

## Polysaccharide surface modified Fe<sub>3</sub>O<sub>4</sub> nanoparticles for camptothecin loading and release

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### Abstract

Fe<sub>3</sub>O<sub>4</sub> nanoparticles were stabilized using different functional polysaccharides, such as chitosan (CS), *O*-carboxymethylchitosan (OCMCS) and (*N*-succinyl-*O*-carboxymethylchitosan (NSOCMCS) to improve their bioactivity. The release profile and the in vitro cancer cell inhibition activity of camptothecin (CPT) loaded polysaccharide modified Fe<sub>3</sub>O<sub>4</sub> nanoparticles were systematically studied. The particle size and size distribution of CPT-loaded polysaccharide modified Fe<sub>3</sub>O<sub>4</sub> nanoparticles were found to be strongly dependent on polysaccharide character. Such polysaccharide character could also affect CPT adsorption efficiency, CPT release behavior and bovine serum albumin (BSA) unspecific binding capacity. After 24 h incubation of 7721 cancer cells with CPT-loaded polysaccharide modified Fe<sub>3</sub>O<sub>4</sub> nanoparticles, significant changes in cell morphology could be discernible from phase contrast microscopy. Cytotoxicity assay showed these polysaccharide modified Fe<sub>3</sub>O<sub>4</sub> nanoparticles did not exhibit noteworthy cytotoxicity against 7721, however, the in vitro inhibition rate of CPT-loaded polysaccharide modified Fe<sub>3</sub>O<sub>4</sub> nanoparticles against 7721 liver cancer cell increased significantly in comparison with that of CPT-free drug.

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### 1. Introduction

Nanotechnology is the utilization of structures and devices with the size ranging from 1 to 100 nm, where the physical, chemical, and biological properties are significantly enhanced/changed or completely different from those of corresponding bulk materials [1]. Superparamagnetic iron oxide nanoparticles (SPION) have been extensively studied recently because of their potential biomedical applications, including in vitro cell separation, contrast agent for magnetic resonance imaging (MRI),

tumor therapy or cardiovascular disease [2–11]. Especially, for drug targeting purposes, SPION in combination with an external magnetic field allows delivering drug loaded particles to their desired target area and fixing them at the local site. Under such medication, drugs are released and act locally, which is known as magnetic drug targeting (MDT) [12–16]. Therefore, the dosage of medication can be reduced and the systemic effect of drugs keeps to a minimum [17,18]. In vivo biomedical applications of SPION always require particle size less than 50 nm, which is easy to eliminate through reticuloendothelial system (RES) [19]. In addition, the particles should have their surface coated with different biocompatible materials, i.e., non-immunogenic, non-antigenic, and protein-resistant. Moreover, in order to transport such hydrophilic substance

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into a biological membrane system, surface modification of the nanoparticles is also a must [20].

Novel technologies in the synthesis of sophisticated coatings optimized properties of SPION have become highly attractive for medical applications in diagnostics and therapy. Three different types of magnetic colloids could be prepared through various stabilization methods [20]. One is to prepare magnetic colloids by coating magnetic core with a suitable surfactant, such as sodium oleate, dextran or PVA on SPION. Another is to synthesize nanocomposites consisting of SPION distributed throughout a non-magnetic coating like starch. The other is to form liposome-like vesicles filled with SPION. Currently, although both synthesized and natural macromolecules have been successfully used to stabilize SPION, natural macromolecules such as proteins and polysaccharides attract much more interest due to their biocompatibility and biodegradability.

Chitosan is a linear polysaccharide composed of 2-amino-2-deoxy- $\beta$ -D-glucan, which has an ideal biocompatibility, biodegradability and low cytotoxicity [21]. Moreover, the chemical modification from chitosan can be instrumental in the design of novel biocompatible materials with tailored chemical and biophysical properties, because it contains both active amino and hydroxyl groups along its backbone. Recently, the stable dispersions of SPION have been successfully prepared by coated with chitosan or its biocompatible derivatives such as OCMCS [22] and NSOCMCS [23]. It has been found that the stabilization of SPION by chitosan, OCMCS and NSOCMCS is dominated by electrostatic repulsion besides steric effects.

Camptothecin (CPT), a plant alkaloid isolated from *camptotheca acuminata*, is found to be a new generation of antitumor agent. It works by inhibiting the activity of topoisomerase I [24–26]. Although CPT has been proven to be strongly effective in vitro, it has not been applied clinically due to its poor water solubility, in vivo low efficacy and severe toxic side effects at its conventional dosage forms. SPION is supposed to be an appropriate carrier to be utilized in tissue specific release, since it could effectively reduce the dosage and the systemic effect of CPT. From our previous work, we have found that the amphiphilic chitosan derivatives such as OCMCS can effectively load hydrophobic CPT and release CPT in a controlled manner due to its stimuli-responsive aggregation behavior in the aqueous media [27]. In addition, the amphiphilic character of OCMCS makes it easy to pass through the dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) bilayer in physiological environment [28]. Therefore, the incorporation of CPT into amphiphilic polysaccharide coated SPION is supposed to be superior due to the synergetic effects of the unique benefit of magnetic nanoparticles and the bioactivity of amphiphilic polysaccharide surface. In this work, we prepared SPIONs with different polysaccharide surface modification and examined the effect of polysaccharide modification on the applications in drug loading and release together with the in vitro inhibition rate against

cancer cells. Different from the common used steric stabilizer, the polysaccharide used are supposed to be able to not only stabilize SPION suspensions, but also facilitate to load CPT effectively, release drug in a controlled manner and improve cancer cell inhibition activity.

## 2. Experiments and protocols

### 2.1. Chemicals and materials

Ferric chloride hexahydrate ( $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ , >99%), ferrous chloride tetrahydrate ( $\text{FeCl}_2 \cdot 4\text{H}_2\text{O}$ , >99%), and ammonium hydroxide (29.4 wt.%) were purchased from Shanghai Chemical Reagent (China). Chitosan (CS), obtained from Lianyungang Biologicals Inc. (China), has a viscosity-averaged molecular weight of  $5.2 \times 10^5$  g/mol and the degree of deacetylation of about 90%. OCMCS, containing about 100 carboxyl groups and 75 amino groups per 100 anhydroglucosamine units of chitosan, was synthesized from above CS by methods reported previously [29]. NSOCMCS was prepared according to our early publication [30]. Fresh prepared deionized water was from Milli-Q water purification system and deoxygenated by bubbling with  $\text{N}_2$  gas for 1 h prior to use. All other chemicals were of reagent grade and used directly without further purification.

### 2.2. Preparation of magnetic colloids

Magnetic  $\text{Fe}_3\text{O}_4$  nanoparticles were prepared without presence of additional stabilize. In a typical experiment, 5 ml of iron solution containing 0.1 M  $\text{Fe}^{2+}$  and 0.2 M  $\text{Fe}^{3+}$  was added slowly to 50 ml of  $\text{NH}_4\text{OH}$  (29.4 wt.%) solution under  $\text{N}_2$  protection and vigorous magnetic stirring for 30 min at room temperature. The suspension color turned black immediately. After stopping stirring, a strong magnet was used to collect the black precipitate, and the supernatant was decanted. The fresh prepared and deoxygenated deionized water was used to wash the precipitate. The solution was then centrifuged for 2 min at a speed of 1800 rpm, and the supernatant was decanted. Such centrifugation-redispersion cycles were carried for three to five times so as to remove excess ammonia from remaining solution. Finally, the black precipitate (magnetite) was obtained by freeze-drying.

### 2.3. CPT loaded into $\text{Fe}_3\text{O}_4$ nanoparticles

The method for preparing polysaccharide modified  $\text{Fe}_3\text{O}_4$  nanoparticles was in accordance with our early work [22,23]. Typically, 250 mg of as-prepared magnetite precipitate was dispersed into 25 ml of 0.2 mg/ml of aqueous solution NSOCMCS (pH 7.4), OCMCS (pH 7.4) and acid chitosan solution (pH 4.0), respectively, to obtain their stable suspensions. At the same time, a predetermined amount (3.48 mg) of CPT was dissolved in 1 ml of alkaline aqueous medium (pH 12, adjusted by 1 M NaOH solution) and

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