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# 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, (i) *in situ* during the synthesis of the nanoparticles, either using the cyclodextrin as reducing agent or as stabilizer; or (ii) 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.



## 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 (Fig. 1): (i) 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); (ii) A controllable shape, size and large surface to volume ratio that allows for an enhanced drug payload and more effective supramolecular and biological interactions; (iii) 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 for 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 oligosaccharides constituted by six (α-CD), seven (β-CD) and eight (γ-CD) D-*gluco*pyranosyl units linked by α-(1→4) bonds forming torus-shaped structures with relatively hydrophobic cavities. CDs and their derivatives are well-

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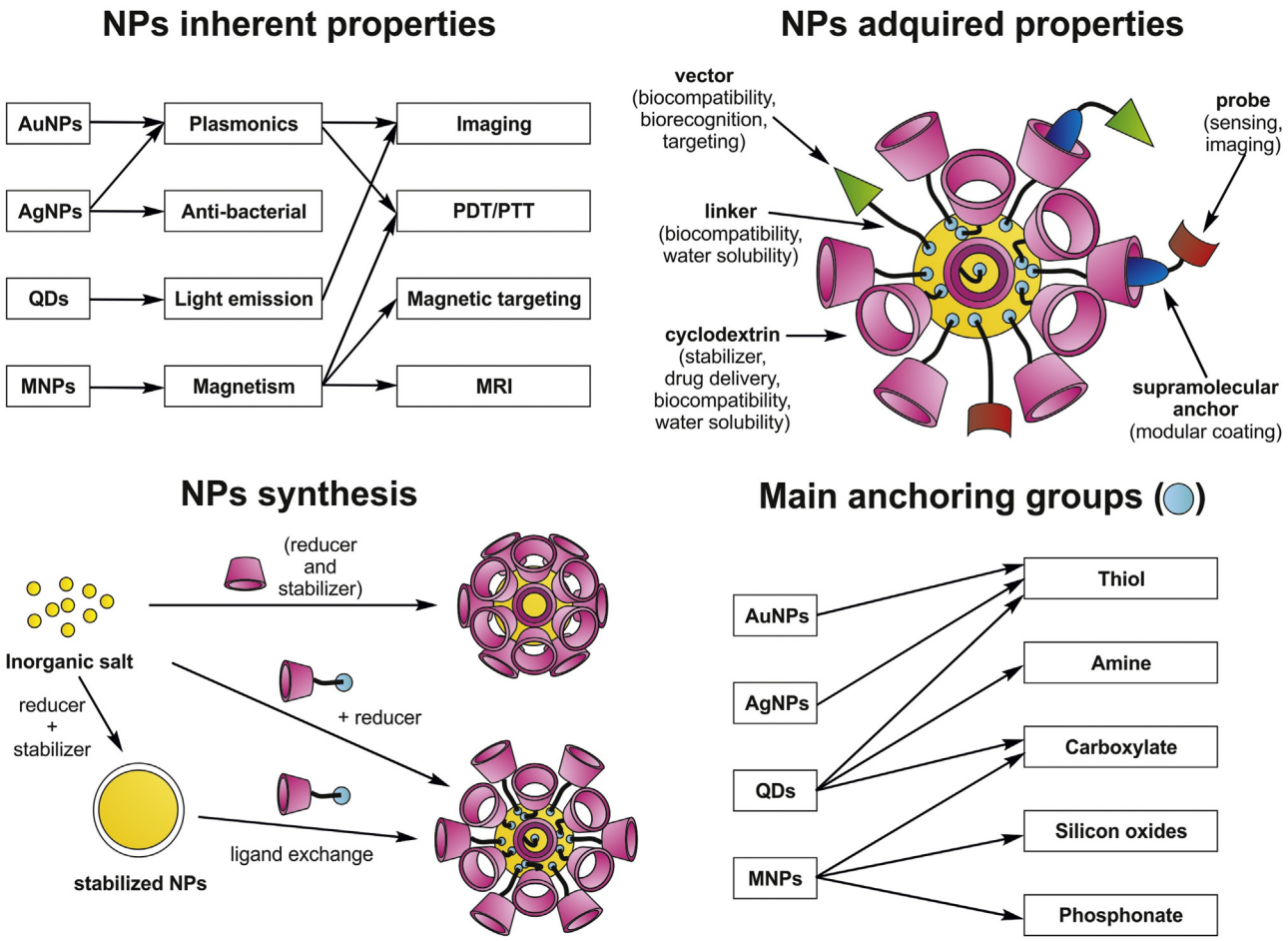


**Fig 1.** Inorganic nanoparticles and their surface modifications: properties and synthetic methods.

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 multivalency 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, thus remaining in the blood circulation for prolonged times. It has also been suggested that the presence of CDs on the 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 NPs and derivatives (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.