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# Conjugation of cyclodextrin to magnetic $Fe_3O_4$ nanoparticles via polydopamine coating for drug delivery

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ABSTRACT

In this study, a novel magnetic nanocarrier for hydrophobic drugs (β-CD–PDA–MNPs) was fabricated using surface coating of $Fe_3O_4$ nanoparticles with polydopamine (PDA) followed by functionalization with 6-thio-β-cyclodextrin (6-thio-β-CD). The obtained magnetic nanoparticles were employed to investigate their interactions with diclofenac (DCF) as a model hydrophobic drug. The resulting β-CD–PDA–MNPs were characterized by various methods including transmission electron microscopy (TEM), X-ray diffraction (XRD), X-ray photoelectron spectroscopy (XPS), thermogravimetric analysis (TGA), and vibrating sample magnetometry (VSM). The newly fabricated magnetic nanocarrier exhibited considerably higher drug loading capacity as compared for its analogue lacking CD ligands. Moreover, the release profile of DCF from β-CD–PDA–MNPs showed a burst release during the initial 8 h followed by the drug sustained release. Facile coating of magnetic nanoparticles with PDA was therefore a robust synthetic procedure for the conversion of the nanoparticles into a drug vehicle.

## 1. Introduction

Development of new drug delivery approaches have been of the significant attention in recent years. Applications of nanoparticles as carriers for delivery of drugs is a particularly attracting strategy because of several unique possibilities offered by the nanocarriers that include accumulation in tissues with defective vasculature (so-called "enhanced permeability and retention (EPR) effect), active entry to the cell, improving solubility and bioavailability of encapsulated drugs, and providing controlled release of the drugs [1–3]. In recent years, due to the wide spread of nanotechnologies in medicine, many various nanocarriers have been applied for medical and pharmaceutical purposes. Modular approach of assembling of nanomaterials allows combination of diagnostic and therapeutic modalities in one probe to achieve not only the treatment of a disease but also the monitoring of the progress of the therapy.

Magnetic nanoparticles (MNPs) are particularly important class of nanomaterials because they can act as contrast agents in magnetic resonance imaging (MRI) and can be further functionalized with therapeutics to act as diagnostic and therapeutic tools (nanotheranostics) [4–7]. Magnetic nanoparticles have long been studied for many potential applications including catalysis [8–11], enzyme immobilization [12–14], MRI [15,16], targeted drug delivery [17–20], treatment of cancer by magnetically induced hyperthermia [21–24] and gene therapy [25]. Superparamagnetic iron oxide nanoparticles (IONPs) are especially promising drug delivery vehicles due to their good biocompatibility, easy synthesis and surface modification for multimodality imaging (fluorescence/MRI, PET/MRI, SPECT/CT) and drug delivery [26]. However, mechanisms of drug loading to IONPs are based on binding to the surface of nanoparticles which limits the drug loading capacity. Specifically, association of hydrophobic drugs can only be achieved after relevant functionalization of the surface of IONPs with ligands that can effectively interact with the drugs [27]. Moreover, small size and large surface area of IONPs can lead to the nanoparticles aggregation. It highlights the importance of techniques of IONPs surface engineering. Particularly, iron oxide core-shell type of nanostructures with different organic or inorganic shell materials were developed to increase the efficacy of IONPs in drug loading, to protect them against aggregation, and to impart the new properties to the nanoparticles e.g. biological recognition functions, thermo-responsiveness, and catalytic properties [28–30].

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six (α-CD), seven (β-CD) or eight (γ-CD) glucose units linked together via α-1,4-glycosidic bonds. The CD's hydroxyl groups are located at the outer

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surface of the molecule making it hydrophilic whereas the inner cavity of cyclodextrins is relatively hydrophobic. It allows CDs to form host-guest complexes with a variety of hydrophobic molecules [31,32]. Basing on host-guest interactions, cyclodextrins were used to increase solubility of hydrophobic drugs in aqueous solutions and improve the drugs stability towards oxidation [33–36]. Moreover, CDs were used in either formation of different nanocarriers or as ligands for improvement of hydrophobic drugs loading into the nanocarriers. Hydrophobic interactions between drugs and CD ligands permitted also controlled release of the drugs from the nanocarriers. When combined with functionalization of nanoparticles with tissue and cell-specific "homing" ligands, CDs can reduce side effects of conventional drugs and enhance therapeutic efficacy of the resulting nanomedicines. Banerjee and Chen [37,38] first reported the application of magnetic nanoparticles functionalized with β-CD/β-CD-citrate as nano-vehicles for delivery of ketoprofen. The authors indicated that the synthesized system can be a promising nano-carrier for the hydrophobic drugs. Huang et al. prepared hybrid $Fe_3O_4$ magnetic nanoparticles modified with β-CD, carboxymethyl-β-CD (CM-β-CD) and 2,6-dimethyl-β-CD (DM-β-CD). Inclusion properties of CD-MNPs as drug carriers were investigated by studying in vitro release of ketoprofen (KP) model drug [39].

Several methodologies have been used for conjugation of cyclodextrin derivatives to magnetic nanoparticles. Traditionally, surface of IONPs was coated with materials containing functional groups for the subsequent reaction with cyclodextin molecules [10,11,17–20,37–39]. Messersmith et al. [40–42] introduced mussel adhesive protein inspired coatings of different surfaces with polydopamine (PDA). Amines and thiols were shown to react with quinoid moieties of PDA. This feature allows facile covalent conjunction of nucleophilic amino and thiol groups in proteins or enzymes to PDA layer [43,44]. As compared to other methods of nanoparticles functionalization, attachment of different ligands via PDA coating is simple, cost-effective, can be generally applied for immobilization of any molecules containing nucleophilic groups, and is mild permitting attachment of biomolecules without impairment of their activity [45]. Coating of magnetic nanoparticles with PDA was extensively applied for separation [46], DNA detection [47], photothermal therapy [48], enzyme immobilization for catalysis and facile recovery of the catalyst [49,45], and for non-invasive labeling, tracking, and delivery of stem cells [50].

In this study, we aimed at utilizing PDA biomimetic coating for conjugation of β-cyclodextrine ligands to magnetic $Fe_3O_4$ nanoparticles to endow them with host-guest interactions properties. Loading and release of hydrophobic drugs based on host-guest interactions should provide multifunctionality through combination of imaging properties of IONPs with drug delivery function of CD ligands attached to the surface of IONPs. We examined the system on anti-inflammatory drug diclofenac (DCF). Magnetic targeting property and the ability of β-CD–PDA–MNPs to form inclusion complex with diclofenac molecules as well as release of the drug were investigated.

## 2. Experimental

### 2.1. Materials

In this work, the following chemicals were used for fabrication of magnetic nanoparticles and drug release studies: β-cyclodextrin (β-CD, purity > 98%), iron (II) chloride tetrahydrate (> 99%), iron (III) chloride hexahydrate (> 99%), diclofenac sodium salt (DCF, > 98%), thiourea (> 99%), dopamine hydrochloride (98%), imidazole (> 99.5) and *p*-toluenesulfonyl chloride (TsCl, > 99%) were purchased from Sigma–Aldrich Chemical Company. Dialysis membranes Spectra/Por® 6 (3500, g $mol^{-1}$ cutoff) were purchased from VWR International. All other chemicals and solvents were of analytical quality and used as received.

### 2.2. Preparation of β-CD functionalized MNPs

#### 2.2.1. Preparation of 1-(*p*-toluenesulfonyl) imidazole (Ts-Im)

1-(*p*-Toluenesulfonyl) imidazole (Ts-Im) was prepared by the method described by Robert Bittman et al. [51]. Briefly, imidazole (65 g, 1 mol) was dissolved in dry $CH_2Cl_2$ and then cooled to 0 °C. The solution of *p*-toluenesulfonyl chloride in dichloromethane (80 g, 0.4 mol) was added dropwise over 2 h. The reaction mixture was allowed to warm to room temperature. It was then filtered through a pad of silica gel, which was washed with 500 mL of 1:1 ethyl acetate-hexane mixture. The filtrate was concentrated under reduced pressure. $^1$H NMR (400 MHz, $CDCl_3$, δ): 2.43 (s, 3H), 7.07(s, 1H), 7.30–7.23 (s, 1H), 7.34 (d, 2H, $J$ = 8.3), 7.80 (d, 2H, $J$ = 8.3), 7.99 (s, 1H).

#### 2.2.2. Preparation of 6-deoxy-O-toluenesulfonyl-β-cyclodextrin (6-TsO-β-CD)

Mono-6-deoxy-6-(*p*-tolylsulfonyl)-β-cyclodextrin (6-TsO-β-CD) was synthesized by the method described by Tang and Ng [52]. Typically, β-cyclodextrin (5.3 g, 5 mmol) was dissolved in 120 mL of water by heating to 60 °C with vigorous stirring. Then, the solution was allowed to cool to room temperature. The as synthesized Ts-Im (4.2 g, 19 mmol) was added to the suspension. After 2 h, a solution of sodium hydroxide in water (2.4 g, 60 mmol) was added dropwise over 20 min. The unreacted Ts-Im was separated by filtration after 10 min and the reaction was quenched by the addition of ammonium chloride (6.4 g, 120 mmol). The mixture was concentrated by blowing of air through it. Finally, the resultant suspension was filtered and the collected solid was washed with ice water then with acetone and dried in a vacuum oven. $^1$H NMR (400 MHz, DMSO-*d*6, δ): 2.43 (s, 3H, $J$ = 6.8), 3.77–3.15 (m, overlap with HDO, 55H), 4.23–4.15 (m, 1H), 4.41–4.29 (m, 2H), 4.59–4.42 (m, 5H), 4.90–4.72 (m, 7H), 5.92–5.58 (m, 14H), 7.44 (d, 2H, $J$ = 8.1), 7.76 (d, 2H, $J$ = 8.1).

#### 2.2.3. Preparation of 6-thio-β-cyclodextrin (6-thio-β-CD)

6-Thio-β-cyclodextrin was synthesized by a method described by Wang et al. [53]. Typically, 2 g of 6-TsO-β-CD and 2 g of thiourea were dissolved in 100 mL of 80% methanol–water mixture (v/v) and the reaction was performed under reflux conditions for 2 days. The solvent of the reaction mixture was then removed under the reduced pressure. The resulting white solid was added to 30 mL methanol and stirred for 1 h. After filtration, the residue was dissolved in 10 wt% NaOH solution and stirred at 50 °C for 5 h. After adjusting pH of the solution to 2, 5 mL trichloroethylene was added to the solution and stirred overnight. The obtained white precipitate was collected through filtration and washed with water. $^1$H NMR (400 MHz, $D_2O$) δ: 2.88–2.75 (m, 1H), 3.16–3.05 (m, 1H), 3.74–3.48 (m, 14H), 4.10–3.75 (m, 28H), 5.26, 4.98 (br. d, 7H).

#### 2.2.4. Preparation of $Fe_3O_4$ magnetic nanoparticles (MNPs)

$Fe_3O_4$ magnetite nanoparticles were prepared by chemical co-precipitation method [44]. Typically, 0.86 g of $FeCl_2{\cdot}4H_2O$ and 2.36 g of $FeCl_3{\cdot}6H_2O$ salts were mixed under nitrogen atmosphere in distilled water with vigorous stirring and the solution was heated to 80 °C. 5 mL of $NH_4OH$ (25%) was added dropwise. The reaction was carried out for another 30 min at 80 °C under stirring to ensure the complete growth of nanoparticles. The resulting particles were washed with distilled water several times and dried in vacuum for 24 h.

#### 2.2.5. Synthesis of PDA coated $Fe_3O_4$ NPs (PDA-MNPs)

To synthesize PDA coated $Fe_3O_4$ NPs, the method of Zhai et al. was used [14]. Bare $Fe_3O_4$ NPs (200 mg) were dispersed in a buffered solution (10 mL, 10 mM Tris–HCl buffer, pH 8.5) for 30 min under sonication. Then, dopamine (20 mg, 2 mg/ml) was added into the suspension and stirred vigorously for 3 h at room temperature. The PDA coated $Fe_3O_4$ NPs (PDA-MNPs) were rinsed with deionized water and ethanol repeatedly, and dried in a vacuum oven at room temperature.