Journal of Photochemistry & Photobiology, B: Biology 160 (2016) 210–216

Contents lists available at ScienceDirect

Journal of Photochemistry & Photobiology, B: Biology

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

Caffeic acid-coated multifunctional magnetic nanoparticles for the treatment and bimodal imaging of tumours

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ARTICLE INFO

Article history:
Received 1 September 2015
Received in revised form 30 March 2016
Accepted 31 March 2016
Available online 13 April 2016

Keywords:
Tumour theranostic
Iron oxide nanoparticles
MRI contrast agent
Photodynamic therapy
Tumour-target ligand

ABSTRACT

Accurate theragnosis of tumour is essential for improving the life rate of tumour patients. Superparamagnetic iron oxide nanoparticles (SPIONs) have been used as both diagnostic and therapeutic agents. However, their application is often limited because of a lack of water solubility, lack of cancer treatment efficacy, and ineffective targeting of tumour cells. In this report, a double ligand (caffeic acid–polyethylene glycol–folic acid; FA–PEG–CA, caffeic acid–polyethylene glycol–pheophorbide-a; PheoA–PEG–CA) coated iron oxide nanoparticle has been fabricated that overcomes the limitations of conventional SPION. Photosensitizer and tumour targeting ligands were coated on SPION using a ligand-substitution method. We confirmed the successful substitution of oleic acid ligands with FA–PEG–CA and PheoA–PEG–CA ligands by FT-IR spectroscopy. The caffeic acid coated iron oxide nanoparticles (CAMNPs) also demonstrated high water solubility in an aqueous environment and folate-mediated active tumour targeting. The water solubility of CAMNPs was evaluated by DLS measurement and TEM images. The cytotoxicity of CAMNPs increased two-fold in MDA-MB-231 cells at a laser irradiation condition. The fabricated CAMNPs retained their ability to function as both MRI diagnostic and tumour-selective therapeutic agents. These results suggest that these efficient characteristics of CAMNPs can be incorporated into applications, thus enhancing the efficacy of clinical cancer treatment.

1. Introduction

In contemporary drug delivery research, nanocarriers with miscellaneous functions are viewed as one of many prominent methods for tumour treatment [1,2]. In particular, various imaging probes have been combined into nanoparticles to constitute an even more sensitive and accurate tumour diagnosis probe [3,4]. Moreover, when therapeutic modalities are incorporated into these nanocarriers, it leads to an even greater potential for therapeutic applications because it enables the simultaneous diagnosis and treatment of tumours [5]. However, nanocarriers often run into many challenges in *in vivo* environments [6]. One of the crucial reasons of failure in cancer therapy that is based on nanocarriers is low delivery efficiency into the tumour microenvironment. This often results because of two causes: first, a high density of cells and drug resistance manifest in tumour cells [7] and, second, an absence of active targeting methods for nanocarriers to be guided to the tumour site [8]. Indeed, these limitations of contemporary nanocarriers cannot be overlooked in order for them to be used in clinical applications.

Superparamagnetic iron oxide nanoparticles (SPIONs) have been widely recognized in previous reports as being capable of magnet-induced hyperthermia [9] and magnetic targeting [10] in addition to functioning as magnetic resonance imaging (MRI) agents [11]. Despite the versatility of SPIONs in therapeutic applications, it has been difficult to reach good clinical outcomes because of their limitations, such as low water solubility for use in *in vivo* applications and active targeting efficacy at tumour sites. In addition, conventional SPIONs, which rely on magnet induced hyperthermia and targeting, were reported to emit heat only at close vicinities to their surfaces and to undergo significant magnetism loss when incorporated into the core of polymeric nanocarriers [9,12,13]. Acknowledging the drawbacks of conventional SPION-mediated therapies, it was believed that additional modalities would enhance their therapeutic effects *in vivo*.

Along with SPIONs, photosensitizers (PS) are also well recognized means of cancer treatment. In photodynamic therapy (PDT), PS emit reactive oxygen series (ROS) when irradiated under a certain wavelength of light. ROS, such as free radicals and singlet oxygen, lead to tumour cell apoptosis [14]. Because ROS directly attack the plasma membrane of tumour cells during PDT, they allow for the drug resistant properties of tumours to be overcome [15]. Even so, it is paramount that PS are in close proximity to the tumour when undergoing light irradiation because ROS have a short reach (15–20 nm) [16]. In this regard, it is essential that the nanocarriers must first be guided to the tumour site

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http://dx.doi.org/10.1016/j.jphotobiol.2016.03.058
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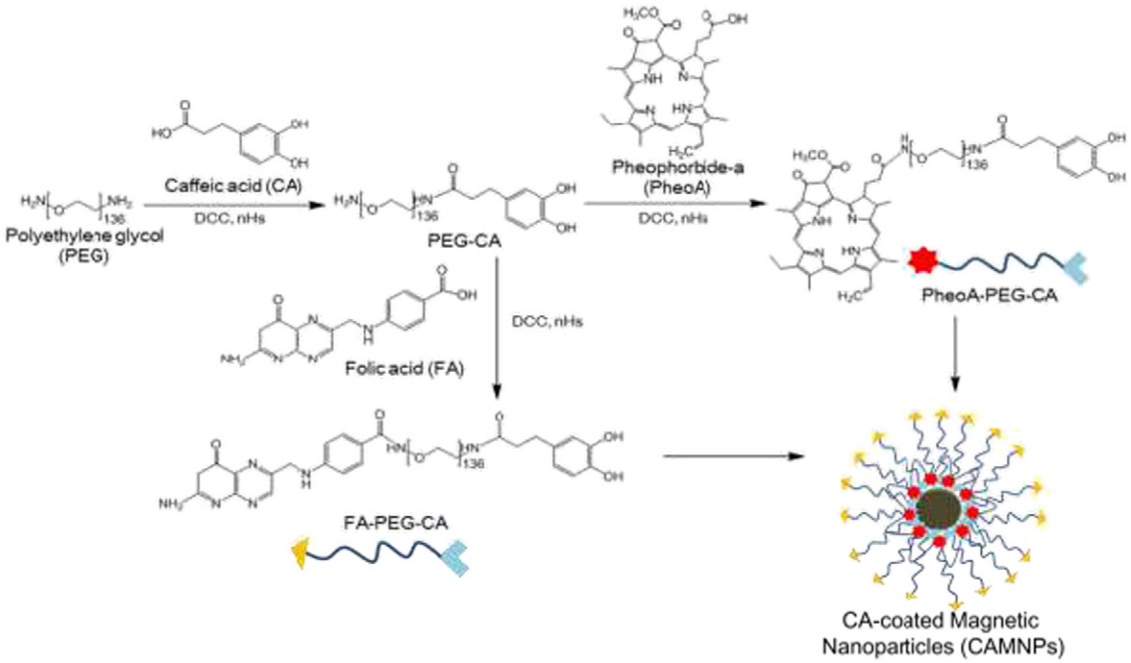

Scheme 1. Schematic representation of the synthetic route of caffeic acid-coated multifunctional magnetic nanoparticles (CAMNPs).

for effective PDT to take place. Conventional nanocarriers used for PDT have often relied on passively targeting tumour cells by the enhanced penetration and retention (EPR) effect and, consequently, have provided limited targeting to tumour sites. However, active targeting can be an effective solution that can be used to enhance tumour site accumulation. Previous reports have performed active targeting by using pH-responsive nanocarriers, targeting ligands, and other methods [11,17].

The goal of this study is to develop caffeic acid-coated multifunctional magnetic nanoparticles (CAMNPs) that are capable of the treatment and bimodal imaging of tumours. CAMNPs composed of polyethylene glycol (PEG), SPIONs, pheophorbide A (PheoA), folic acid (FA) and caffeic acid (CA) will be introduced; their features can effectively aid in their use in clinical applications by enabling simultaneous cancer therapy and bimodal imaging. SPIONs are used as a contrasting agent

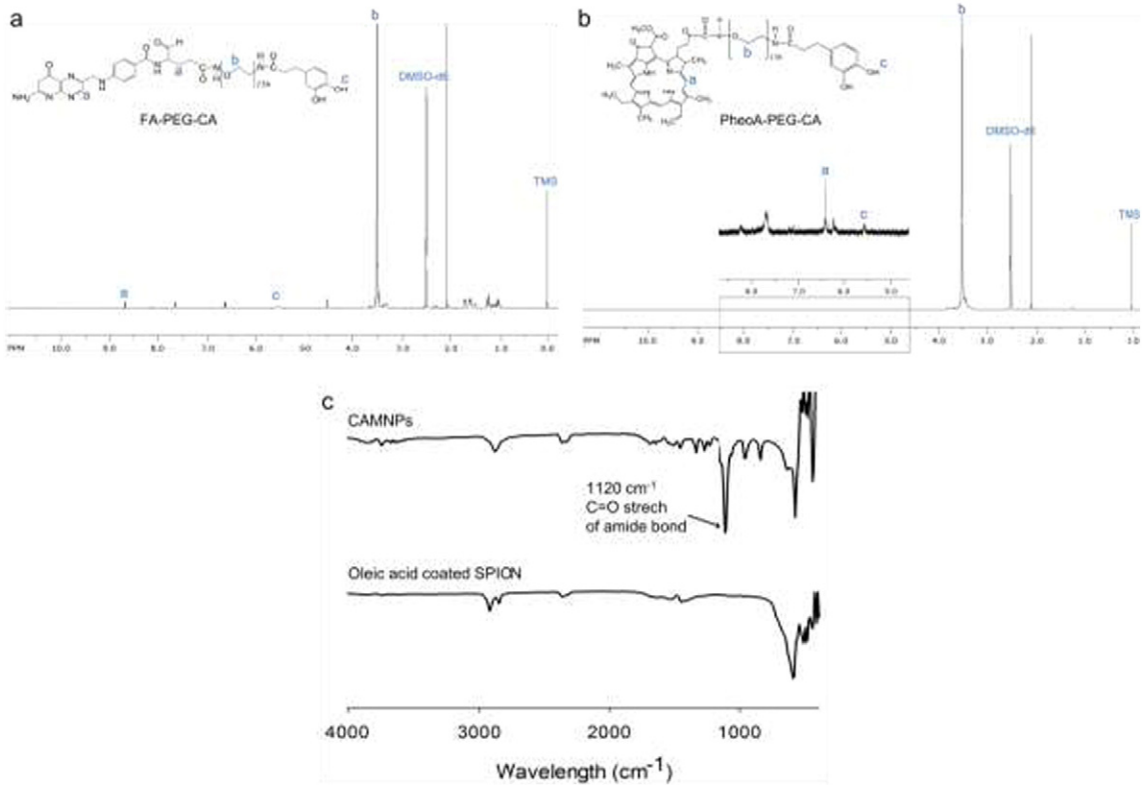

Fig. 1. a) ^{1}H NMR analysis of FA–PEG–CA. The synthesized FA–PEG–CA exhibited a —CH peak of FA at 8.7 ppm and a —OH peak of CA at 5.6 ppm. b) ^{1}H NMR analysis of PheoA–PEG–CA. The synthesized PheoA–PEG–CA exhibited a —CH peak of PheoA at 6.5 ppm and a —OH peak of CA at 5.6 ppm. c) FT-IR analysis of CAMNPs.