deoxy-6-mercapto-CD (Liu et al., 1999), obtaining AuNP@SβCD-II. CD can also be introduced as CD-linked disulfide, normally having a spacer connected to one of the CD glucose

units, either through the primary or the secondary face (Aykaç et al., 2014), to obtain particles ranging from 12 to 30 nm size.

In addition, AuNPs stabilized with unmodified α-, β- and γ-CDs (AuNP@αCD, AuNP@βCD, and AuNP@γCD) can be obtained when $HAuCl_4$ is reduced with $NaBH_4$ or sodium citrate in the presence of native CDs (Liu et al., 2003). The size of the NPs depends on the concentration of CD and ranges from 2 to 8 nm, when $NaBH_4$ is used, and 4 to 15 nm, when sodium citrate is used. CDs remain intact, and it was suggested that the stabilization of gold colloids by CDs is due to hydrophobic-hydrophobic interactions between AuNPs and CDs. Futhermore, unmodified β-CD in alkaline aqueous solution can be used as reducing agent, instead of sodium citrate or $NaBH_4$, to afford AuNP@βCD of *ca.*10 nm size in which CD acts as both a reducing and stabilizing agent (Pande et al., 2007). In these reaction conditions, the reduction of metal salts to the corresponding metal nanoparticles involves the oxidation of primary C-6 alcohols to carboxylate anions. The results suggest that both oxidized and non-oxidized β-CD molecules are present and that the negative charge-bearing β-CD molecules provide a dense coating on the surfaces of the metal particles, and thereby providing stabilization.

2.2 Biomedical applications

Multi-inclusion site NPs are very convenient platforms for an efficient loading of drugs by host-guest complexation (Table 1). For example, the synthesis of 3.8 nm-diameter AuNP@monoS$(CH_2)_6$SβCD-I (Figure 2a), consisting in β-CD units linked to the NPs surface via Au-S bond through the hexamethylene S$(CH_2)_6$S spacer, which in turn is connected to one of the C-6 of the macrocycle, was carried out by applying method I using mono{6-deoxy-6-[(mercaptohexamethylene)thiol]}-β-CD (Gimenez et al., 2005). AuNP@monoS$(CH_2)_6$SβCD-I is able to load violacein, a natural product that has shown antitumoral, antibacterial, antiulcerogenic, antileishmanial, and antiviral activities. Cell viability measurements indicated that violecein-loaded AuNP@monoS$(CH_2)_6$SβCD kept the cytotoxicity of violacein on myeloid leukemia HL60 cells, reducing the activity on normal V79 cells.

Similarly, the larger AuNP@SβCD-II (Figure 2b) of a dimeter above 30 nm, when loaded with baicalin (BC), a flavone glycoside of natural occurrence, showed an enhanced antiproliferative effect, as confirmed with MCF-7 cells, and could induce apoptosis of such cells (Lee et al., 2016). Likewise, AuNP@monoSβCD-I were prepared (Yang et al., 2010) to use them as nanocarriers of lignans (Bakar et al., 2015). The authors investigated the anti-proliferative properties of pinoresinol, lariciresinol and secoisolariciresinol-loaded AuNP@monoSβCD-I (Figure 2c) on the MCF-7 cell lines. Such lignans, also called phytoestrogens, have strong effects on the treatment of carcinomas. They found that lignin-bound AuNP@monoSβCD-I prevented the proliferation of the MCF-7 cells significantly better than the free lignans.

Alternatively, the multi-cavity platform can be used for carrying a prodrug. A 4.7 nm AuNP@SβCD-I was obtained with a higher CD density on the NPs surface that that theoretically expected (Li et al., 2008) due to the formation of intermolecular disulfide linkages. AuNP@SβCD-I binds an adamantane-appended Pt(IV) prodrug of cisplatin through a guest−host interaction (Figure 2d). Exposure of SK-N-SH neuroblastoma

cells to prodrug-loaded AuNP@SβCD-I resulted in the uptake and clustering of the NPs in the nuclear region of the live cell. Nevertheless, the loaded nanocarrier showed less cytotoxic activity than cisplatin itself (Shi et al., 2013).

AuNP@SβCD-II (Figure 2e, 13 nm of average diameter) were used as nanoplatform for the delivery of DNA with its controlled-release in living cells via simultaneous light and host−guest mediations (Zheng et al., 2014). DNA is loaded on the AuNP@SβCD-II as azobenzene conjugate to control the drug loading/release through UV-light irradiation. The azobenzene moiety is photoresponsive and can be reversibly isomerized from the *trans* form to the *cis* form upon UV-light and visible irradiations, the former forming a stable inclusion complex with β-CD, while the latter does not. A drawback of the use in living cells of UV-light for the external control of the drug release is the large dose of UV-light irradiation needed, which would be sufficient to induce cell apoptotic events or other side effects. To overcome this problem, the authors used the very good β-CD guest ferrocene to assist the irradiation by displacing the azobenzene group out of the CD cavity. The application of this approach reduced the dose of UV-light irradiation, thus, about 62.4% gene silencing was achieved within 30 min, which is significantly higher than that without ferrocene competition.

Taking advantage of the ability of multi-CD systems to form nano-assembled particles, AuNP@SβCD-II (Figure 2f) have been used as platform for the formation of a vesicles able to load Doxorubicine (DOX) (Ha et al., 2013). The supramolecular attachment of PEG and poly(*N*-isopropylacrylamide) (PNIPAM) on the surface of AuNP@SβCD-II through the host–guest binding interaction between adamantane groups (ADA) and CD moieties, led to the formation of NPs that become amphiphilic in water above body temperature, and then self-assemble into vesicles. PNIPAM changes its hydrophobic nature to hydrophilic when the temperature decreases, causing the vesicles disassembly and thus triggering the release of DOX. Such temperature-dependent behavior was showen to be reversible.

A different strategy for the construction of β-CD-containing AuNPs is based on the self-assembly of sulphated β-CD on polyethyleneimine (PEI)-capped AuNPs through electrostatic interactions (AuNP@PEI-βCD) (Qiu et al., 2016). A series of PEI-capped AuNPs were prepared by heating $HAuCl_4$ in the presence of 0.6, 2, 10, 25 and 70 kDa branched PEI at several ratios obtaining NPs ranging from 42 to 96 nm (Figure 2g). Simple addition of water solution of β-CD sulphate sodium salt to a solution of AuNP@PEI afforded AuNP@PEI-βCD. Tanshinone IIA and α-mangostin, that have been found active against several types of cancer cells, were loaded into AuNP@PEI-βCD (1.3% and 4.6% w/w, respectively). *In vitro* tests showed that drug-loaded AuNP@PEI-βCD enhanced their activity against prostate cancer cell lines PC-3 and DU145.

A redox-responsive DOX release system based on mesoporous silica nanoparticles in which AuNP@SβCD acts as gatekeeper has been prepared (Silveira et al., 2015). The system consists in SBA-15 (Santa Barbara Amorphous) and MCM-41 (Mobil Crystalline Materials) having ferrocene moieties on their surfaces, thus the silica NPs are loaded with DOX and then capped with AuNP@SβCD-I (Figure 2h). The assembly of AuNP@SβCD-I on the surface of the silica NPs relies on the high stability of the

complex formed by ferrocene moieties with the CD units from AuNPs. Oxidation of the ferrocene group to ferrocenium group triggers the disassembly of AuNP@SβCD-I, and thereby drug release. Average size of AuNP@SβCD-I is of 3.8 nm, slightly larger than the pore size of the silica NPs. Control release studies showed that AuNP@SβCD-I locks efficiently the silica NP pores and DOX release was highly dependent on the concentration of O_2 and pH. Reduction of cell viability in B16F10 cells treated with DOX-loaded ferrocene-containing SBA-15 and MCM-41 capped with AuNP@SβCD-I was observed. Confocal images showed the fluorescence of DOX inside the cells indicating internalization of the DOX-loaded nanovehicle and subsequent DOX release.

NPs combining various functionalities on their surface can be prepared by attaching further ligands in addition to CD or by attaching those functional moieties in a supramolecular manner by CD inclusion complexation.

As an example of the first case, a AuNP-based nanocarrier having a carbohydrate as targeting ligand for site-specific delivery has been developed (Figure 3a) (Aykaç et al., 2014). The synthesis of the nanocarrier (AuNP@2monoβCD-Lac-II) was achieved by the ligand exchange strategy on citrate-stabilized AuNP with a 1:1 mixture of bisalkyltetra(ethylene glycol) disulfides appended with β-D-lactose and β-CD moieties. β-CD was linked to the spacer through one of the C-2 hydroxyl groups (secondary face). β-D-Lactose was chosen because its specific interaction with galectin 3 (Gal 3), a lectin that is over-expressed in some tumor cells. Dynamic light scattering (DLS) showed a hydrodynamic diameter of 20.6 nm. AuNP@2βCD-Lac-II demonstrated both specific interaction with Gal-3 and ability to load anticancer chemotherapeutics methotrexate.

A different approach for the site-specific delivery of anticancer drug DOX is based on a modular system constituted by a CD-modified AuNP (AuNP@6monoβCD-I) that serves as scaffold for the coupling of a cancer-targeted peptide and DOX prodrug via host-guest interactions (Figure 3b) (Chen et al., 2015). The synthesis of AuNP@6monoβCD-I was performed by using the disulfide bond-containing lipoamide derivative of mono-6-ethylenedimane-β-CD through reduction of $HAuCl_4 \cdot H_2O$ with $NaBH_4$ in DMSO (Wang et al., 2007). The resulting AuNP displays multiple β-CD units linked to the NP surface through a flexible spacer linked to C-6 of one of the glucopyranosyl units. The peptide conjugate adamantane-PEG_8-GRGDS and the pH-sensitive hydrazone-linked adamantane-DOX conjugate were coupled on the CD-AuNP surface via host-guest interaction affording a flexible supramolecular multifunctional NP with the capability to selectively eliminate cancer cells. The *in vitro* studies indicated that the NP was preferentially uptaken by cancer cells via receptor-mediated endocytosis. DOX was released rapidly upon the intracellular trigger of the acid microenvirenment of endo/lysosomes, bringing about apoptosis.

β-Lapachone (LAP) is an anticancer drug that exhibits potent cytotoxicity against various cancer cell lines. It sinergically reacts with several other anticancer drugs (e. g. taxol) but particularly with ionizing radiation (IR) as shown in *in vivo* models. However, the use of LAP is hampered by several drawbacks, such as low water solubility and non-specific distribution that leads to systemic toxicity. To overcome such limitations, two of multifunctionalized AuNPs able to carry LAP were prepared to evaluate the properties of the nanodevice for active-targeting tumor cells and enhanced

in vivo radiotherapeutic efficiency (Jeong et al., 2009). AuNPs containing on the surface β-CD and PEG (AuNP@SβCD-PEG-II) were synthesized by treating citrate-stabilized AuNPs with per-6-deoxy-6-mercapto-β-CD and PEG-SH (2000 MW) (Figure 3c). An additional functionality, anti-epidermal growth factor receptor antibody (anti-EGFR) was also incorporated to the NPs to endow the nanodevice tumor-targeting properties. Average diameters obtained by Dynamic Light Scattering (DLS) measurements were 40.4 and 46.7 nm for AuNP@SβCD-PEG-II and AuNP@SβCD-PEG-antiEGFR-II, respectively. *In vivo* experiments showed that the effect of LAP-loaded AuNP@SβCD-PEG-antiEGFR-II on the radiation-induced tumor growth delay appeared to be greater than that of LAP-loaded AuNP@SβCD-PEG-II.

AuNPs containing on the surface β-CD and PEG (AuNP@βCD-PEG-II) (Figure 3d), rhodamine B linked β-CD and PEG (AuNP@RhoβCD-PEG-II), β-CD, PEG and biotin (AuNP@βCD-PEG-Biotin-II), and rhodamine B linked β-CD, PEG and biotin (AuNP@RhoβCD-PEG-Biotin-II) were synthesized by treating citrate-stabilized AuNPs with a 1.2:1 and 12:10:1 mixture of per-6-deoxy-6-mercapto-β-CD/mono-Rhodamine B-linked per-6-deoxy-6-mercapto-β-CD and methoxy poly(ethyleneglycol)thiol (for AuNP@βCD-PEG-II and AuNP@RhoβCD-PEG-II) and a thiolated Biotin derivative (for AuNP@βCD-PEG-Biotin-II and AuNP@RhoβCD-PEG-Biotin-II) (Heo et al., 2012). The resulting AuNPs range in size from 20 to 41 nm and combine on their surface the presence, via Au-S bond, of drug pockets, PEG chains for promoting the formation of a solvated antifouling shell and rhodamine B for microscopy analysis. In addition, Biotin was used as a cancer-specific targeting ligand. The delivery system was completed with the loading of the water-low soluble effective chemotherapeutic paclitaxel (PCX). Such a drug effectively releases from PCX-loaded AuNP@βCD-PEG-II in the presence of Glutathione (GSH) at an intracellular concentration. The study showed the potential of AuNP@RhoβCD-PEG-Biotin-II as theranostic agent. The NP showed a higher affinity to cancer cells such as HeLa, A549, and MG63 as compared to NIH3T3 cells. In addition, when loaded with PCX displayed significant anti-cancer effects against HeLa cancer cells with almost no cytotoxicity against normal NIH3T3 cells.

The authors also used AuNP@βCD-PEG-II (Figure 3d) to load curcumin (CUR) for the development of a therapeutic agent for preventing and treating osteoporosis (Heo et al., 2014). Previous research had shown the osteoclastogenesis inhibitory effect of AuNPs under *in vitro* conditions. CUR is also known for its inhibitory effects on osteoclastogenesis and preventing osteoporosis, however its low aqueous solubility and rapid degradation at physiological pH are drawbacks for clinical applications. Intracellular uptake analysis showed that CUR loaded AuNP@βCD-PEG-II can effectively be uptaken into the cell and locate into the intracellular compartment. The complex inhibited the osteoclast differentiation of marrow-derived macrophages through suppression of the receptor activator of nuclear factor κb ligand-induced signaling pathway without inducing cytotoxicity. *In vivo* results of an ovariectomy induced osteoporosis model showed that the complex significantly improved bone density and prevented bone loss.

The *in situ* synthesis of β-CD-coated AuNPs from a methacrylate copolymer containing mono-6-amino-β-CD, PEG and catechol, and $HAuCl_4$ in water gave NPs (AuNP@POL-βCD) with a size of around 90 nm (Marcelo et al., 2015). The resulting AuNP@POL-βCD consisted in AuNPs covered by a polymer shell that displays PEG and CD units what enable it to load drugs through CD inclusion complexation (Figure 3e). Such loading ability was investigated with DOX that forms very stable complexes with AuNP@POL-βCD, resulting in a drug loading of 0.01 mg per mg of NP. The DOX complexation led to fluorescence quenching allowing the analysis of the recovery of DOX fluorescence after its delivery and obtaining DOX release kinetics data. This behavior allows for the tracking in real time of the DOX cellular release. DOX is transported to the cytoplasm of HeLa cells and its release from AuNP@POL-βCD was detected by a strong increment in its fluorescence intensity.

The intracellular aggregation of AuNPs in cancer cells can prolong their retention in cells and induce apoptosis. In addition, the aggregation can transform NPs from being biocompatible into cytotoxic under NIR irradiation. Incubation of carcinoma cells (HepG2) with the oxidized form of PEG capped with two ferrocene units (Fc^+-PEG-Fc^+) and AuNP@SβCD-II showed that they are internalized into the cancer cells (Wang et al., 2016). Intracellular GSH triggers NPs aggregation by reducing the ferrocenium moiety to ferrocene thereby enabling host-guest self-assembly of AuNP@SβCD-II due to the inclusion complexation of the ferrocene moiety into the CD cavity (Figure 3f). The apoptosis of cancer cells was significantly enhanced up to 36.4%.

Another approach to develop a theranostic agent used AuNPs decorated with mono-6-thio-β-CD (AuNP@monoSβCD-II) having galactoside supramolecularly attached as targeting moiety (Hu et al., 2016). Treatment of citrate-stabilized AuNPs with mono-6-deoxy-6-mercapto-β-CD gave AuNP@monoSβCD-II of 13.8 nm of diameter (N. Zhang et al., 2008). The supramolecular assembly of fluorophore-labeled conjugates containing terminal galactoysl and adamantane moieties of several lengths on AuNP@monoSβCD-II gave galactose-coated AuNPs with quenched fluorescence (Figure 3g). Fluorescence recovery was observed upon specific interaction of the nanocomposite with galactose protein receptor peanut agglutinin (PNA), probably as a result of a metal-enhanced fluorescence (MEF) mechanism. An evaluation of the nanocomposite for receptor-targeted cell imaging was performed using a hepatome cell line (Hep-G2) that express galactose receptor asialoglycoprotein (ASGPr). Interestingly, treatment of galactose-containing AuNP@monoSβCD-II with Hep-G2 and control cells led to a fluorescence enhancement in the former. The loading of anticancer drug hydroxycamptothecin into the nanocomposite resulted in enhanced toxicity for Hep-G2. In addition, irradiation of the cells at 600 nm further suppressed the cell viability of Hep-G2, but not the control cells. This is due to that the expected specific aggregation of the nanocomposite in cells enhances the production of reactive oxygen species (ROS).

3. Silver nanoparticles and silver-gold bimetallic nanoparticles

3.1 Synthetic strategies

As for the case of AuNPs, reduction of Ag^+ is the most common chemical method for the preparation of AgNPs (Pacioni et al., 2015; Polte et al., 2012). Reduction of Ag^+ with $NaBH_4$ tipically provides AgNPs with average size of 2-6 nm. Turkevich's method for the synthesis of AuNPs has been also extended to silver (Lee and Meisel, 1982; Pillai and Kamat, 2004) obtaining citrate-stabilized AgNPs of larger size.

Similarly to what it has been mentioned above for AuNPs, AgNPs stabilized with unmodified β-CD (AgNP@βCD) can be obtained when $AgNO_3$ is reduced with $NaBH_4$ (Jaiswal et al., 2010) or sodium citrate (Sathiya Priya et al., 2013) in the presence of CDs. A more exhaustive study on the preparation of CD-coated AgNPs using citric acid (CA) as reducing agent was performed with native α-, β-, and γ-CD (Suárez-Cerda et al., 2014). TEM analysis showed that the average size of nanoparticles AgNP@αCD-II, AgNP@βCD-II, and AgNP@γCD-II is 1.5 nm, 1.0 and 3 nm, respectively. AgNP@γCD-II and AgNP@αCD-II present a narrower and wider nanoparticle size distribution, respectively. Unmodified β-CD in alkaline aqueous solution can be used as reducing agent to obtain AgNP@βCD (He et al., 2004; Pande et al., 2007; Premkumar and Geckeler, 2014). The particle size (2 to 13 nm) decreased with increasing concentration of β-CD. Also, the size and the shape was dependent on the NaOH concentration (Premkumar and Geckeler, 2014). Moreover, microwave irradiation afforded AgNP@βCD of smaller size (1.2-4.4 nm) and more narrowly distributed.

The NPs stabilizing effect of α-CD, β-CD, partly hydroxypropylated β-CD (HP-β-CD) and γ-CD was further investigated to obtain gold-silver and silver-gold bimetallic NPs (Bhoi et al., 2016; Pande et al., 2007). AuNP@CD and AgNP@CD, obtained from an aqueous solution of $HAuCl_4$ and $AgNO_3$, respectively, in the presence of CD and NaOH, can be subsequently treated with $AgNO_3$ and $HAuCl_4$, respectively, to give Au/Ag@CD (where Au_{core}-Ag_{shell}) and Ag/Au@CD (where Ag_{core}-Au_{shell}). The mild reduction conditions provided by CD along with their protective and stabilizing effects seem to prevent the galvanic reaction in the formation of Ag_{core}–Au_{shell} bimetallic NPs. TEM micrographs showed the symmetric and spherical shape of the NPs as well as the very narrow size distribution of all the samples. The particles size was around 15 nm. An interesting property of these NPs is their high antioxidant activity that is retained for a longer time, which could be useful for the detection and quenching of reactive organic species (ROS).

Finally, the analogue of AuNP@SβCD for silver, where CD is attached to the NP surface through S-Ag bonds (Figure 4a), is prepared by simply mixing per-6-deoxy-6-mercapto-β-CD with citrate-stabilized AgNPs in water giving AgNP@SβCD with an average size of ~10 nm (Chen et al., 2010).

3.2 Biomedical applications as antibacterial agents

The development of AgNPs-based drug delivery systems have received special attention because the inherent antimicrobial properties of silver (Griffith et al., 2015). In addition to a broad-spectrum of antimicrobial activity, they are relatively thermally stable and show low toxicity to human cells. Recently, the growing concern in finding alternative antibacterial agents against antibiotic-resistant bacteria has reinforced such interest. The mechanism for the antimicrobial activity is probably due to the rapid release of Ag^+ ions but is not fully understood. It seems to involve, in an interconnected manner, catalytic

generation of reactive oxygen species (ROS), the interaction with thiol residues of respiratory enzymes of bacterial cells, and the interaction with DNA, preventing DNA replication. Covering the surface in cyclodextrin derivatives has arisen as a very convenient strategy to confer water solublity and biocompatibility to AgNPs. Interestingly, AgNP@βCD synthesized by using $NaBH_4$ as reducing agent (AgNP@βCD-I) (4-7 nm size) (Jaiswal et al., 2010) and citrate (AgNP@βCD-II) (Sathiya Priya et al., 2013) demonstrated significantly enhanced antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, as compared with the uncapped AgNPs. A similar response was observed against *Escherichia coli* by AgNPs of size smaller than 2 nm coated with carboxymethylated β-CD (AgNP@CMβCD) (Wang et al., 2013). In this research, CM-β-CD was used not only as stabilizing reagent but also as the reducing reagent during the formation process of Ag nanoclusters, as the metal particles are normally referred when their size is smaller than 2 nm. The authors used nanoclusters because they are much more fluorescent than larger AgNPs.

The enhanced antibacterial activity of β-CD-capped AgNPs may be attributed to the combined effect of a high surface-to-volume ratio that leads to a higher level of interaction with the bacterial cell surface increasing the Ag^+ ion absorption inside the bacterial cell (Jaiswal et al., 2010; Sathiya Priya et al., 2013).

AgNP@βCD-I (4-7 nm) also showed an improved efficacy against biofilm formation of *Straphylococcus epidermis* (Jaiswal et al., 2015), but also reduced cytotoxicity when compared with uncapped AgNPs. AgNP@βCD-I decreased ROS generation and caused no change in mitochondrial membrane potential in the human kerationocyte cells (HaCat).

A supramolecular capping of AgNPs (George et al., 2011, 2010) has been developed consisting in reduction of $AgOCOCH_3$ in the presence of dodecylamine, that also functions as reducing agent (Hiramatsu and Osterloh, 2004). In a second step, dodecylamine-coated AgNPs (approx. 12 nm average size) are transferred from an organic to an aqueous phase that contains βCD. The resulting β-CD-capped AgNP@$DocNH_2$ was tested *in vitro* for the antibacterial activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Serratia marcescens*, *Escherichia coli* and *Klebsiella pneumonia*, and for the antifungal activity against *Aspergillus fumigatus*, *Mucor ramosissimus* and *Chrysosporium species*. Both tests showed that β-CD-capped AgNP@$DocNH_2$ exhibits an efficient antibacterial activity, being a powerful antifungal agent.

3.3 Biomedical applications as drug delivery systems

A synergistic effect with an enhanced antibacterial activity has been reported when a combined treatment of AgNP and antibiotic was employed (Griffith et al., 2015). However, there are very few cases reported in which the drug inclusion complexation properties of CD are used when coating AgNPs. The synthesis of Bovine Serum Albumin (BSA)-coated AgNPs bearing β-CD available for encapsulation of clotrimazole (CTL) has been reported (Gaurav et al., 2015). CTL is an imidazole derivative with a broad spectrum of antimycotic activity. AgNPs were synthesized by the $NaBH_4$ reduction method with an average size of 37.5 nm, and then incubated with

BSA leading to BSA-surface coating of AgNPs of an average size of 54.2 nm and Zeta potential value of -18.06 mV, indicative of the relative colloidal stability. Then, the β-CD·CTL complex is conjugated with AgNP@BSA through reaction with BSA amino residues using EDC as coupling agent. The resulting CTL-loaded AgNP@BSA-βCD (Figure 4b) showed an increased hydrodynamic size of 68 nm. The cell cytotoxicity of CTL-loaded AgNP@BSA-βCD was lower than that of both AgNP and AgNP@BSA-βCD. The evaluation of the antifungal activity against normal and CTL resistant *Candida* cells showed an improved and possible additive effect with not much differentiated inhibition in both CTL resistant and normal fungal cells.

AgNP@γCD (20-30 nm) has been prepared to load antibiotic chloramphenicol (CPM) (Gannimani et al., 2016). Docking and molecular dynamics studies carried out with inclusion complexes of CPM with α-, β-, and γ-CD suggested that the last CD would be the best host for the drug. Further NMR analysis confirmed the theoretical studies on the stability of the γ-CD·CPM complex. CMP-loaded AgNP@γCD (Figure 4c) was characterized by DLS and Raman spectroscopy and exhibited a synergistic antibacterial effect against *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*. Such enhancement was attributed to two mechanisms of action of CMP, causing the cease the growth of bacteria by affecting the protein synthesis, and of the silver ions exerting their bactericidal properties.

4. Quantum Dots

4.1. Synthetic strategies

Quantum dots (QDs) are colloidal semiconductor nanocrystals of nanometric size that present unique optical and electronic properties such as intense fluorescence with a narrow emission spectrum. The composition of most QDs is based on the combination of a transition metal from groups XI or XII (mostly Cd, but also Cu, Ag or Zn) with a chalcogen, a non-metallic element from group XVI (S, Se, Te). On occasions, basic metals (Ga, In, Pb), metalloids (Si, Ge, As) and other non-metallic elements (P) can also be used (Chen et al., 2013). Size, composition, shape, and surface state are key factors that accurately modify physical features of these nanocrystals (Alivisatos, 1996; El-Sayed, 2004), and thus precise and reproducible synthetic methods have been developed for each type of QDs (Reiss et al., 2016). Currently, interest is moving rapidly to more Earth-abundant and less toxic chemical compositions.

Many desired applications for QDs are biological and biomedical, and thus require these nanocrystals to be highly water-soluble and biocompatible. However, most extended synthetic methods employ hydrophobic surfactants such as 1-octadecene (ODE), octadecylamine (ODA), tri-*n*-octylphophine (TOP), or tri-*n*-octylphosphine oxide (TOPO) that cover the nanocrystals limiting their growth in a controlled fashion and protecting them against oxidation, but also making resulting QDs water-insoluble. A number of strategies have been developed to modify their surfaces with polar compounds that not only make the nanocrystals water-soluble while ensuring stability in aqueous solutions, but also in some cases provide reactive functional groups for subsequent functionalization with biorecognizable molecules, drugs or molecular carrier moieties such as CDs. These strategies include covalent bond formation, passive adsorption, electrostatic forces and multivalent chelation (Gao et al., 2005), and can be

categorized into two main approaches: (i) use of amphiphilic molecules interacting with the hydrophobic surfactants that cover QDs, and (ii) replacement of these surfactants by polar coating molecules (the ligand exchange strategy) (Bilan et al., 2015; Lim et al., 2016). The former procedure usually involves amphiphilc block copolymers based on acrylic acids and grafted with hydrophobic chains that intercalate between surfactants molecules, but other small amphiphilic molecules such as calixarenes, phospholipids or amphiphilic carbohydrates have also been used. However, the most straightforward ligand exchange strategy is to add molecules or conjugates containing thiol groups (for example, using mercaptoacetic acid, mercaptopropionic acid, mercaptosuccinic acid, dithiothreitol, GSH, dithiothreitol, or cysteine) that form covalent linkages with the QD core or the ZnS shell. Compounds other than thiols such as amines, carboxylates and phosphonates have also been used in this regard, as not only exchange agents after QDs synthesis in organic solvents but also stabilizing agents for direct QDs synthesis in aqueous solutions (Lesnyak et al., 2013). In general, ligand-exchange procedures lead to much smaller (i. e., more biodistributable) QDs, and thus are the strategies of choice when biofunctional and/or biorelevant molecules are intended to decorate the surface of the nanocrystals.

CD-capped QDs are suitable candidates to design nanosystems that combine the outstanding optical properties of the QDs with CDs biocompatibility, water solubility and ability to form inclusion complexes with drugs or analytes. Coating has been achieved through a large variety of conditions. For example, preparation of CdSeQDs containing β-CD (CdSeQD@SβCD) with an average particle size of 4 nm in diameter (according to TEM measurements) has been carried out by refluxing a DMF solution containing cadmium acetate, thiourea and per-6-deoxy-6-mercapto-β-CD (Figure 5a) (Palaniappan et al., 2004). The one-pot approach has been also developed for the preparation of CdSeQD@mono-SβCD and CdSe/CdSQD@mono-SβCD in aqueous solutions using mono-6-deoxy-6-mercapto-β-CD as capping agent (Figure 5b) (Palaniappan et al., 2006). However, attempts to obtain CdSeQD@SβCD by treating $CdCl_2 \cdot H_2O$ with per-6-deoxy-6-mercapto-β-CD in water failed, as well as the attempt to apply ligand-exchanged method with mercaptoacetic acid (MAA)-capped QDs (Adeli et al., 2011). Nevertheless, CdSeQD@MAA-SβCD is obtained by treatment of an aqueous solution of $CdCl_2 \cdot H_2O$ with MAA and per-6-deoxy-6-mercapto-β-CD giving 7.5 nm size NPs (Figure 5c), according to DLS experiments.

CdSe/ZnSe core-shell nanocrystals of 4-5 nm-size coated with CD (CdSe/ZnSeQD@AACD) have been synthesized by a ligand-exchanged method using TOPO-coated CdSe/ZnSeQD with conjugates of amino acids with β-CD (Figure 5d). In this case, the amino acid is attached at one of β-CD C-6 through an amino acid N-C covalent bond. Thus, the β-CD-amino acid carboxyl groups are the anchoring groups that replace the TOPO ligand coated on the NPs surface (Zhao et al., 2011).

(3-Aminophenyl)boronic acid (APBA) was coupled through amide bond formation to QDs having their surfaces modified with mercaptopropionic acid (MPA) and GSH, respectively (CdTeQD@MPA and CdSe/ZnSQD@SG, respectively). Subsequent treatment with βCD gave CdTeQD@MPA-APBA-βCD and CdSe/ZnSQD@SG-APBA-βCD, respectively, in which β-CD is linked to the NPs surface through B-O bonds (Figure 5e) (Ai et al., 2012; Freeman et al., 2009).

Another explored approach involves the electrostatic assembly of a star-shaped cationic oligoethylenimine (OEI) polymer based on a β-CD core on the MAA-coated CdSe/CdSQD@MAA with a size of 4.6 nm (Wu et al., 2013). The resulting CdSe/CdSQD@MAA-OEIβCD showed a positive zeta potential, which was different to that shown by the negatively charged CdSe/CdSQD@MAA (Figure 5f).

QDs are also coated with CDs in a supramolecular manner. A typical way is to decorate the QD with ligands that form inclusion complexes with CDs. For example, a ultrasound-mediated self-assembly of α-, β-, and γ-CD on TOPO-capped CdSe/ZnS QDs led to CDs-coated QDs due to the formation of CD·TOPO compexes (Li and Han, 2008). TOPO-CD complexation also mediated the self-assembly of mannose and galactose clusters based on a β-CD core on the surface of CdSe/ZnS QDs (Figure 6a) (Bavireddi and Kikkeri, 2012). CdS QDs having diazobenzene (AZ) on the surface interact with β-CD to afford a β-CD-coated QDs (Figure 6b). The β-CD encapsulation of multiple hydrophobic ligands on the CdS QDs periphery, such as diazobenzene moieties, not only improves the water solubility, but also reduces the toxicity as suggested by *in vivo* experiments. Moreover, the diazobenzene-coated CdS QDs can be released from β-CD under UV irradiation (Li et al., 2010). Similarly, CdSe/ZnS QDs decorated with ketoprofen (KP) is efficiently capped with β-CD functionalized with pyrene (Pyr) at the secondary face due to the inclusion of the KP-containing linker into the CD cavity (Figure 6c) (Aguilera-Sigalat et al., 2012).

4.2 CD-capped QDs as nanocarriers

Many QDs modified with CD derivatives are used as biosensors that take advantage of the ciclooligosaccharide ability to encapsulate different analytes in close vicinity of the nanocrystal core. These imaging and diagnostic applications are out of the scope of this review, although some examples can be found in Table 2. Nevetherless, there are some cases that report the use of CD-capped QDs as nanocarriers for drugs and genes (Table 3). For instance, CdSeQD@MAA-SβCD (Figure 5c) forms water-soluble complexes with PCX and folic acid (FA), the latter most likely through electrostatic interactions with carboxylate groups (Adeli et al., 2011). PCX-loaded CdSeQD@MAA-SβCD *in vitro* studies on tumor cell lines c26 proved to increase PCX internalization into the cells, increasing the anticancer effect. However, FA/PCX-loaded CdSeQD@MAA-SβCD showed a lower anticancer effect, due to the lower number of PCX molecules.

CdSe/ZnSeQD@AACD was designed as siRNA delivery nanosystem (Figure 5d) that is able to track such delivery by taking advantages of its optical properties (Zhao et al., 2011). *In vitro* experiments of cytotoxicity and internalization in normal and cancer cells showed that the presence of βCD on these NPs improved their biocompatibility and reduced the cytotoxicity. CdSe/ZnSeQD@AACD accumulated in vesicles in the cytoplasm of the cells as shown by TEM images and provided a bright and stable fluorescent signal for intracellular siRNA imaging in live cells. Moreover, CdSe/ZnSeQD@AACD allows for the simultaneous delivery of siRNA and DOX, as an anticancer drug than can form complexes with the CD moieties, and thus to fight multi-drug resistance in cancer (Li et al., 2012). The nanocarrier was designed to target the MDR1 gene to reverse the multidrug resistance of HeLa cells. Experiments carried out with DOX-resistant cell line (HeLa/Dox) showed that siRNA/DOX-loaded

CdSe/ZnSeQD@AACD was able to penetrate cell membranes through endocytosis, and provide endosomal release of the siRNA and DOX, leading to reduced levels of MDR1 gene expression, enhanced intracellular DOX accumulation and an increased potency of DOX to induce apoptosis in HeLa/Dox cells.

CdTe/ZnSQD@MPA-APBA (Figure 5e) was used to build a co-delivery system able to effectively enhance osteogenic differentiation and enable long-term tracking of human mesenchymal stem cells (hMSCs), both *in vitro* and *in vivo* (Li et al., 2016; Xu et al., 2016). CdTe/ZnSQD@MPA-APBA was conjugated with mono-6-amino-6-deoxy-β-CD leading to a CD-coated CdTe/ZnSQD@MPA-APBA-βCDNH_2 having free amino groups for further functionalization. Then, RGD peptide was coupled to the periphery of the NP by amidation reaction in order to endow to the NP with targeting properties, but also with a binding site for siRNA. The resulting CdTe/ZnSQD@MPA-APBA-βCD-RGD with an average diameter of 5 nm was able to load siRNA and dexamethasone (DEX) or kartogenin (KGN), an osteogenesis and chondrogenesis promoter of stem cells, respectively

Also, nanocarrier CdSe/CdSQD@MAA-OEIβCD (Figure 5f) has been designed for the co-delivery of DNA and PCX as well as for simultaneous cellular imaging (Wu et al., 2013). In this case, the previously formed inclusion complex between star-shaped β-CD core-based cationic OEI polymer and PTX was used to bind CdSe/CdSQD@MAA. The resulting PCX-loaded CdSe/CdSQD@MAA-OEIβCD was then treated with plasmid DNA (pDNA) affording NPs of diameters ranging from 200 to 400 nm containing both PCX and pDNA. It was observed that co-delivery exerted a synergetic effect acting as anticancer drug and enhancing the gene expression in MDA-MB-231 human breast cancer cells. In addition, it was possible to track the co-delivery in both transfected and untransfected cells using fluorescent laser scanning confocal microscopy.

A different approach involves the functionalization CdSe/ZnSe QDs with an inclusion complex formed by glycyrrhizic acid (GLA) and β-CD (Zhao et al., 2012). In this case, the TOPO ligands in CdSe/ZnSeQD@TOPO are replaced by the GLA·β-CD complex, the carboxylate group from GLA serving as anchoring group. CdSe/ZnSeQD@ GLAβCD (Figure 6d) showed an improved antitumor activity inducing apoptosis in hepatocarcinoma cells.

5. Magnetic particles

5.1 Synthetic strategies

The concept of magnetic drug targeting takes advantage of the properties of the iron oxide magnetic nanoparticles (MNPs) combined with the application of an external magnetic field that enables the delivery of NPs to the desired target site and to fix them at that site while the drug is released. In order to apply MNPs as delivery systems a modification of their surface is required to make them biocompatibles, suitable for the attachment of functional moieties to provide binding sites for bioactive molecules and targeting ligands (Reddy et al., 2012). The main representatives of MNPs are magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3), whose biocompatibility has favoured the proliferation of studies on their biomedical applications. Various reviews from the

literature collect exhaustive information on their biomedical and pharmaceutical applications as well as the method of preparation (Laurent et al., 2008; Reddy et al., 2012). MNPs coated with CDs may carry drugs included in the CD cavity and magnetically guide to a specific biological site.

A large number of physical, chemical and microbial methods for the preparation of Fe_3O_4 and γ-Fe_2O_3 colloids has been reported. Similarly to other metallic NPs, the surface of plain MNPs is too reactive and has to be covered in appropriate coating materials to ensure their physical and chemical stability. Such polymeric and lipid-like species are usually added during or immediately after the MNPs formation, and in some cases they also help to tune the nanoparticles size. Interestingly, CDs and their derivatives can also be used as stabilizers, leading directly to MNPs coated with these cyclooligosaccharides. For instance, water-soluble Fe_3O_4 MNPs stabilized with β-CD have been prepared directly from the co-precipitation of Fe^{2+} and Fe^{3+} ions in the presence of β-CD (MNP@βCD) (Yallapu et al., 2011) or surfactants and β-CD, the NPs size being dependent on β-CD and surfactant concentration (Xia et al., 2007). Also, the treatment of Fe_3O_4 MNPs with 2-hydroxypropyl- (HPβCD), carboxymethyl- (CMβCD), citric acid (CAβCD) and dopamine- (CAβCD) β-CD conjugates leads to the modification of the MNPs surface affording MNP@HPβCD (H. Zhang et al., 2008), MNP@CMβCD (Li et al., 2011) and MNP@CAβCD (Jayaprabha and Joy, 2015), and MNP@DOβCD (Nguyen et al., 2016), respectively. MNP@CMβCD has been treated with epichlorohydrin to promote cross-linking of CD on the particle surface.

The attachment of CDs to NMPs can also be achieved through self-assembly with the the NP stabilizers. For example, oleic acid-stabilized Fe_3O_4 MNPs were supramolecularly coated with α-CD through the formation of an inclusion complex between surface-bound surfactant molecules and α-CD being stable for long periods in water (Wang et al., 2003). If the NP stabilizers bear adequate functional groups, CDs can be attached covalently to the stabilizer moiety. Thus, citrate-linked β-CD was grafted by amidation reaction to gum arabic (GA)-coated Fe_3O_4 MNPs. Such GA-coated NPs were prepared by co-precipitating Fe^{2+} and Fe^{3+} ions, (Figure 7a). The resulting MNP@GA-βCD had an average hydrodynamic diameter of 26.2 nm (Banerjee and Chen, 2007). GA-coated MNPs has been also conjugated with β-CD using hexamethylene diisocyanate as a linker giving rise MNP@GA-βCD-2, with a mean diameter of 17.1 nm (from TEM) and hydrodynamic diameter distribution in the range of 33.3–66.5 nm (Banerjee and Chen, 2008).

Other very convenient capping agents are the bifunctional trialkoxysilane derivatives which can be attached to the MNPs via a silylation reaction with the iron oxide hydroxyl groups, leading to the formation of covalent Fe-O-Si bonds. The MNP surface silylation by this method provides additional orthogonal groups, such as halide, amino, and epoxide, that enable the NP for further functionalization with β-CD as a second layer of coating. For example: 1) coupling of β-CD with 3-chloropropylsilane-coated MNPs giving rise MNP@PTES-βCD (Figure 7b) (Hayashi et al., 2010); 2) reaction of 6-monotosylate-β-CD with (3-aminopropyl)silane-coated MNPs to give MNP@APTES-βCD (Figure 7c) (Cao et al., 2009); and 3) reaction of β-CD with (3-glycidyloxypropyl)silane-coated MNPs leading to MNP@GLY-βCD (Figure 7d) (Lv et al., 2014). The MNPs surface silylation with triethoxysilylpropylsuccinic anhydride

(SAS) rendered MNP@SAS having carboxylic acid groups on the NP periphery that can serve as anchoring groups of CM-β-CD through a PEG spacer (Figure 7e) (Mu et al., 2015). As well, MNP@APTES has been conjugated with β-CD through a succinate (SA)-spacer (Figure 7f) (Anirudhan et al., 2013). The silane-based approach was also used for a three-steps synthesis of CD-coated MNPs (MNP@MPTMS-PA-βCD) (Figure 7g) that involved: 1) MNP surface modification with 3-mercaptopropyltrimethoxysilane; 2) thiol-ene reaction with 5-acrylamidoisophthalic acid; and 3) esterification with β-CD (Tarasi et al., 2016).

Similarly, MNPs can be coated with bifunctional phosphonic acid derivatives that provide a reactive group for further functionalization. This method has been used for the preparation of CD-decorated NPs MNP@APPA-βCD by reaction of 6-monotosylate-β-CD with (3-aminopropyl)phosphonate (APPA)-coated MNPs (Figure 7h) (Tudisco et al., 2012).

Coating MNPs with β-CD-containing polymers provides another way for the attachment of the macrocycle on the surface of the NPs. A convergent approach involves the grafting of a PEI-based polymeric β-CD (PEI-β-CD) through amidation coupling with MNPs decorated with carboxylic groups (Luo et al., 2012), the average diameter for the resulting MNP@PEI-βCD being 160 nm (Figure 8a). In a divergent approach, βCD grafted to a MNP subsequentialy coated with hydroxyapatite and PEI, using hexamethylenediidsocynate as cross-linker agent to give MNP@HAP-PEI-βCD (Figure 8b) (Akrami et al., 2015). Also, CD-decorated MNPs (MNP@PNG-βCD) was accomplished by coupling of 6-(2-aminoethylamino)-6-deoxy-β-CD on a functionalized PNIPAM coated MNP (Figure 8c) (Lv et al., 2015).

Finally, β-CD has also been attached to a mesoporous silica surface as shell of a NP with a Fe_3O_4 core by "clicking" 6-azido-6-deoxy-β-CD with alkyne-decorated hybrid Fe_3O_4/SiO_2 NP of *ca.* 80 nm (Lee et al., 2012) and by amidation coupling of CM-β-CD with amino-containing hybrid Fe_3O_4/SiO_2 NP (Badruddoza et al., 2013) providing Fe_3O_4/SiO_2@TAβCD and Fe_3O_4/SiO_2@CMβCD, respectively (Figures 8d and 8e, respectively). Moreover, β-CD conjugated with GSH has been used as thiol nucleophile for the β-CD coating of Fe_3O_4/SiO_2 NP derivative by nucleophilic ring opening of epoxide present on the NP surface (Figure 8f) (Sahu and Mohapatra, 2013).

5.2 CD-capped NMPs as drug delivery systems

The ability of CD-coated MNPs to function as nanocarriers has been demonstrated in several cases (Table 4). For instance, MNP@HPβCD, with range of size of 10-20 nm, showed a load capacity for DOX of 87.8 μg/mg after incubation for 72 h (H. Zhang et al., 2008). Similarly, MNP@GA-βCD (Figure 7a) and its analogous MNP@GA-HPβCD (in the range of 17.7–56.1 nm), and NMNP@GA-βCD-2 having βCD linked to the NP through a longer spacer, are able to load KP (2.47 mg/g and 1.68 mg/g) and retinoic acid (RA, 4.09 mg/g), respectively, due to the inclusion of the drug into the CD cavity (Banerjee and Chen, 2009, 2008, 2007). The *in vitro* drug release profile has shown for the three cases an initial fast release followed by a slow sustained release phase.

Adequately functionalized MNPs can combine potential applications in hyperthermia therapy, targeted drug delivery and external control drug release (Hayashi et al., 2010). Thus, β-CD macrocycle from MNP@PTES-βCD (Figure 7b) was tosylated to allow the introduction of an azido group. The reaction of the resulting azide-containing NP with alkynylated folic acid (FA) by azide-alkyne cycloaddition yielded MNP@PTES-βCD-FA with a mean size of 8.2 nm and a hydrodynamic diameter of 12.4 nm. FA is a specific ligand to folate receptors (FRs) that are overexpressed in breast cancer tumors. MNP@PTES-βCD-FA is able to load tamoxifen (TMX) and generates heat under high-frequency magnetic field (HFMF). Furthermore, TMX release was accomplished by on-off switching HFMF.

MNP@APTES-βCD (Figure 7c) is able to load KP (L. Huang et al., 2014), DOX and epirubicin (EPI) (Wang et al., 2015). After complexion, *in vitro* experiments showed that KP release from MNP@APTES-βCD was fast at an initial stage followed by a slow and steady release. The loading abilities for DOX and EPI are 70.27 and 39.46 mg/g, respectively. The release of DOX and EPI from MNP@APTES-βCD is pH dependent. Cellular uptake indicates that DOX or EPI can be selectively delivered to target site and released from the internalized carriers causing inhibition of the growth of tumor.

The synthetic approach to obtain MNP@APTES-βCD (Figure 7c) can be applied to synthesize MNP@APTES-βCD-scFV, a multifunctional system containing single-chain antibody (scFv) as well as β-CD (X. Huang et al., 2014). scFV was chosen for specifically targeting to Endoglin, a protein that is over expressed in ovarian tumor vasculature. Docetaxel (TXT)-loaded MNP@APTES-βCD-scFV inhibited Skov3 ovarian cancer cells but not normal HUVECs *in vitro*. MNP@GLY-βCD (Figure 7d), with a mean aggregation diameter of about 186 nm, formed inclusion complexes with anilino-1-naphthalenesulfonic acid ammonium salt (ANS) (Lv et al., 2014), the release of which *in vitro* sowed a similar behavior to that mentioned above for KP with MNP@APTES-βCD.

MNP@PEG-CTX-CMβCD (Figure 7e), composed of a PEG-coated magnetic iron oxide NP conjugated with CD and chlorotoxin (CTX), was designed to carry simultaneously in a non-covalent manner PTX and fluorescein (FL)-adamantane conjugate to target brain tumor glioblastoma multiform (GBM) (Mu et al., 2015). CTX is a specific ligand of metalloproteinase-2 that is overexpressed on the surface of many brain tumors but not on normal brain tissue. PTX-loaded MNP@PEG-CTX-CMβCD showed greatly improved potency against GBM cells, unlike CTX-free MNPs. The enhanced tumor cell killing ability was shown in both PTX-resistant and nonresistant GBM cell lines, the enhanced cell killing being apoptosis-dependent.

MNP@APTES-SA-βCD (Figure 7f) (Anirudhan et al., 2013) was incorporated to a hydrogel prepared by chitosan crosslinking with glutaraldehyde. The resulting material is able to encapsulate indomethacin (IND), a non-steroidal anti-inflammatory drug. The encapsulation efficacy was found to increase with the increased amount of IND loading. The same strategy was employed on MNP@CMβCD (Ding et al., 2015), although in this case 5-fluorouracil (5-FU) was loaded before promoting crosslinking of the complex with chitosan. The loading efficiency of this nanosystem was found to be 44.7

%. Both hydrogels showed a drug release behavior that is pH, swelling and diffusion dependent.

MNP@PEI-βCD (Figure 8a) is able to function as a redox-responsive controlled camptothecin (CAMP) release system, as well as respond to external magnetic fields. The system showed high endocytosis efficiency and could deliver CAMP-loaded MNP@PEI-βCD within cells in situ to induce cell apoptosis (Luo et al., 2012). The biocompatible and haemocompatible MNP@PEI-βCD and MNP@HAP-PEI-βCD (Figure 8b) (Akrami et al., 2015) allowed encapsulation of CUR into the CD as well as into the polymeric coating. The drug release profile was shown to be pH sensitive. CUR-loaded MNP@PEI-βCD and MNP@HAP-PEI-βCD inhibited MCF-7 breast cancer cells more efficiently than free CUR as a result of enhanced uptake in breast cancer cells.

Based on the well-known thermosensitive response of PNIPAM that undergo dramatic swelling/shrinking change, PNIPAM-based MNP@PNG-βCD (Figure 8c) allows for temperature-switched controlled release of the drug (Lv et al., 2015). At temperature above the lower critical solution temperature (LCST) of PNIPAM, ANS-loaded MNP@PNG-βCD releases ANS rapidly, but very slowly at temperature below the LCST.

The synthesis of a multifunctional derivative of Fe_3O_4/SiO_2@CMβCD (Figure 8e) was carried out with the objective of constructing a nanosystem that meets several functions such as magnetism, fluorescence, cell-targeting, and drug delivery (Badruddoza et al., 2013). In this case, the silica shell is incorporated to the system to reduce toxicity. The nanosystem was prepared following a multi-step synthesis that involved incorporation of fluoresceyl thiourea, to provide fluorescent properties, then attachment of FA, as targeting ligand, and finally conjugation of CM-β-CD, as drug reservoir. The system is able to load RA and showed preferential internalization into the target MCF-7 and HeLa tumor cells. Alternatively, luminescent properties can be endowed to MNPs by deposition of luminescent YPO_4:Tb onto a mesoporous silica surface as shown for Fe_3O_4/SiO_2@SG- βCD-FA (Figure 8f) (Sahu and Mohapatra, 2013). The silica coating improves the water solubility of the system and reduces the probability of fluorescence quenching. In this case, after the lumniscent component is included on the silica matrix, the MNP surface is functionalized with epoxide. The presence of epoxide groups allows for the attachment of, first, βCD as βCD-GSH conjugate, and, then FA as FA-PEG-NH_2, by epoxide-opening reaction. Fluorescent Fe_3O_4/SiO_2@SG-βCD-FA forms stable complexes in aqueous medium with 5-FU of an overall size of 71 nm. The 5-FU-loaded Fe_3O_4/SiO_2@SG-βCD-FA showed a faster drug release at lower pH due to the instability of the 5-FU–CD inclusion complex.

When silica shells are constructed on MNPs, cargo is usually located within its pores rather than CD cavities. The cyclooligosaccharide can be then used as gatekeeper to block the guests in the shell and avoid release. This is the case of the biocompatible nanosystem Fe_3O_4/SiO_2@CBA-βCD (Figure 8g). The amino-decorated Fe_3O_4 core-SiO_2 shell NPs was functionalized with 4-carboxyphenylboronic acid (CBA) by amidation reaction. The resulting Fe_3O_4/SiO_2@CBA can form borate esters on its surface upon reacting with β-CD affording Fe_3O_4/SiO_2@CBA-βCD, where CDs serve as gatekeepers

of the silica pores. CD-gatekeeping function in Fe_3O_4/SiO_2 NPs can be controlled by D-frutose or pH. Thus, β-CD moieties from Fe_3O_4/SiO_2@CBA-βCD are removable by both using D-fructose, which bind more strongly to the boronic acid unit than the β-CD moieties, and pH variation. Thus, Fe_3O_4/SiO2@CBA-βCD exhibited an increased drug loading capacity and sustained release (Qiu et al., 2015).

Apart from SiO_2, NMPs can also be covered with a Au shell to obtain the advantages of the combined properties of Fe_3O_4 and Au NPs. Thus, Fe_3O_4/Au@HPβCD (Figure 8h) (average hydrodynamic diameter of 80 nm) were synthesized from $HAuCl_4$ using sodium citrate as a reducing agent in the presence of Fe_3O_4 NPs, leading to Fe_3O_4/Au core-shell NPs with free-carboxylic groups on the surface. Then, HPβCD was coupled via carbodiimide activation through amidation reaction (Lian et al., 2016). CUR loading capacity of Fe_3O_4/Au@HPβCD was 660 μg/5 mg. CUR release is controllable by pH.

The chemical conjugation of β-CD onto the surface of a polymeric-coated MNPs gave rise to a biocompatible nanosystem MNP@PTPM-PEI-βCD (Figure 8i) able to self-assemble with polymeric PTX (Jeon et al., 2016). Such nanosystem was prepared by successive coating with: first, a cross-linked polymer containing trimethoxysilyl, PEG and succinimide moieties; second, low molecular weight PEI; and third, attachment of βCD by reaction of 6-tosyl-6-deoxy- βCD with PEI amino groups. The multivalent binding interaction of polyPTX with MNP@PTPM-PEI-βCD afforded NPs of 221 nm according to DLS, much larger size that that found for MNP@PTPM-PEI-βCD (31.82 nm). polyPTX·MNP@PTPM-PEI-βCD showed enhanced anticancer effects *in vivo* due to the magnetically induced targeting effects.

A PEG-coated magnetic nanocomposite is obtained when 5-FU-loaded MNP@βCD is treated with a PEG solution in water. The resulting PEG-coated 5-FU-loaded MNP@βCD nanocomposite (177 nm) in an aqueous solution of PEI led to the formation of PEI-PEG-coated 5-FU-loaded MNP@βCD (MNP@βCD-PEG-PEI) nanocomposite of an average particle size of 230 nm (Prabha and Raj, 2016). The drug encapsulation efficiency (EE) and drug loading capacity (LC) for 50% of 5-FU concentration of 5-FU-loaded-MNP@βCD, PEG-coated 5-FU-loaded MNP@βCD and PEI-PEG-coated 5-FU-loaded MNP@βCD nanocomposite systems were found to be 64%, 72% and 89% (for EE) and 45.2%, 49.7% and 57.9% (for LC), respectively. In addition, 5-FU was released faster in pH 6.8 than in the acidic mediums (pH 1.2). The MTT assay, shows that while unloaded PEI-PEG-coated-MNP@βCD nanocomposites were found to be nontoxic to mouse fibroblast L929 cells and MCF-7 cells, PEI-PEG-coated 5-FU-loaded MNP@βCD nanocomposite were toxic to MCF-7 cell line.

5.3 CD-capped NMPs as contrast agents for magnetic resonance imagen (MRI)

In addition to their abilities as drug delivery systems, CD-coated NMPs has also been explored as contrast enhancement agents in magnetic resonance imaging (MRI) due to the effect of the superparamagnetic magnetite cores on T_1 and/or T_2 relaxation times (Table 4). This feature may allow increasing the detection limits of the technique to gain insight within the body tissues. For example, based on the calculation at 400 MHz of the relaxivity ratio for MNP@CAβCD (Jayaprabha and Joy, 2015) it was concluded that this nanosystem can be also used as a negative contrast agent for MRI. Additionally, MNP@CAβCD forms inclusion complexes with CUR with a loading efficiency larger

than that on native β-CD. The *in vitro* release profile was similar to that mentioned above with an initial stage of rapid release, followed by release at a constant rate.

Similarly, MNP@βCD and MNP@βCD coated with pluronic polymer were synthesized to explore their application for MRI (Yallapu et al., 2012, 2011). They also exhibited superior hyperthermia effects, enhanced cellular uptake, good loading ability for CUR with improved anti-cancer efficacy. MNP@βCD coated with pluronic polymer load 5-fluorouracil (5-FU) and progesterone (up to 10% drug loading) with a drug release mechanism controlled by diffusion (Ragab et al., 2012).

MNP@DOβCD is converted in a targeted nanocarrier through supramolecular assembly of c(RGDfC)-PEG-adamantane conjugate and PCX, where c(RGDfC) is a peptide highly specific to metastatic tumor cells (Nguyen et al., 2016). The nanocarrier showed an increased T2 relaxivity, improved cellular uptake and efficient PCX loading as well as sustained release at the desired time point.

Finally, The multimodal hybrid Fe_3O_4/SiO_2@TAβCD (Figure 8d) (Lee et al., 2012) has been proven to be a convenient nanodevice for anticancer drug delivery and MRI. The carrier can incorporate DOX into the silica pores and release the drug from the internalized carrier due to a GSH-mediated cleavage of the CD gatekeeper in A549 cells. As a result, apoptotic and clonogenic death occurred. The accumulation of DOX-loaded Fe_3O_4/SiO_2@TAβCD in tumor cells could be monitored by *in vivo* MRI. Thus, MRI showed the inhibition of the tumor growth by DOX-loaded Fe_3O_4/SiO_2@TAβCD.

Conclusions:

Gold, silver, quantum dots and magnetic nanoparticles provide suitable platforms for the assembly of cyclodextrins on their surfaces thereby endowing them with drug encapsulation properties. Thus, the remarkable optical, electronic, and magnetic properties of these inorganic nanoparticles can be combined with the drug-carrying ability of cyclodextrins for the development of multi-functional nanodevices. Such all-in-one nanodevices can bring together, in a comprehensive manner, two or more methods of diagnostic and treatment, including targeted drug delivery, which may lead to a synergistic effect.

But the role of CDs goes beyond. They also act as stabilizers of the colloidal nanoparticles in water solution or can be used as reducing agents for the preparation of the NPs from their inorganic precursors. Moreover, the size of some nanoparticles can be controlled by varying the concentration of cyclodextrins during colloid formation and growing. However, most synthetic routes involving the coating of nanoparticles with cyclodextrins followed post-synthetic approaches that cover a large range of possibilities, including direct anchoring of the macrocycle, anchoring through a linker, or linked to a polymeric layer.

Cyclodextrins contribute to provide biocompatibility to the NPs and in fact the cyclodextrin coating of nanoparticles contributes to reduce the cytotoxicity of the nanoparticles and improve the cell internalization. Cyclodextrin-modified nanoparticles display a multivalent presentation of quasi-hydrophobic cavities that leads to enhance

the nanoparticle-drug complex stability and higher-loading capacities of hydrophobic drugs. Cyclodextrin binding pockets are not only available for accommodating drugs, but also for the supramolecular assembly of targeting motifs and optical probes, and for the formation of larger supramolecular entities.

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Figure legends:

Figure 1. Inorganic nanoparticles and their surface modifications: properties and synthetic methods.

Figure 2. Cyclodextrin-modified AuNPs. The number of CH_2SH groups in b), d), e), f) and h) has been reduced to four for clarity.

Figure 3. Cyclodextrin-modified AuNPs. The number of CH_2SH groups in c) and e) has been reduced to four for clarity.

Figure 4. Cyclodextrin-modified AgNPs. The number of CH_2XH groups (X = S or O) in a) and c) has been reduced to four for clarity.

Figure 5. QDs capped with cyclodextrins. The number of CH_2SH groups in c) has been reduced to four for clarity.

Figure 6. QDs capped with cyclodextrins. Then number of CH_2SR groups in a) has been reduced to four for clarity.

Figure 7. MNPs decorated with cyclodextrins.

Figure 8. Cyclodextrin-modified MNPs.

Table 1. CD-capped AuNPs as drug delivery systems

NP	Core size (nm)	Drug	Target	Reference
AuNP@monoS$(CH_2)_6$SβCD-I (Fig.2a)	3.8	Violacein	HL60	Gimenez et al. 2005
AuNP@SβCD-II (Fig. 2b)	30	Baicalin	MCF-7	Lee et al. 2016
AuNP@monoSβCD-I (Fig. 2c)		Pinoresinol Lariciresinol Secoisolariciresinol	MCF-7	Bakar et al., 2015
AuNP@SβCD-I (Fig. 2d)	4.7	Adamantane-appended cisplatin	SK-N-SH	Shi et al., 2013
AuNP@SβCD-II (Fig. 2e)	13	Azobenzene-appended DNA	A549	Zheng et al., 2014
AuNP@SβCD-II (Fig. 2f)	3.1	Doxorubicin (DOX)	A549	Ha et al., 2013
AuNP@PEI-βCD (Fig. 2g)	42-96	Tanshinone IIA α-mangostin	PC-3 DU145	Qiu et al., 2016
AuNP@SβCD-I (Fig. 2h)	3.8	Doxorubicin (DOX)	B16F10	Silveira et al., 2015
AuNP@2monoβCD-Lac-II (Fig. 3a)	20.6	Methotrexate (MTX)	Gal3 lectin	Aykaç et al., 2014
AuNP@6monoβCD-I (Fig. 3b)	3.3	Doxorubicin (DOX)	U87 COS7	Chen et al., 2015
AuNP@SβCD-PEG-II AuNP@SβCD-PEG-antiEGFR-II (Fig. 3c)	40.4-47.0	β-Lapachone (LAP)	A549 A431 RKO	Jeong et al., 2009
AuNP@βCD-PEG-II AuNP@RhoβCD-PEG-II AuNP@βCD-PEG-Biotin-II AuNP@RhoβCD-PEG-Biotin-II (Fig. 3d)	20-41	Paclitaxel (PCX)	HeLa A549 MG63	Heo et al., 2012
AuNP@βCD-PEG-II (Fig. 3d)	20-40	Curcumin (CUR)	BMMs RANKL	Heo et al., 2014
AuNP@POL-βCD (Fig. 3e)	90	Doxorubicin (DOX)	HeLa	Marcelo et al., 2015
AuNP@SβCD-Fc-PEG-Fc-II (Fig. 3f)	25	Ferrocene-PEG conjugates	HepG2	Wang et al., 2016
AuNP@monoSβCD-II (Fig. 3g)	13.8	Hydroxycamptothecin	HepG2	Hu et al., 2016

Table 2. CD-Capped QDs as sensors and imaging agent

NP	Core size (nm)	Application	Analyte/Target	Reference
CdSeQD@SβCD (Fig. 5a)	4.0	Sensing	1-adamantaneacetic acid Ferroceneacetic acid Ferrocenemethanol (Dimethylaminomethyl)ferrocene	Palaniappan et al., 2004
CdSeQD@mono-SβCD and CdSe/CdSQD@mono-SβCD (Fig. 5b)	4.0-4.3	Sensing	1-adamantaneacetic acid Ferroceneacetic acid Benzoquinone	Palaniappan et al., 2006
CdTeQD@MPA-APBA-βCD CdSe/ZnSQD@SG-APBA-βCD (Fig. 5e)	3.4	Sensing Visible biomarker for HepG2 fluorescence imaging	Adamantanecarboxylic acid *p*-hidroxytoluene D,L-phenylalanine D,L-tyrosine *p*-nitrophenol Amantadine	Ai et al., 2012; Freeman et al., 2009
CdSe/ZnSQD@TOPO@CD- Man/Gal (Fig. 6a)	3.5-3.8	Visible biomarker for HepG2 fluorescence imaging	Concanvalin A (ConA) Galanthus nivalis lectin (GNA) Peanut agglutinin (PNA)	Bavireddi and Kikkeri, 2012
CdSQD@AZ@CD (Fig. 6b)	7	Photoswitcher		Li et al., 2010
CdSe/ZnS QDs decorated with ketoprofen (Fig. 6c)		Sensing	Benzophenone Phenol Indole Adamantane carboxylic acid	Aguilera-Sigalat et al., 2012

Table 3. CD-Capped QD as therapeutic principles nanocarriers

NP	Core size (nm)	Drug	Target	Reference
CdSeQD@MAA-SβCD (Fig. 5c)	7.5	Paclitaxel (PCX) Folic acid (FA)	c26	Adeli et al., 2011
CdSe/ZnSeQD@AACD (Fig. 5d)	4-5	siRNA Doxorubicin (DOX)	HeLa	Zhao et al., 2011; Li et al., 2012
CdTe/ZnSQD@MPA-APBA-βCD-RGD (Fig. 5e)	5	siRNA Dexamethasone (DEX) Kartogenin (KGN)	hMSCs	Li et al., 2016; Xu et al., 2016
CdSe/CdSQD@MAA CdSe/CdSQD@MAA-OEIβCD (Fig. 5f)	4.6	DNA Paclitaxel (PCX)	MDA-MB-231	Wu et al., 2013
CdSe/ZnSQDs@GLAβCD (Fig. 6d)	4-5	Glycyrrhizic acid (GLA)	HepG2	Zhao e al., 2012

Table 4. MNPs and their biomedical applications

NP	Core size (nm)	Drug	Application (target)	Reference
MNP@HPβCD	10-20	Doxorubicin (DOX)	Nanocarrier	H. Zhang et al., 2008
MNP@GA-βCD (Fig. 7a) MNP@GA-HPβCD MNP@GA-βCD-2	17.5-56.1	Ketoprofen (KP) Retinoic acid (RA)	Nanocarrier	Banerjee and Chen, 2009, 2008, 2007
MNP@PTES-βCD (Fig. 7b) MNP@PTES-βCD-FA	8.2	Tamoxifen (TMX)	HFMF-responsive nanocarrier (glioma cells)	Hayashi et al., 2010
MNP@APTES-βCD (Fig. 7c) MNP@APTES-βCD-scFv	13-14	Ketoprofen (KP) Doxorubicin (DOX) Epirubicin (EPI) Docetaxel (TXT)	Nanocarrier (MCF-7, Skov3)	L. Huang et al., 2014 Wang et al., 2015
MNP@GLY-βCD (Fig. 7d)		Anilino-1-naphthalenesulfonate (ANS)	Nanocarrier	Lv et al., 2014
MNP@PEG-CTX-CMβCD (Fig. 7e)	15	Paclitaxel (PCX) Fluorescein (FL)-adamantane conjugate	Nanocarrier (GBM)	Mu et al., 2015
MNP@APTES-SA-βCD (Fig. 7f) MNP@CMβCD	10-16	Indomethacin (IND) 5-Fluorouracil (5-FU)	Nanocarrier hydrogels	Anirudhan et al., 2013 Ding et al., 2015
MNP@MPTMS-PA-βCD (Fig. 7g)	30-40	Docetaxel (DTX)	Nanocarrier (HEK293, HeLa, MDA-MB-231)	Tarasi et al., 2016
MNP@APPA-βCD (Fig. 7h)	20	Diclofenac	Nanocarrier	Tudisco et al., 2012
MNP@PEI-βCD (Fig. 8a)	147	Camptothecin (CAMP)	Redox-responsive nanocarrier (HepaG2)	Luo et al., 2012
MNP@HAP-PEI-βCD (Fig. 8b)	240	Curcumin (CUR)	pH-responsive nanocarrier (MCF-7)	Akrami et al., 2015
MNP@PNG-βCD (Fig. 8c)	190	Anilino-1-naphthalenesulfonate (ANS)	Temperature-responsive nanocarrier	Lv et al., 2015
Fe_3O_4/SiO_2@TAβCD (Fig. 8d)	22	Doxorubicin (DOX)	Nanocarrier (A549) MRI	Lee et al., 2012
Fe_3O_4/SiO_2@CMβCD (Fig. 8e)	70	Retinoica acid (RA)	Theranostic (MCF-7, HeLa)	Badruddoza et al., 2013
Fe_3O_4/SiO_2@SG-βCD-FA (Fig. 8f)	52	5-Fluorouracil (5-FU)	pH-responsive theranostic (HeLa, L929)	Sahu and Mohapatra, 2013
Fe_3O_4/SiO_2@CBA-βCD (Fig. 8g)	80	Rhodamine 6G (Rh6G)	D-fructose/pH-responsive nanocarrier (HEK293T)	Qiu et al., 2015
Fe_3O_4/Au@HPβCD (Fig.	25	Curcumin (CUR)	pH-responsive	Lian et al.,

8h)			nanocarrier	2016
MNP@PTPM-PEI-βCD (Fig. 8i)	25	Polymerized paclitaxel (pPTX)	Nanocarrier (HeLa, MCF-7, CT26)	Jeon et al., 2016
MNP@βCD-PEG-PEI	230	5-fluorouracil (5-FU)	Nanocarrier (MCF-7, L929)	Prabha and Raj, 2016
MNP@CAβCD	5.0-7.7	CUR	Nanocarrier MRI	Jayaprabha and Joy, 2015
MNP@βCD MNP@βCD coated with pluronic polymer	7.9-9.8	Curcumin (CUR) 5-fluorouracil (5-FU) Progesterone	Nanocarrier (A2780CP,MDA-MB-231, PC-3) MRI	Yallapu et al., 2012, 2011 Ragab et al., 2012
MNP@DoβCD assembled of c(RGDfC)-PEG-adamantane	8	Paclitaxel (PCX)	Nanocarrier (HeLa) MRI	Nguyen et al., 2016