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Review

Colloidal particles containing labeling agents and cyclodextrins for theranostic applications

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ABSTRACT

This review aims to give to the reader some new light on cyclodextrin (CD)-based theranostic agents in order to complete our recently published review dedicated to CD-particles conjugates in drug delivery systems (Zafar et al., 2014). CDs are biocompatible sugar-based macrocycles used in a wide range of biomedical applications. Here, we mainly focus on fundamental theranostic approaches combining the use of cyclodextrin molecules and colloidal particles as theranostic agents. The system's key features are discussed and a few recent pertinent applications are presented. CDs are used in order to enhance theranostic properties by providing apolar cavities for the encapsulation of hydrophobic moieties. Thus, CD molecules are used to enhance the loading capacity of particles by hosting active molecules. The relevance of CDs in enhancing the labeling properties of particles and the preparation of controlled drug release particles is also highlighted.

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1. Introduction

Nowadays, the combination of diagnostic and therapy in life science is of great interest in order to perform in one step both the disease identification and drug delivery. To target such objective and principally to develop novel personalized treatments with improved safety and efficacy, well-defined colloidal carrier will be of great interest. In this domain, various processes including chemistry, self-assembly and formulation lead to more and more sophisticated nanoparticles (nanospheres and nanocapsules). Nanoparticles act as excellent carriers of therapeutic drugs and genes delivery by virtue of their large surface area to volume ratio and also assist in targeted delivery and controlled release of therapeutics at diseased sites *via* well-defined target. Nanoparticles for medical uses are mainly polymer based and in some case inorganic core coated with polymer layer with different functional groups to provide flexibility of encompassing multiple

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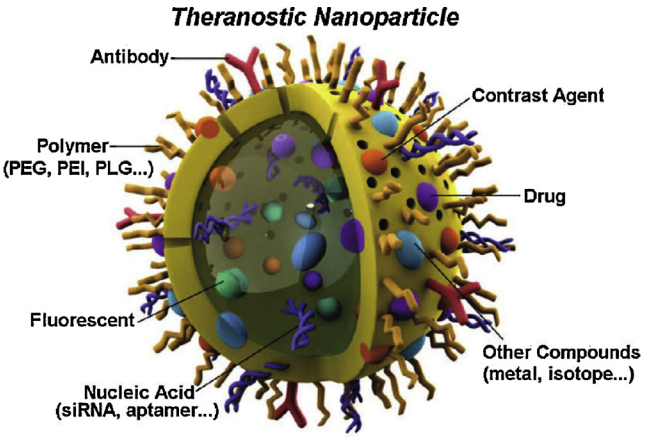

Fig. 1. Theranostic nanoparticle: surface functionalized with antibody and polymers. The interior core of nanoparticle can be encapsulated with active agents, such as nucleic acids, imaging contrast agents, drugs, and fluorescent materials to accomplish different theranostic requirements (Ma et al., 2011).

functionalities. This flexibility is a major boost for emergence of theranostics in nanomedicine. Examples of various drug delivery forms that have been used for theranostic applications include liposomes (Laouini et al., 2012; Tapia et al., 2013), micelles and nanocomposites (Roveimiab et al., 2012; Ahmad, 2013). The integral components of theranostic agents are: signal emitter, therapeutic payload, payload carrier and targeting ligands (Fig. 1 and Table 1).

Iron oxide nanoparticles bearing chlorotoxin (a peptide possessing strong affinity for majority of brain tumors) displayed accumulation in brain tumors six times higher than non-targeted nanoparticles in genetically engineered mice with brain tumors (Veiseh et al., 2009). Similarly, a magnetopolymeric nanohybrid conjugated with an antibody specific to human epidermal growth factor receptor (HER2) showed tumor targeting and growth inhibition three times higher than control nanoparticles having inappropriate antibody (Yang et al., 2007). Multiple ligands can also be attached on single particle surface to achieve multi-valency and multi-functionality (Fang and Zhang, 2010).

The release of the drug at specific site can be controlled by keeping a check/control over certain specific parameters such as pH, ionic strength, temperature, hydrolytic, enzymatic degradation and application of external stimulus like radiofrequency electromagnetic waves and light excitation. In future, theranostic agents may also offer a cost effective course to battle baleful and debilitating illnesses like cardiovascular diseases, neurodegenerative diseases and cancer.

Substances like iron oxide, silica, gold and gadolinium are commonly used in the formulation of theranostic agents (Fig. 2) and in some cases two of these are combined together to confer better and specific qualities on the resultant particles.

Cyclodextrins (CDs) first discovered by Villiers in 1891, possess extensive applications in diverse fields of drug delivery and pharmaceutical industry. They contain sugar (α-D-glucopyranose) molecules bound together in a ring form *i.e.*, cyclic oligosaccharides. These are also referred to as cycloamyloses, cyclomaltoses or Schardinger dextrins and have no reducing properties. These are highly biocompatible macrocycles that are capable of encapsulating hydrophobic agents in their non-polar cavity. During their reversible complexation with drugs no covalent bonds are formed or broken (Zafar et al., 2014). In this short review, we focus on the role of cyclodextrins (CDs) in altering the properties of theranostic particles.

2. Iron and cyclodextrin based theranostic agents

Magnetic nanoparticles (MNPs) are widely used for miscellaneous medical purposes such as nanocarriers for drugs encapsulation, drugs delivery, contrast agents in magnetic resonance imaging (MRI) and also in local hyperthermia and magnetic targeting (Yallapu et al., 2012; Laurent et al., 2010; Shubayev et al., 2009). Magnetic particles largely used in numerous *in vivo* and in biomedical application are reported by various authors which include Ahsan et al. (2013); Ahmd et al. (2012); Medeiros et al. (2013) and Rahman and Elaissari (2012). The iron oxide generally used in magnetic particles preparation is biodegradable and upon degradation in body it becomes part of natural iron stores like hemoglobin in red blood cells. The small size of superparamagnetic iron oxide nanoparticles (SPIONS), the most common iron oxide based material used in various *in vivo* applications (Fig. 3), assists their movement in tissues, endocytosis and intracellular interaction with cancer cells. SPIONS also offer various advantages such as easy to prepare *via* classical chemistry and also noninvasive material for MRI application (Kievit and Zhang, 2011). However, high aggregation of generally non-coated magnetic nanoparticles (MNPs) poses a major obstacle not only for *in vitro* application but also for their *in vivo* biomedical usage. This problem can be overcome by surface engineering of MNPs through application of stabilizer coatings such as surfactants, synthetic and natural polymers (Shubayev et al., 2009) and also chemical grafting of some biomolecules in order to induce sterical stabilization. Some of the polymer coatings confer advantage of changing the contrast imaging properties suitable for T_1 and T_2 imaging (Yallapu et al., 2012).

Cyclodextrins have been used principally in conjugation with magnetic nanoparticles to achieve better theranostic applications.

Table 1
Properties of different components of theranostics agents (Fang and Zhang, 2010).

No.	Component	Properties
1.	Signal emitter	a. These agents have optical, magnetic or radioactive properties to assist in imaging b. Embedded/encapsulated/conjugated on carrier surface
2.	Therapeutic payload	a. Genes, proteins, chemotherapy drugs or combination of these agents b. Embedded/conjugated on carrier surface
3.	Payload carrier	a. Mostly polymeric materials are employed which have multiple functional groups for conjugation of signal emitters and therapeutic payloads b. Polymers can be immobilized on nanoparticles surface during synthesis of nanoparticles cores (Veiseh et al., 2009) or by surface modification after synthesis of core c. Biodegradable in nature d. Usually comprise of multiple amide-ester, glycosidic bonds in their backbone which can be easily cleaved hydrolytically/enzymatically when carrier arrive at targeted site e. Examples include: poly(ethylene glycol) (PEG), dextran, carboxydextran, β-cyclodextrin(β-CD), poly(DL-lactide-co-glycolide) (PLGA) and poly(L-lysine) (PLL)
4.	Targeting ligand	a. Bind to certain disease markers on target cells allowing transport of theranostics agent to target site b. Always covalently attached to surface of carrier c. Examples include oligosaccharides, aptamers, peptides, antibodies and specific proteins