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Biodistribution and *in vivo* performance of fattigation-platform theranostic nanoparticles

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ABSTRACT

This study was aimed at characterizing superparamagnetic nanoparticles surface-functionalized with gelatin-oleic acid (GOAS-MNPs) and loaded with paclitaxel by assessing the pharmacokinetics and biodistribution of paclitaxel in tissues and the *in vivo* efficacy of antitumor activity after the administration of the drug. Initially, instrumental analysis was performed to examine the particle size distribution, surface charge, and morphology of the paclitaxel-loaded GOAS-MNPs. Furthermore, we evaluated their magnetic properties and performed T2-weighted magnetic resonance imaging (MRI) on cells. We intravenously administered Taxol® and paclitaxel-loaded GOAS-MNPs and compared the pharmacokinetics, biodistribution, and antitumor efficacies of the two formulations. Determination of the pharmacokinetics and the biodistribution of paclitaxel-loaded NPs showed that this formulation increased the systemic circulation time of paclitaxel and regulated its transport to tissues. The *in vivo* antitumor efficacy of the paclitaxel-loaded NPs was better than that of Taxol® at the same dose. Furthermore, the paclitaxel-loaded GOAS-MNPs were found to be effective as contrast agents for enhanced MRI in cancer cells. Thus, GOAS-MNPs could be an effective diagnostic system for cancer and for the delivery of paclitaxel with better therapeutic effects and a significant reduction in toxicity.

1. Introduction

Paclitaxel is effective against various cancers and shows particularly promising results in patients with breast and ovarian cancers [1]. Because paclitaxel is highly hydrophobic and poorly soluble in aqueous media, it has a low therapeutic index [1,2]. Recently, increasing efforts have been made toward developing paclitaxel formulations for cancer treatment. Many studies are being performed to develop a paclitaxel formulation with reduced toxicity compared to that caused by Cremophor® EL. Various approaches, such as the formation of emulsions [3], liposomes [4], conjugates [5], nanoparticles (NPs) [6–10], lipid nanocapsules [1] and water-soluble prodrugs [11,12], have been investigated to increase drug efficacy and reduce the side effects of the Taxol® formulation.

Recent advances in the field of nanotechnology have enabled the development of promising diagnostic agents for the imaging of health and disease conditions and for drug discovery and therapeutic delivery [13]. Especially, hybrid materials and inorganic materials are promising materials for theranostics [9,10,14–28]. Compared to conventional dosage forms, NPs have many advantages. In addition to protecting a drug from biodegradation, NPs can target the delivery of the drug to the site of action and reduce the side effects of chemotherapy [26,29,30]. The most promising application of NPs is their use in anticancer treatment. Generally, solid tumors show hypervascular permeability and impair lymphatic drainage, which creates enhanced permeability and retention (EPR) at the tumor site [31–33]. Thus, NPs show significant accumulation in the tumor and may be useful as sustained-release formulations for injection because of their small size. Furthermore, magnetic resonance imaging (MRI) is an appealing noninvasive approach for clinical diagnosis [34]. However, MRI may lack the sensitivity required to scan small tumors because of the low contrast between tumor tissue and normal tissues. Thus, it is very interesting to develop magnetic nanoparticles (MNPs) with dual roles as carriers for the delivery of anticancer drugs and as imaging contrast agents for biomedical applications. Iron oxide NPs can serve as contrast agents in MRI and enhance the detection of lesions within the body [35]. Therefore, MNPs could be used simultaneously to visualize tumors with MRI and to administer drug therapy.

We have successfully synthesized surface-functionalized magnetic nanoparticles (GOAS-MNPs) in our previous studies [36]. These paclitaxel-loaded NPs had lower cytotoxicity but a similar anticancer effect as that of Taxol®. In this study, we characterized and evaluated the *in*

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vivo efficacy of this nanoparticle system as a novel drug-delivering MRI contrast agent. We determined the pharmacokinetic behavior, biodistribution, and *in vivo* antitumor activity of this system and compared them with those of Taxol®. These studies proved that these paclitaxel-loaded NPs had many advantages, such as better antitumor efficacy and increased systemic circulation time.

2. Materials and methods

2.1. Materials

Fetal bovine serum (FBS), Dulbecco's modified Eagle's medium (DMEM), penicillin-streptomycin mixtures and trypsin-EDTA were supplied from Gibco BRL (Carlsbad, CA, USA). EMT-6 and CT26 cell lines were purchased from American Type Culture Collection (ATCC, USA). Tetraethyl orthosilicate (TEOS), iron (II) chloride, iron (III) chloride, *N*-hydroxysuccinimide (NHS), dicyclohexylcarbodiimide (DCC), N^1-(3-trimethoxysilylpropyl)diethylenetriamine (DETA), gelatin (GEL), 2,4,6-trinitrobenzenesulfonic acid (TNBS), 1-ethyl-3-(3-dimethylamino-propyl)carbodiimide (EDC), Cremophor EL, 2-(*N*-morpholino)ethanesulfonic acid (MES), and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide) (MTT) were purchased from Sigma (St. Louis, MO, USA). Anhydrous dimethylformamide (DMF) was purchased from J. T. Baker (Phillipsburg, USA). Oleic acid (OA) was supplied from Shinyo Pure Chemicals Co., Ltd. (Osaka, Japan). Triethylamine was purchased from Showa (Osaka, Japan). Agar was obtained from Difco Laboratories (Detroit, USA). Paclitaxel was supplied from Dae Woong Pharmaceutical Co., Ltd. (Seoul, Korea).

2.2. Methods

2.2.1. Preparation of surface-functionalized magnetic nanoparticles (GOAS-MNPs)

GOAS-MNPs were developed in several primary steps according to the methods used in our previous studies [36]:

(1) Iron oxide NPs, *i.e.*, MNPs, were prepared by co-precipitation of $FeCl_3 \cdot 6H_2O$ and $FeCl_2 \cdot 4H_2O$ with ammonium hydroxide according to the method reported previously [37].
(2) Iron oxide NPs were added to 100 mL of absolute ethanol (0.5 mg/mL), 5 mL of water, 2.5 mL of ammonium hydroxide (28–30 wt%), and 1 mL TEOS. This mixture was allowed to react for 5 h. Then, silanization of the NPs was performed to functionalize the amines on the surface of the NPs [38]. We used 20 mL of 1% DETA in 1 mM acetic acid to disperse 30 mg of silica-coated iron oxide NPs. The amine-functionalized nanoparticles (AS-MNPs) were formed by a 30 min reaction at room

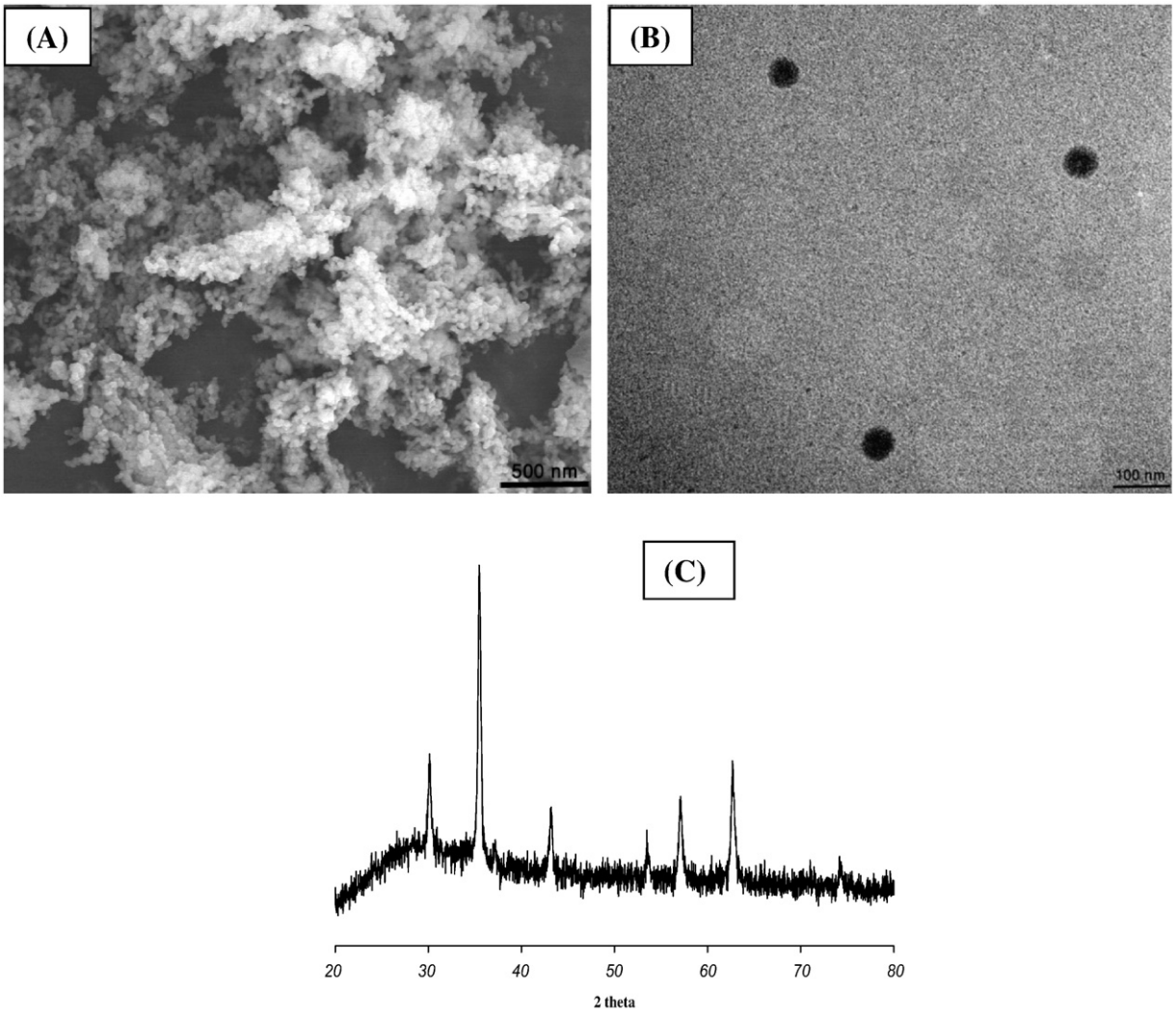

Fig. 1. Characterization of paclitaxel-loaded surface-functionalized magnetic nanoparticles (GOAS-MNPs) using scanning electron microscopy (SEM) (A), transmission electron microscopy (TEM) (B), and powder X-ray diffraction (PXRD) patterns (C).