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Original Research Paper

Porous magnetite secondary particles prepared by surfactant-free solvothermal method with non-contact heat-assisted drug releasing property

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ABSTRACT

Porous magnetite (Fe_3O_4) secondary particles were prepared by a surfactant-free solvothermal method of up to 4 h. Fe_3O_4 secondary particles prepared for 3 h were about 300 nm in average diameter, composed of aggregated primary particles, and had a porous structure. Potential application of the Fe_3O_4 secondary particles as a drug delivery agent was evaluated by estimating their release of property. The amount of ibuprofen released was increased when an alternating current magnetic field (ACMF, 120 kHz and 7.8 kA/m) was applied to the prepared magnetite clusters in phosphate buffered saline (PBS) solution. Moreover, as-prepared samples dispersed in water well and exhibited quick magnetic separation with the help of an external magnetic field from a magnet.

1. Introduction

Magnetic iron oxide (Fe_3O_4 and γ-Fe_2O_3) particles have been applied in various biomedical fields, such as magnetic resonance imaging (MRI), targeted drug delivery, hyperthermia, and magnetic separation owing to their low toxicity, chemical stability, and nearly superparamagnetic behavior [1–3]. Recently, many researchers have focused on the synthesis of monodispersed magnetite (Fe_3O_4) particles with uniform shape and size having large magnetization [4–7].

When Fe_3O_4 particles are prepared for magnetic materials to be used in drug delivery systems, there are two main requirements: targeted delivery capability and controlled release behavior. Targeted delivery means that drug-loaded particles can be exactly transported to targeted tissues. A controlled drug release behavior enables the amount of drugs in targeted tissues such as tumors to be increased, or prevents drugs being released in normal tissues, thereby improving the therapeutic efficiency and minimizing side effects [8–10].

Fe_3O_4 particles have also been used as magnetic agents in hyperthermia, a therapy used to destroy tumor tissues without any surgical treatments. In hyperthermia therapy, Fe_3O_4 particles exposed to an external alternating current magnetic field (ACMF) generate heat through magnetic relaxation losses (Néel and Brown) or hysteresis losses. This heat generation is used to increase the temperature of tumor tissues to 41–46 °C for over 30 min which is enough high to kill the tumor tissues, which have low heat-resistance [11,12].

Many researchers reported that Fe_3O_4 particles were prepared for application of drug carriers or hyperthermia [13–15]. But they have focused on only drug releasing or heating. There are few reports that drug releasing is controlled by heat generated by ACMF in Fe_3O_4 particles.

Fe_3O_4 particles can be prepared by a variety of processes including sol–gel, co-precipitation, ultrasound irradiation, and solvothermal methods, and thermal de-composition of metal organic compounds. Among them, solvothermal methods are nontoxic and very simple solution processes, and enable the synthesis of high quality particles with high crystallinity in uniform sizes and shapes [1–6].

In this study, porous Fe_3O_4 secondary particles were prepared by a surfactant-free solvothermal method using only iron (III) chloride hydrate and sodium acetate trihydrate dissolved in ethylene glycol (EG). And their drug release properties with and without induced heating were investigated to evaluate their applicability to controlled drug releasing.

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Ibuprofen was used as a model release drug for drug delivery. Ibuprofen is a well-known non-steroidal anti-inflammatory drug (NSAID). This drug can relieve pain in a variety of cases, including headaches, toothaches, menstrual cramps, joint pain and backaches. When human body temperature is increased, it can be used to reduce fever. However, ibuprofen is a poorly water-soluble drug (5.2 mg/mL in phosphate buffered saline at pH 7.2). The maximum amount of ibuprofen taken per day must be restricted owing to side effects such as chest pain, headache, and vomiting [14,15].

2. Experimental

2.1. Chemical materials

Iron (III) chloride hydrate ($FeCl_3{\cdot}6H_2O$), ethylene glycol (EG, $HOCH_2CH_2OH$), sodium acetate trihydrate ($CH_3COONa{\cdot}3H_2O$) and ibuprofen (IBU, $C_{13}H_{18}O_2$) were purchased from Wako Pure Chemical Company. All of the chemical reagents and solvents were used without further purification.

2.2. Synthesis of porous magnetite (Fe_3O_4) secondary particles

Porous Fe_3O_4 secondary particles were prepared by a solvothermal method without any surfactant. Firstly, iron (III) chloride hydrate (20 mmol) and sodium acetate trihydrate (60 mmol) were dissolved in 240 mL of ethylene glycol with magnetic stirring at 500 rpm at room temperature. After stirring for 30 min, the mixture became dark-yellow. The mixture was then divided into five Teflon lined stainless-steel autoclaves (100 mL capacity). The temperature was increased at rate of 20 °C/min and kept at 200 °C for 0, 1, 2, 3 or 4 h. The obtained samples were allowed to cool to room temperature naturally, separated from solution, washed with ethanol and deionized water several times to remove any impurities, and then dried at 60 °C for 24 h.

2.3. Drug loading and releasing property experiment

Ibuprofen was chosen as a model for drug release. The loading and release of the ibuprofen were carried out by method reported prior other researches [9,10]. Fig. 1 shows illustration of drug loading process. To load drug on Fe_3O_4 particles, firstly, as-prepared porous Fe_3O_4 secondary particles (0.1 g) were added to 50 mL of ibuprofen (40 mg)/ethanol solution at room temperature and ultrasonicated for 10 min to attain a high dispersion of the particles. The mixture was stirred for 24 h at 300 rpm to load the ibuprofen into the porous Fe_3O_4 secondary particles. The ibuprofen-loaded porous Fe_3O_4 secondary particles were separated from the mixture using a permanent magnet and dried at 60 °C for 24 h.

To analyze the release of ibuprofen, the obtained ibuprofen-loaded porous Fe_3O_4 secondary particles were first added to phosphate buffered saline (PBS, pH 7.2) at 37 °C and stirred at 100 rpm. At given time intervals, 3 mL of the solution was extracted for UV–vis absorption analysis at a wavelength of 264 nm, and 3 mL of fresh PBS was added to the release mixture to maintain the same volume.

2.4. Heating property experiment

The temperature of the mixture was detected using a fiber optic sensor placed at the center of the sample under an ACMF generated by a high-frequency induction heating oscillator (2 kW, 120 kHz) with copper coils (∅70 mm × 15 turns). The heating properties of the prepared samples were measured by applying an ACMF with a magnetic field amplitude of 6.7, 7.8, and 8.3 kA/m, respectively.

2.5. Measurements

The structural and morphological properties of the prepared samples were investigated by X-ray diffraction (XRD; Rigaku RINT/2100) using Cu-Kα radiation (λ = 1.54056 Å, 40 kV, 40 mA), transmission electron microscopy (TEM; Hitachi S-8100), field emission scanning electron microscopy (FE-SEM; Hitachi S-4500). Magnetic properties were measured at 300 K using a vibrating sample magnetometer (VSM; TM-VSM1530-HCC-D).

Nitrogen adsorption-desorption measurements were performed on a BET surface analyzer Specific surfaces areas and pore volumes were calculated by the Brunauer–Emmett–Teller (BET SORP18) method. Pore size distribution of sample was estimated from adsorption branches of isotherms Barret–Joyner–Halenda (BJH) method. The UV–vis absorption spectra of the prepared samples were measured by UV–vis spectrophotometer (Hitachi U-4100). The drug release property caused by heating produced by ACMF was estimated from the fluorescence intensity of the samples by using fluorescence spectroscopy (JEOL).

3. Results and discussion

3.1. Formation mechanism and properties of porous Fe_3O_4 secondary particles

Ethylene glycol (EG) was used as a strong reducing agent and a solvent with a relatively high boiling point. Sodium acetate trihydrate was added as an electrostatic stabilizer to prevent primary particles from agglomerating [13]. In EG solution, sodium acetate trihydrate is ionized into CH_3COO^- and Na^+, and CH_3COO^- bonds to the surface of primary particles during the solvothermal process. This causes electrostatic repulsion among neighboring primary particles. However, primary nanoparticles typically aggregate into larger particles to reduce their high surface energy [16–18].

Fig. 2(a) shows images of a sample in which ferric chloride hydrate and sodium acetate trihydrate were mixed in EG solution and stirred for 30 min at room temperature with no thermal treatment. Fig. 2(b) shows that agglomerated particles with irregular shape and varied size were obtained after the reaction mixture

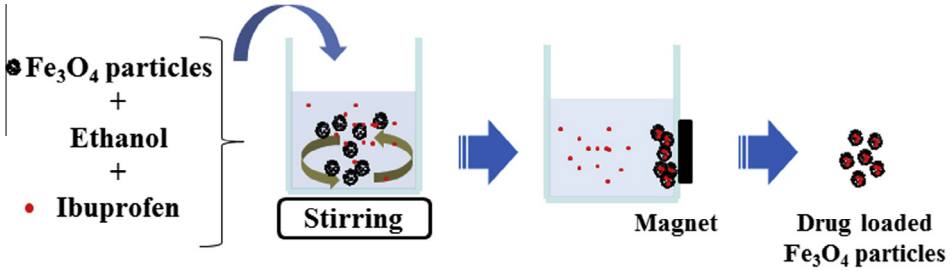

Fig. 1. Illustration of drug loading process.