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Synthesis of thermosensitive magnetic nanocarrier for controlled sorafenib delivery

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ABSTRACT

Allyl glycidyl ether/*N*-isopropylacrylamide-grafted magnetic nanoparticles were prepared using silica-coated magnetic nanoparticles as a substrate for radical copolymerization of allyl glycidyl ether and *N*-isopropylacrylamide. Chitosan was coupled with the prepared nanoparticles by opening the epoxy ring of the allyl glycidyl ether. The thermosensitive magnetic nanocarrier (TSMNC) obtained can be applied as a potent drug carrier. The TSMNC structure was characterized using Fourier transform infrared spectroscopy, X-ray diffraction, thermogravimetric analysis, differential scanning calorimetry, vibrating sample magnetometer, and elemental analysis. Its morphology and size were investigated using field emission scanning electron microscopy, transmission electron microscopy and dynamic light scattering. The feasibility of employing the TSMNC for adsorption and in vitro controlled release of the chemotherapeutic agent sorafenib was tested. The effect of the adsorption parameters of pH, temperature, and loading time of sorafenib onto TSMNC was evaluated. The adsorption data was fitted to the Langmuir and Freundlich isotherms and the relevant parameters derived. The drug release profile indicated that 88% of the adsorbed drug was released within 35 h at 45 °C and drug release was Fickian diffusion-controlled. The results confirmed that the TSMNC has a high adsorption capacity at low temperature and good controlled release in a slow rate at a high temperature and could be developed for further application as a drug nanocarrier.

1. Introduction

The development of nanotechnology has strongly affected the synthesis and application of nanoparticles [1]. Metal nanoparticles have diverse applications for advanced materials, semiconductors, sensors, catalysis, and nano-medicine [2]. Magnetic nanoparticles offer ease of availability and low-cost precursors [3,4]. Moreover, their ease of synthesis with adjustable and uniform support particles 1–100 nm in size and their magnetic properties are beneficial for applications in magnetic resonance imaging [5] and drug delivery [6,7]. The ability of magnetic nanoparticles for further functionalization makes them good candidates for preparation of smart hybrid nano-sized particles having advanced applications in biological systems, especially in drug delivery [8].

Smart magnetic nanoparticles have core/shell structures with iron cores and stimuli-responsive moiety shells [9,10]. Magnetothermally-responsive composites with highly engineered systems for drug delivery must be thermally responsive and include magnetic nanoparticles. These composites deliver therapeutic agents to cancer cells by means of an external magnetic field. The drug is released by alteration of the thermo-responsive moiety in response to temperature change by an external heat source (e.g., a hot water bag) [11]. The creation of magnetic nanoparticles using *N*-isopropylacrylamide is a good strategy for preparation of thermo-responsive magnetic nanocomposites [12]. The application of *N*-isopropylacrylamide to biological systems is linked to its specific lower critical solution temperature (LCST) of 32 °C, which is approximately its physiological temperature [13,14].

Chitosan is a biodegradable polymer with unsurpassed bioproperties that is primarily applied for biomedical purposes, mainly in the design of drug delivery systems [15]. Its properties have attracted attention over those of other available commercial adsorbents. Chitosan is an abundant, non-toxic, low-cost biopolymer with a high adsorption capacity and can be obtained from natural resources. Chitosan's macromolecular structure includes functional groups on its surface that have a good affinity for adsorbing drugs [16].

Chitosan/*N*-isopropylacrylamide derivatives offer novel systems having the properties of both and drug loading can occur at temperatures below the LCST. These assemblies are primarily in nanoparticle form and are capable of delivering drugs to specific locations and then collapsing to release the drugs when the temperature is increased to above the LCST [17–21].

Advanced primary liver cancer (hepatocellular carcinoma) is a common malignant tumor with the third highest rate of mortality worldwide [22,23]. Sorafenib, a drug with FDA approval, is prescribed for

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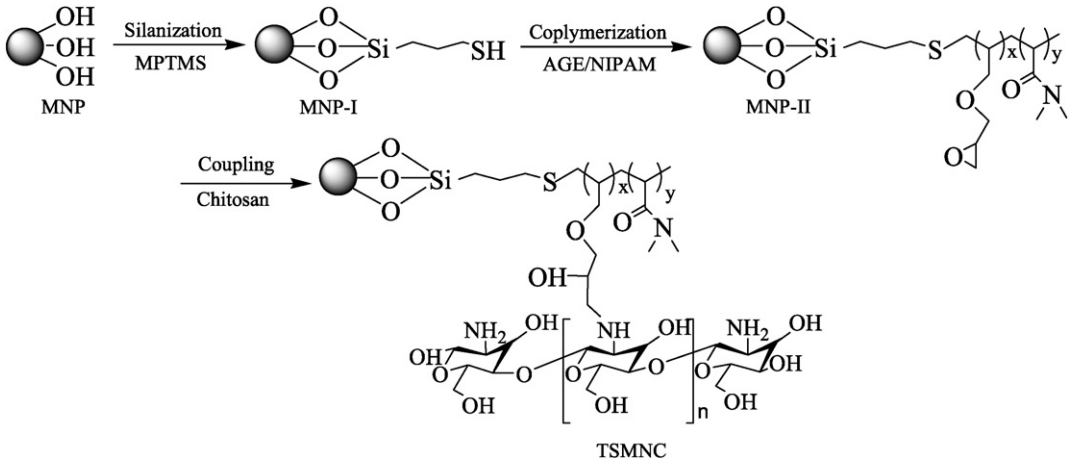

Fig. 1. Preparation of TSMNC.

patients with hepatocellular carcinoma [24]; however, the water immiscibility of this drug is a factor limiting its use. The low bioavailability of sorafenib could prompt treatment with a high dosage that is toxic and has strong side effects [25,26]. These complications could be reduced by the application of a nanocarrier as a drug vector to improve sorafenib delivery and control its release. This would decrease toxicity and leave healthy organs immune while a high dosage accumulates in the affected organs [27,28]. Engineered magnetic nanoparticles offering good biocompatibility and an appropriate size are good candidates for this.

The present study functionalized magnetic nanoparticles (MNP) with chitosan for adsorption of sorafenib (SFB) and *N*-isopropylacrylamide to control release in response to changes in temperature. Fig. 1 shows the steps required for this process. First, magnetic nanoparticles were prepared by co-precipitation and were silanized with 3-mercaptopropyltrimetoxysilane (MPTMS) to provide suitable functionality for radical polymerization. Allyl glycidyl ether (AGE) and *N*-isopropylacrylamide (NIPAM) were then copolymerized onto MNP-I in the presence of 2-azobisisobutyronitrile as an initiator. Finally, chitosan was coupled with MNP-II via epoxide ring-opening of the allyl glycidyl ether species to obtain the TSMNC.

2. Experimental and methods

2.1. Instruments

Characterization of the products was done by comparison of their Fourier transform infrared (FTIR) spectra with those reported in the literature. A Perkin-Elmer spectrometer (version 10.03.07) was applied to record the infrared spectra. X-ray diffraction (XRD; D8; Advance Bruker; AXS) was utilized for recording X-ray diffraction data. Thermogravimetric analysis (TGA) was performed with a Scinco STA1500 (Korea). The particle size distribution (PSD) was measured by a dynamic light scattering particle size analyzer (Horiba; LB-550). A vibrating sample magnetometer (VSM) was used for VSM/AGFM (Meghnatis Danesh Pajouh; Iran) at room temperature with a magnetic field. Differential scanning calorimetry (DSC) was carried out using a DSC602/Bäher thermoanalyzer. Elemental analysis was employed to detect the percentage of carbon, hydrogen, and nitrogen using a thermo-Finnigan flash (EA1112; Italy). Transmission electron microscopy (TEM) was carried out using a Philips EM30. A Hitachi S-4160 was used for field emission scanning electron microscopy (FE-SEM). The surface area of the TSMNC was calculated by Brunauer, Emmett and Teller (BET) method using N_2 adsorption-desorption isotherms data on a NOVA 1000 series instrument (Quantachrome, USA). A Cecil CE7250 UV–Vis spectrophotometer was applied to determine SFB loading and release. Data analysis was carried out using Sigma Plot 12 software (Systac) followed by analysis of variance.

2.2. Reagents and solutions

N-isopropylacrylamide, chitosan (low molecular weight; 71 kDa) and 2-azobisisobutyronitrile were purchased from Sigma-Aldrich. The 3-mercaptopropyltrimethoxysilane, anhydrous toluene, allyl glycidyl ether, solvents, acetic acid, ammonia solution, and other inorganic acids (99.9% purity) were provided by Merck (Germany). Sorafenib was purchased from Hangzhou (China). The stock solution (500 mg L^{-1}) of SFB was prepared in methanol. A stock of 200 mg L^{-1} of TSMNC was prepared as follows: 10 mg of TSMNC was well-dispersed in 2.5 mL of buffer solution using a homogenizer at 4500 rpm and then diluted to 50 mL. To adjust the pH of the solutions, either an acetate buffer or a phosphate buffer was used wherever suitable.

2.3. Synthesis of thermosensitive magnetic nanocarrier

2.3.1. Preparation and silanization of MNP

Magnetic nanoparticles were synthesized by co-precipitation method [29]. Briefly, 1.35 g (6.8 mmole) of iron (II) chloride tetrahydrate ($FeCl_2 \cdot 4H_2O$) and 3.68 g (13.6 mmole) of iron (III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) were admixed in 100 mL of deionized water and transferred to a three-neck flux furnished with an overhead stirrer and a condenser. The solution was then heated to 85 °C and 100 mL of NH_4OH (0.1 M) was added drop wise under a nitrogen atmosphere. The reaction proceeded for 2 h at 85 °C and then was allowed to cool naturally

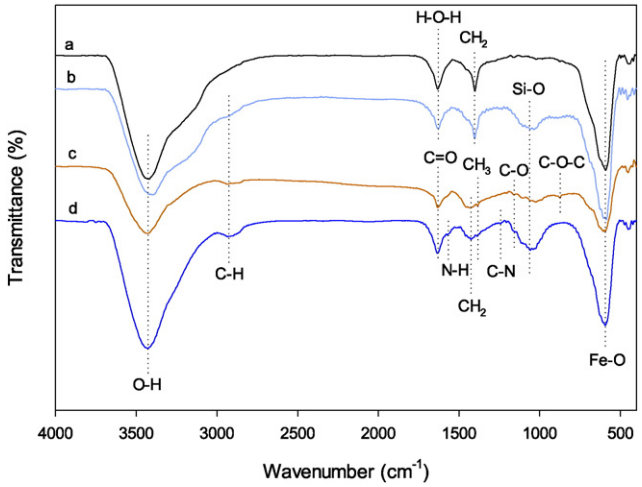

Fig. 2. FTIR spectrum of: (a) MNP; (b) MNP-I; (c) MNP-II; (d) TSMNC.