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The characteristics, biodistribution, magnetic resonance imaging and biodegradability of superparamagnetic core–shell nanoparticles

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ABSTRACT

An efficient contrast agent for magnetic resonance imaging (MRI) is essential to enhance the detection and characterization of lesions within the body. In this study, we described the development of biodegradable nanoparticles with a core–shell structure to formulate superparamagnetic iron oxide (CSNP–SPIO) for MRI. The developed nanoparticles were composed of a hydrophobic PLGA core and a positively-charged glycol chitosan shell. The results obtained by transmission electron microscopy, energy dispersive X-ray analysis, electron energy loss spectroscopy, and X-ray diffraction measurement confirmed that the prepared nanoparticles had a core–shell structure with SPIO in their core area. No aggregation of nanoparticles was observed during storage in water, as a result of the electrostatic repulsion between the positively-charged nanoparticles. The magnetic properties of nanoparticles were examined by a vibrating sample magnetometer and a superconducting quantum interference device; the results showed that the superparamagnetism of SPIO was preserved after the CSNP–SPIO formulation. In tracking their cellular internalization pathway, we found that CSNP–SPIO accumulated in lysosomes. In the biodistribution study, a high level of radioactivity was observed in the liver shortly after administration of the ^{99m}Tc-labeled CSNP–SPIO intravenously. Once taken up by the liver cells, the liver turned dark on T_2^* images. Following cellular internalization, CSNP–SPIO were broken down gradually; therefore, with time increasing, a significant decrease in the darkness of the liver on T_2^* images was found. The aforementioned results indicate that the developed CSNP–SPIO can serve as an efficient MRI contrast agent and could be degraded after serving their imaging function.

1. Introduction

Magnetic resonance imaging (MRI) has become an appealing noninvasive approach in clinical diagnosis; a key to this success has been the development of efficient magnetic contrast agents [1]. The application of magnetic contrast agents in MRI enhances the detection and characterization of lesions within the body [2]. Dextran-based superparamagnetic iron oxide (SPIO) nanoparticles have been extensively used clinically as MRI contrast agents. These dextran-based SPIO nanoparticles are taken up by phagocytic cells and accumulate in the reticuloendothelial system (RES) such as the Kupffer cells of the liver; thus, they are commonly used as a contrast agent for liver MRI [3]. However, SPIO nanoparticles are not strongly associated with dextran and can be readily detached, leading to their aggregation and precipitation under physiological conditions [4]. Additionally, these dextran-based SPIO nanoparticles are limited in their capacity of drug loading and the drug dissociates rapidly after administration intravenously [5].

Biodegradable polymers such as poly(D,L-lactic-co-glycolic acid) (PLGA) have been used to encapsulate SPIO in the form of nanoparticles [6]. These nanoparticles can be utilized for multifunctional biomedical applications with simultaneous drug-delivery and

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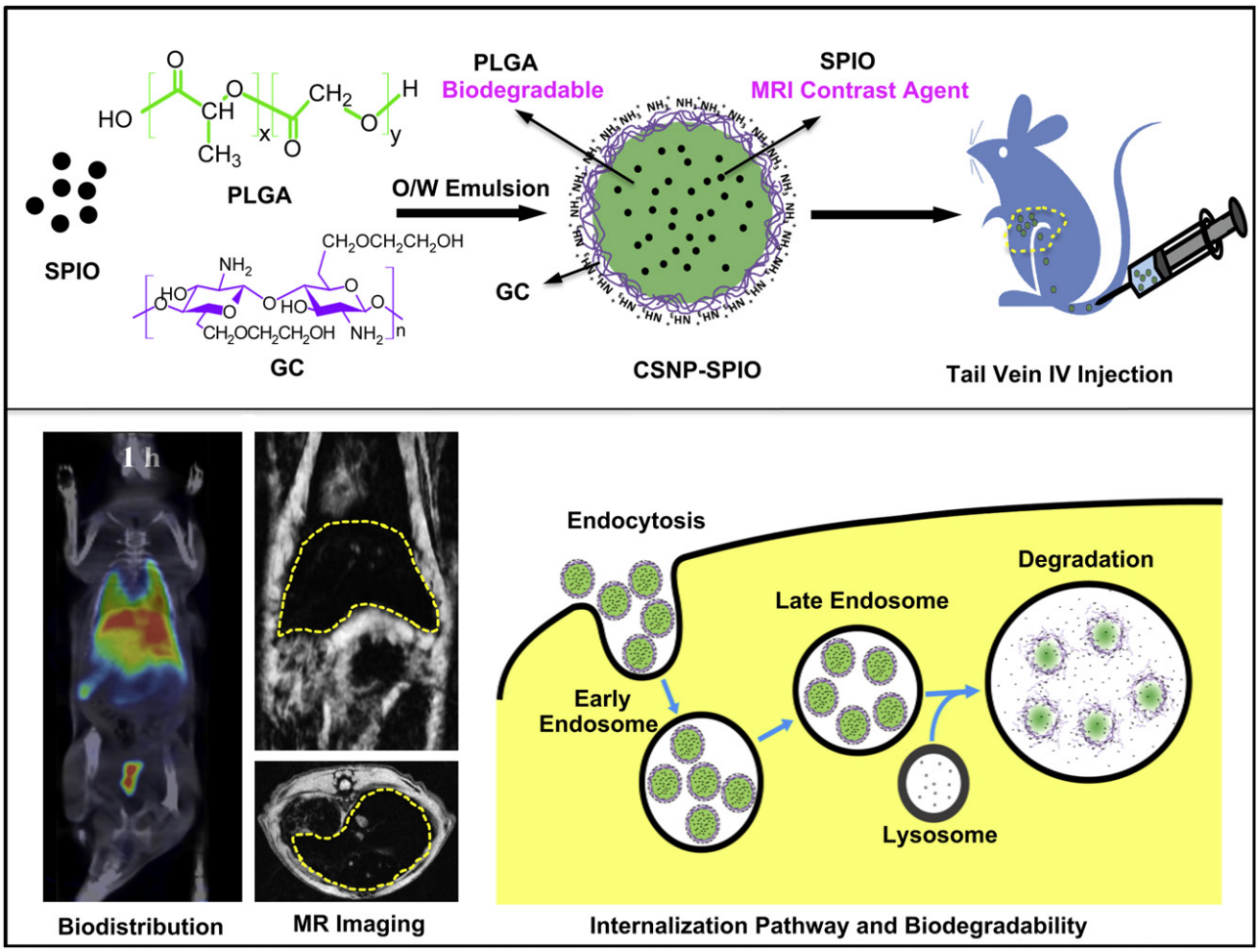

Fig. 1. Schematic illustrations of polymeric nanoparticles with a core–shell structure developed in the study for loading superparamagnetic iron oxide (CSNP–SPIO). The study was designed to investigate the characteristics, biodistribution, magnetic resonance imaging, and biodegradability of the developed CSNP–SPIO. PLGA: poly(D,L-lactic-co-glycolic acid); GC: glycol chitosan.

imaging capabilities [7]. However, the lack of functional groups on the surface of PLGA nanoparticles for covalent modification has limited their potential for surface tethering targeting ligands [8].

In this study, we describe the development of biodegradable nanoparticles with a core–shell structure to formulate SPIO (CSNP–SPIO) for MRI. The developed nanoparticles are composed of a hydrophobic PLGA core and a hydrophilic glycol chitosan (GC) shell (Fig. 1). GC is a derivative of chitosan and has been used as drug-delivery carriers [9–11]; it is hydrophilic, biodegradable, and low immunogenic [12]. It has been reported that nanoparticles surface-modified by GC significantly decrease their excretion from the body and thus prolong their circulation time in blood; this might maximize the likelihood of their reaching targeted tissues [13]. The study was designed to investigate the characteristics, biodistribution, MRI, and biodegradability of the developed CSNP–SPIO (Fig. 1).

2. Materials and methods

2.1. Materials

PLGA (lactide/glycolide molar ratio of 75:25, inherent viscosity 0.17 dl/g) was obtained from BioInvigor (Taipei, Taiwan). Polyvinyl alcohol (PVA, MW = 30–70 kDa), GC (MW = 250 kDa), and dichloromethane (DCM) were acquired from Sigma–Aldrich (St. Louis, MO, USA). SPIO were prepared according to a previously reported thermal decomposition method [14]. All other chemicals and reagents used were of analytical grade.

2.2. Preparation of CSNP–SPIO

CSNP–SPIO were prepared by an emulsion–diffusion–evaporation method. Briefly, PLGA (10 mg/ml) and SPIO (2 mg/ml) were dissolved in DCM. The prepared organic solution (4 ml) was added into an aqueous solution (8 ml) containing PVA (1.0% w/v) and GC (0.2% w/v) and then emulsified with a homogenizer (Polytron PT-1200, Kinematic AG, Littau, Switzerland) for 5 min and followed by 10 min of sonication (Sonics & Materials, Newtown, CT, USA). The mixture was then transferred into 100 ml deionized (DI) water and allowed to stir overnight at room temperature in a fume hood to evaporate the organic solvent. The prepared CSNP–SPIO were collected by centrifugation (60 min, 9000 rpm), washed three times with DI water, and then resuspended in DI water.

The size distribution and zeta potential of the prepared nanoparticles were measured using a dynamic light scatter (DLS, Zetasizer, 3000HS, Malvern Instruments Ltd., Worcestershire, UK). Aggregation of the prepared nanoparticles may occur, thus leading to lose their structural integrity [15]. To study their stability, the prepared nanoparticles were suspended in DI water at 4° C for up to 1 month and their particle size and zeta potential during storage were monitored by DLS. X-ray

Table 1
Particle size, polydispersity index, and zeta potential of PLGA nanoparticles (NP), core–shell nanoparticles (CSNP), and core–shell nanoparticles loaded with SPIO (CSNP–SPIO) in deionized water ($n = 5$).

	Particle size (nm)	Polydispersity index	Zeta potential (mV)
NP	180.7 ± 8.1	0.12 ± 0.01	−8.2 ± 0.9
CSNP	208.5 ± 11.3	0.13 ± 0.04	29.6 ± 4.0
CSNP–SPIO	273.6 ± 15.7	0.13 ± 0.01	28.1 ± 3.2