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Design of iron oxide nanoparticles decorated oleic acid and bovine serum albumin for drug delivery

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ABSTRACT

This study aimed to originally develop a new nanoparticulate drug delivery system of iron oxide nanoparticles (Fe_3O_4) for biomedical applications. Oleic acid and bovine serum albumin were decorated on the surface of iron oxide nanoparticles in new pattern by conjugation. The decoration was kicked off by the functionalization of arginine on the surface of the iron oxide nanoparticles. It was then followed by the conjugation of oleic acid and bovine serum albumin through the amide bond. Scanning electron microscopy, transmission electron microscopy, powder X-ray diffraction and Fourier transform infrared spectroscopy were used to characterize and determine mechanism of the decorated nanoparticles. Paclitaxel was chosen as the model drug in the study. The nanoparticles demonstrated a potential utility in delivery of anticancer drugs.

1. Introduction

One of the most important applications of nanotechnology is nanomedicine, which applies the technique to the prevention, diagnosis and treatment of diseases (Tran et al., 2014; Bamrungsap et al., 2012; Song et al., 2013). Fabrication of nanoparticles has drawn much interest in developing a new generation of more effective cancer therapies since nanoparticles show highly promising in the improvement of drug efficacy, especially drugs with a narrow therapeutic window or low bioavailability such as anticancer drugs (Praetorius and Mandal, 2007). Moreover, nanoparticles are under particular researches since they can selectively access to tumor due to their small size and versatile modified physicochemical properties (Gill, 2013). Solid tumors facilitate preferential accumulation of nanosized drug delivery systems due to their specific structure where the vasculature is different in both functional and morphological aspects, from the one in normal tissues (Vasir et al., 2005; Jiang et al., 2014). Generally, tumor blood vessels are larger in size, more heterogeneous in distribution and more permeable (Jang et al., 2003). The increased vascular permeability and the impaired lymphatic drainage in rapidly growing tumors allow an accumulation of nanoparticles in the tumor (Tiwari and Tiwari, 2013). When the absorption occurs, the drug is released. The technique overcomes disadvantages of the conventional solution including rapid clearance from the blood circulation due to low molecular weight, and low accumulation at the tumor site for treatment. In addition, anticancer drugs tend to present with a large volume of distribution leading to toxicity toward healthy tissues due to their small size and/or their high hydrophobicity in the conventional treatment.

A tool for observation of tumor response during cancer therapy is very important and indispensable in treatment of this disease. Magnetic resonance imaging (MRI) is a common approach widely used for diagnosis in biomedical application. Development of contrast agents for further improving tissue resolution on the image hence, have drawn much interest.

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Novel nanomedicine based drug delivery systems as directions to deliver anticancer drugs to tumor for effective therapy and diagnostics have been incessantly investigated (Tran et al., 2012). Those systems not only reduce side effects of anticancer drugs but also utilize the nanostructure as an MRI contrast agent. Iron oxide nanoparticles (IONPs) have emerged as feasible materials for tumor imaging and targeted anticancer drug delivery (Kumar et al., 2010; Munnier et al., 2008; Liu et al., 2009; Häfeli et al., 2009; Talelli et al., 2009). Various IONPs have been clinically used as contrast agents due to their high contrast effects and biocompatibility. However, the use of these products as a drug carrier system has been still under investigation. It has been reported that under physiological pH conditions the IONPs are not charge and precipitated because the isoelectric point of IONPs is 7 (Acton, 2013). Consequently, agglomerated particles are rapidly cleared by macrophages in the reticuloendothelial system (RES) before they can reach to target cells (Moghimi et al., 2001; Romberg et al., 2008; Torchilin and Trubetskoy, 1995; Vittaz et al., 1996). One of the feasible approaches is coating the nanoparticles by a biocompatible material (Neuberger et al., 2005), which can act to shield the IONPs from surrounding environment and can also be functionalized then. Type of surface coating, its concentration and a wide variety of experimental factors such as stirring rate, stirring time, pH, etc. determine the overall size of the colloids which may also play a significant role in biodistribution (Roohi et al., 2012; Smolensky et al., 2011; Mohammad-Beigi et al., 2011). Besides, the drug loading capacity of the hydrophobic part depends on compatibility between hydrophobic functional groups and poorly water-soluble drugs encapsulated (Smejkalova et al., 2014). A design of surface-modified IONPs hence, would determine drug loading capacity and probably encapsulation efficiency also (Smejkalova et al., 2014). Oleic acid (OA) is a biocompatible fatty acid and also an agent that induces the stability of many nanoparticle systems. It can play a role of a capping agent for the particles to form a protective monolayer through a strong bond. Nanoparticles with a hydrophobic coating through the attachment of the polar end groups to the surface hence are obtained with monodisperse and highly uniform (Bronstein et al., 2007; Zhang et al., 2006). The system with oleic acid coating only is not suitable for biomedical applications because they possess hydrophobic surfaces with a large surface area to volume ratio which cause agglomeration and formation of large clusters, resulting in the increased particle size (Huang et al., 2013). However, OA is the essential part of the IONPs coating for anticancer hydrophobic drug to be loaded (Jain et al., 2005). Therefore, for biomedical applications in aqueous environments, in addition to OA part, the presence of a hydrophilic coating is favorable. Albumin nanoparticles have recently withdrawn attraction due to the preparation under mild conditions and the capability of various kinds of molecules incorporation (Karimi et al., 2013). Bovine serum albumin (BSA) is a preferable carrier in drug delivery systems to facilitate sophisticated biological nanostructures easily adaptable to human body (Jahanshahi and Najafpour, 2006). The surface of the IONPs hence, was further conjugated with BSA. Paclitaxel, a hydrophobic anticancer agent, was chosen in the study as the model drug. The decorated multifunctional nanoparticles in this research is expected to offer advantages over conventional formulations in further studies including combination of effective tumor treatment and tumor observation during the therapy, and reducing the side effects of chemotherapy.

2. Materials and methods

2.1. Materials

L-Arginine, iron oxide nanoparticles (Fe_3O_4 – LOT#MKBG0737V), N-hydroxysuccinimide (NHS), dicyclohexylcarbodiimide (DCC), 2-(N-morpholino)ethanesulfonic acid (MES) were purchased from Sigma–Aldrich (St. Louis, MO, USA). N,N-Dimethylformamide, oleic acid, triethylamine, sodium hydroxide, potassium dihydrogen phosphate were purchased from Xilong Group (China). Bovine serum albumin (BSA – LOT#0000079719) powder was purchased from Himedia Laboratories Pvt. Ltd. (India). Sodium phosphate was purchase from Guangdong Guanhua Sci-Tech Co., Ltd. (China). 1-Ethyl-3-(3-dimethylamino-propyl) carbodiimide hydrochloride (EDC) was purchased from Merck Schuchardt (Germany). The solvents used were high-performance liquid chromatography (HPLC) grade. All other chemicals were of analytical grade and were used without further purification.

2.2. Methods

2.2.1. Preparation of IONPs decorated by OA and BSA

2.2.1.1. Amine functionalization of IONPs. 500 mg IONPs was firstly dispersed in 50 ml pH 6 (KH_2PO_4 0.1 M, adjusted by NaOH 1 M) by the tip sonicator in 5 min with 25 W of power supply (Qsonica, Model No. Q700) at room temperature. L-Arginine was dissolved in pH 6 buffer (prepared as mentioned above) to yield a solution of 1.25 mg/ml. Then, 50 ml L-arginine solution was added to dispersed-IONPs. This mixture was continuously sonicated in 30 min with 10 W of power supply at room temperature. The amine-functionalized IONPs **(A-IONPs)** were separated by an external magnet (5 cm in length) and the solution was discarded. 100 ml of distilled water was then added to the nanoparticles for washing. The washing process was repeated thrice. The sample was then dried in oven at 40 °C.

2.2.1.2. Conjugation of OA to A-IONPs. OA was conjugated to the free amine on IONPs through an amide bond linkages between carboxylates and amines (Hermanson, 2008). Firstly, 100 mg OA was activated by DCC and NHS (1:1:1) in 20 ml dimethylformamide containing 1% triethylamine (DMF-TEA) for 30 min. A dispersion of 500 mg A-IONPs in 50 ml DMF-TEA was then added to the above mixture so that the activated OA could react with the free amine on IONPs. This mixture was magnetically stirred in 120 min for the reaction (stirring rate 700 rpm with 5 cm in length of magnetic bar). The final product **(OA-IONPs)** was separated by an external magnet and washed with dimethylformamide (similar to washing process in Section 2.2.1.1). The sample was then dried in oven at 40 °C.

2.2.1.3. Conjugation of BSA to OA-IONPs. BSA was also conjugated to the residual free amine on OA-IONPs through an amide bond linkages between carboxylates and amines (Hermanson, 2008). First, 150 mg of BSA was activated by 408 mg of EDC and 302 mg of NHS in 250 ml MES buffer (pH 6). This mixture was kept magnetically stirring for 30 min at room temperature (stirring rate 700 rpm with 5 cm in length of magnetic bar). The activated BSA was then reacted with the residual amine group by adding 250 ml of pH 7.5 (16% of NaH_2PO_4 0.1 M and 84% of Na_2HPO_4 0.1 M, adjusted by NaOH 1 M) containing 300 mg of OA-IONPs to the above mixture. The BSA-conjugated OA-IONPs (**BOA-IONPs**) were obtained after