Journal of Magnetism and Magnetic Materials 381 (2015) 278–284

Contents lists available at ScienceDirect

Journal of Magnetism and Magnetic Materials

journal homepage: www.elsevier.com/locate/jmmm

Core–shell composite particles composed of biodegradable polymer particles and magnetic iron oxide nanoparticles for targeted drug delivery

Chiemi Oka [a], Kazunori Ushimaru [a], Nanao Horiishi [b], Takeharu Tsuge [a], Yoshitaka Kitamoto [a,*]

[a] Department of Innovative and Engineered Materials, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama 226-8502, Japan
[b] Bengala Techno Laboratory, 9-5-1006, 1-1 Kodai, Miyamae-ku, Kawasaki 216-0007, Japan

ARTICLE INFO

Article history:
Received 27 June 2014
Received in revised form
4 September 2014
Accepted 6 January 2015
Available online 7 January 2015

Keywords:
Iron oxide nanoparticle
Composite particle
Drug delivery
Biodegradable polymer

ABSTRACT

Core–shell composite particles with biodegradability and superparamagnetic behavior were prepared using a Pickering emulsion for targeted drug delivery based on magnetic guidance. The composite particles were composed of a core of biodegradable polymer and a shell of assembled magnetic iron oxide nanoparticles. It was found that the dispersibility of the nanoparticles is crucial for controlling the core–shell structure. The addition of a small amount of dispersant into the nanoparticle's suspension could improve the dispersibility and led to the formation of composite particles with a thin magnetic shell covering a polymeric core. The composite particles were also fabricated with a model drug loaded into the core, which was released via hydrolysis of the core under strong alkaline conditions. Because the core can also be biodegraded by lipase, this result suggests that the slow release of the drug from the composite particles should occur inside the body.

1. Introduction

Recently, the unique properties of magnetic nanoparticles have attracted attention for the development of targeted drug delivery systems. Magnetic drug carriers such as magnetic capsules and magnetic nanoparticles encapsulated with a smart polymer have been reported [1–4]. These magnetic drug carriers can be delivered to the required area through the use of external magnets. However, drug release from these carriers is often not controlled because the release occurs even in a neutral buffer solution [4–6]. In addition, some carriers are composed of substances that have the potential to be retained inside the body, such as FePt nanoparticles and silica particles [1,2,7]. The lack of control of drug release and the retention of carrier substances has thus limited the development of practical magnetic drug carriers. Therefore, there is a strong need for magnetic drug carriers that enable controlled drug release and are passed from the body in a certain way after treatment.

Polyhydroxyalkanoates (PHAs) are biopolymers with high biocompatibility and biodegradability, and PHA particles have been studied as drug carriers for sustained drug release applications [8–12]. Xiong et al. reported the fabrication of model drug-loaded PHA particles and their intracellular sustained release behavior [10]. Furthermore, some researchers have reported that the degradation of PHA rarely occurs in the absence of degrading proteins, unlike other biodegradable polymers such as poly(lactic acid) (PLA) [13–15]. For example, the molecular weight of PHA did not change at 37 °C in a pH 7.4 phosphate buffer for a period of more than 84 days [13]. Therefore, PHA particles have the potential to serve as drug carriers that can release drugs only inside the body, because drug release from such drug-loaded PHA particles cannot happen without the decomposition of PHA.

Iron oxide (either magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3)) nanoparticles are magnetic materials that have previously been used in biomedical applications, including as magnetic beads for magnetic separations and contrast agents for magnetic resonance imaging [16]. It has also been reported that iron oxide nanoparticles not only have high biocompatibility but are also biodegradable [17]. In addition, these nanoparticles often exhibit superparamagnetic behavior [18]. Hence, despite possessing a high magnetic response, iron oxide nanoparticles can be dispersed into a liquid. These properties indicate that iron oxide nanoparticles are suitable for use in magnetic drug carriers, because they are not toxic to humans and are not retained in the human body.

Based on the above facts, we proposed that the combination of drug-loaded PHA particles and iron oxide nanoparticles promises

* Corresponding author. Fax: +81 45 924 5433.
E-mail address: kitamoto.y.aa@m.titech.ac.jp (Y. Kitamoto).

http://dx.doi.org/10.1016/j.jmmm.2015.01.005
0304-8853/

to provide novel smart magnetic drug carriers. Such magnetic carriers would be expected to not only be magnetic for targeted drug delivery via magnetic guidance, but also enable controlled drug release only inside the body due to their biodegradability. In addition, although it is not experimentally demonstrated in the present paper, we expect that the composite particles should also allow a second drug release mechanism via the melting of the PHA particles using the heat generated by the iron oxide nanoparticles when exposed to an applied high frequency magnetic field, similar to that observed for magnetic hyperthermia. We have already confirmed that our iron oxide nanoparticles can generate the heat. Therefore, we consider the composite structure should lead to a magnetic drug carrier possessing two types of drug release mechanisms: sustained release by biodegradation and rapid release by melting of the PHA.

Herein, we describe core–shell composite particles consisting of a core of PHA particles and a shell of assembled iron oxide nanoparticles. The composite particles were fabricated via a modified emulsification solvent diffusion method using a Pickering emulsion [19–21]. The emulsification solvent diffusion method generally facilitates the fabrication of polymer particles, including PHA particles [10]. In this method, a surfactant is used as a stabilizer for the emulsion, and it is thought that this surfactant remains on the surfaces of the resulting particles [22,23]. In other words, the prepared polymer particles have a core–shell structure with a core composed of polymer particles and a very thin surfactant shell. We thus presumed that if iron oxide nanoparticles were used instead of the surfactant, core–shell composite particles consisting of a core of polymer particles and a shell of assembled iron oxide nanoparticles would be obtained. It is known that solid SiO_2 and TiO_2 nanoparticles can be used like surfactants as stabilizers for emulsions [24,25]. Such an emulsion stabilized by nanoparticles is often referred to as a Pickering emulsion. Furthermore, some researchers have reported the preparation of Pickering emulsions stabilized by iron oxide nanoparticles [20]. Therefore, in this study, an emulsification solvent diffusion method was designed using a Pickering emulsion in order to fabricate composite particles. Because the core–shell composite particles were expected to be applicable to magnetic drug carriers, we investigated the loading and release of the hydrophobic, fluorescent model drug pyrene by measuring the fluorescence of the particles.

2. Materials and methods

2.1. Materials

Japanese Industrial Standard (JIS) grade iron (II) chloride tetrahydrate ($FeCl_2 \cdot 4H_2O$), iron (III) chloride hexahydrate ($FeCl_3 \cdot 6H_2O$), sodium hydroxide (NaOH), and dichloromethane and Wako special grade polyvinylpyrrolidone (PVP) (M_w=25,000) were obtained from Wako Pure Chemical Industries, Ltd. Poly(3-hydroxybutyric acid)/poly(3-hydroxyvaleric acid) copolymer (PHB-*co*-HV) (natural origin, M_w=400,000–750,000, PHV content 24%) and pyrene (85%) were obtained from Aldrich Chemical Company, Inc.

2.2. Preparation of PHA and iron oxide composite particles

Iron oxide nanoparticles (either Fe_3O_4 or γ-Fe_2O_3) were synthesized via a co-precipitation of Fe^{2+} and Fe^{3+} aqueous salt solutions using an alkaline NaOH solution according to the method reported by Nedkov et al. [26]. Briefly, an aqueous mixture of Fe^{2+} and Fe^{3+} chlorides (0.09 M) was prepared at a molar ratio of 1:1 taking the natural oxidation of Fe^{2+} into account. The subsequent co-precipitation process was performed by adding the mixture into an aqueous NaOH solution (0.1 M) at 80 °C. The precipitated nanoparticles were separated from the solution by centrifuging at 5000 rpm for 10 min and then washed three times with water. Finally, the nanoparticles were redispersed in water via sonication at a concentration of 15 mg/mL.

Core–shell composite particles consisting of PHA particles and iron oxide nanoparticles were prepared using a modified emulsification solvent diffusion method that involved the formation of a Pickering emulsion [19–21]. Three types of composite particles were prepared via the formation of a dichloromethane in water emulsion stabilized by iron oxide nanoparticles. Briefly, PHB-*co*-HV (50 mg) was added to dichloromethane (1 mL), and the mixture was stirred to ensure that all of the PHB-*co*-HV dissolved. Separately, three types of iron oxide dispersions were prepared by adding the above iron oxide suspension (200 μL) to each of three aqueous PVP solutions (30 mL; 0, 0.5, and 3 wt% PVP). The PVP thus acted as a dispersant for the iron oxide nanoparticles. To form the emulsions, each suspension was sonicated for 2 min, and then the PHB-*co*-HV dichloromethane solution was rapidly added. After sonication for a further 10 min, each mixture was gently stirred for 3 h at room temperature. The resultant composite particles were collected by centrifugation at 9000 rpm for 10 min and then washed three times with water.

2.3. Preparation of PHA and iron oxide composite particles loaded with a model drug

The pyrene-loaded composite particles were prepared by adding pyrene to the PHA/dichloromethane solution used in the above method for preparation of the composite particles. The concentration of pyrene was adjusted to 1 mg/mL. Except for the addition of pyrene, the particles were prepared as described above. The presence of the loaded pyrene was confirmed by excimer fluorescence analysis of the particles after exposing them to UV rays.

2.4. Characterization

The morphological properties of the prepared particles were determined via scanning electron microscopy (SEM) (Hitachi, S-4800) and transmission electron microscopy (TEM) (Hitachi, H-8100). The specimens for SEM analysis were prepared by placing a drop of the dilute suspension onto a glass plate and drying under reduced pressure at room temperature. Before observation, an approximately 5-nm-thick osmium conductive metal coating was applied to each specimen. For the TEM analyses, the specimens were prepared by placing a drop of the dispersion on a carbon-coated TEM grid and then drying. The crystallographic properties of the iron oxide nanoparticles were analyzed using an X-ray diffractometer (Rigaku, RINT2100V) with Cu K_α radiation (λ=0.1542 nm). The magnetic properties were measured using a Physical Property Measurement System (Quantum Design, PPMS), and the distribution of hydrodynamic diameters of the iron oxide nanoparticles were determined based on dynamic laser scattering (DLS) measurements obtained using a particle characterization instrument (Horiba SZ-100).

2.5. Confirmation of model drug loading and non-enzymatic release

PHA degrades in aqueous acidic or alkaline media [27–29]. Hence, in this study, the release of the model drug was investigated via hydrolysis of the PHA particles using an alkaline solution. Specifically, the composite particles were dispersed in a 0.1 M aqueous NaOH solution and then placed in a petri dish. They were subsequently collected at the center of the dish using a magnet, and then the florescence was observed. Next the