Synthesis and Characterization of Multifunctional Dextran/Pluronic F127-Iron oxide Nanocarrier for Doxorubicin Delivery in Liver Cancer Treatment

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Liver cancer remains a leading cause of cancer-related mortality worldwide, claiming the lives of millions globally. It accounts for about 9.1% of all cancer deaths worldwide with 782,000 new cases diagnosed in 2012. Application of nano-drug delivery system (NDDS) has attracted remarkable attention in the medical field. The NDDS can not only improve targeted drug delivery to the liver or improve the bioavailability of drug, but also can reduce the side effects of chemotherapy. Therefore, the objective of the study was to develop dextran and Pluronic F127 stabilized magnetic iron oxide nanoparticles (DSPIONs and PSPIONs) through a solvothermal method. The developed nanoparticles will be used as carriers of doxorubicin (DOX) drug for the treatment of liver cancer. Furthermore, several characterization techniques such as TEM, CryoTEM, XRD, FTIR, XPS, TGA, XANES, EXAFS, SANS, and SAXS were used to further analyze the properties of the prepared nanoparticles. Furthermore, the XRD patterns indicated the crystallization of the prepared nanoparticles with diffraction peak of at $2\theta = 35.44°$ corresponded to that of magnetite (Fe_3O_4) (311). The XANES spectra of the Fe atom in the different samples depicted an absorbance feature (Fe = 7112 eV) of a *1s* to *3d* transition. The SANS spectra was used to probe changes in the core-shell structure of dextran/Pluronic F127 micelles as a function of increasing DOX and polymer concentrations in order to predict the drug loading and release mechanisms. Regarding the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, no significant cell toxicity was observed among the cells (293T, HepG2 and Huh7) treated with different concentrations of IONPs, DIONs, and PIONPs. This study established a multidisciplinary work to stablish new formulation of DOX in treatment of liver cancer with consequent improvement treatment. DIONs and PIONPs based drug delivery system would be a potential tool to enhance targeting delivery of conventional chemotherapeutic drugs and MRI imaging.

Keywords: Drug delivery, Magnetic iron oxide nanoparticles, Dextran/Pluronic F127, Doxorubicin, Liver cancer, SANS, XANES/EXAFS.

Introduction

Nanomaterials have recently emerged in the research fields of chemistry, biotechnology, and biomedicine. In biomedical applications, inorganic nanomaterials (INMs) have attracted much attention in bio imaging, targeted drug delivery and cancer therapies [1,2]. Through nanomaterials fabrication into vesicles, innumerable nanocarriers have been developed for bioimaging/diagnosis and delivery of drugs and various therapeutic agents into targeted sites [3]. Nanocarriers usually incorporate drugs via encapsulation, surface attachment or entrapping, which alters the drug pharmacokinetics in vivo. Recently, the development of synthesis techniques, including the ability to fabricate molecules and supramolecular structures for intended functions, has promoted the use of engineered nanomaterials. This has led to the emergence of new DDSs based on inorganic nanoparticles. Compared with the conventional DDSs, most inorganic-based DDSs are still in their pre-clinical stage of development. However, due to the ease of synthesis and modification, the inorganic nanoparticle size, shape and surface properties can be facilely controlled [2,3]. Among these inorganic nanomaterials, iron oxide nanoparticles have been one of the potential nanoparticles for biomedical applications. Iron oxide nanoparticles are biocompatible, biodegradable and non-cytotoxic and also show interesting properties, such as super-paramagnetism, irreversibility of high field magnetization, high photo thermal effect. One sensational news is that super-paramagnetic nanoparticles based on Fe_3O_4 have have been approved as high-performance contrast agents in magnetic resonance imaging (MRI). Fe_3O_4 nanoparticles can be used as a contrast agent which will enhance the contrast and imaging effect of MRI [3].

Experimental

Iron oxide nanoparticles were synthesized via solvothermal method whereby 1.08 g of $FeCl_3.6H_2O$, 0.25g of trisodium citrate and 1.6 g of sodium acetate were dissolved in a mixture of EG (40 mL) and DEG (10 mL) under vigorous stirring for 30 min. The solution was then

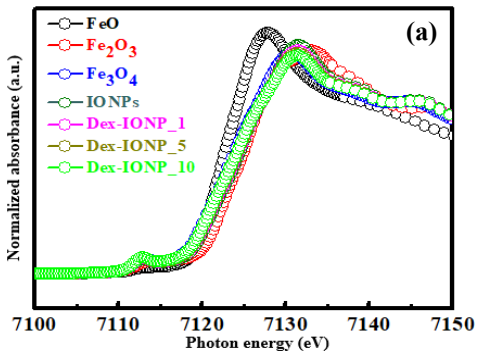
transferred into a Teflon- lined stainless-steel autoclave and heated for 10 h at 200℃, and then coated with different dextran and pluronic F127 concentrations.

Results

The XANES spectra was performed to provide information about on-site symmetry, chemical species and oxidation state of the absorbing atom. XANES spectra for iron oxide nanoparticles and dextran coated iron oxide nanoparticles were recorded. As illustrated in **Fig. 1(a)**, The XANES spectra for iron oxides indicate that they are Fe_3O_4 nanoparticles. This is because the main peak of the magnetic nanocarrier is located between Fe^2 and Fe^3 iron with the curve fitting more to Fe_3O_4. Standard Fe–O bond distance was determined using EXAFS spectra in IONP and Dex–IONP samples and was 1.95 Å, with co-ordination numbers, 3.71, 3.90, 4.08, 4.13 and 3.72 respectively (**Fig. 1(b)**. The SANS spectra for F127 coated nanoparticles indicate that they had an ellipsoid shape as shown in **Fig**. **1(c).**

Discussion

The obtained results indicate that the magnetic nanocarriers were synthesized properly and are crystalline in nature as illustrated by the XANES spectra in **Fig. 1(a)**. XRD patterns also confirmed the crystallinity of the prepared nanocarriers as characteristic peak (311) for magnetite nanoparticles was observed. The EXAFS spectra results illustrated that the Fe-O distance is about constant (1.95 ± 0.02 Å) for all the samples. The CN value was (4± 0.05) since Fe_3O_4 has an inverse spinel structure, this indicates the tetrahedral structure around the center Fe atom, the slight decrease in the CN of the polymer coated nanoparticles is due to the protective function of polymer to the particles, as it stabilizes it. The ellipsoid shape of nanoparticles as indicated by SANS spectra is important for efficient drug loading and long half-life of the magnetic nanocarriers in the circulation, thus delivering enough drug to the cancerous cells in the targeted side. The magnetite iron oxide nanoparticles coated with different concentrations of dextran and pluronic F127 also possessed no cytotoxicity to cells. Overall the obtained results show that the magnetic nanocarriers are suitable to be used as drug delivery vehicles to targeted sites without causing damage to normal cells.



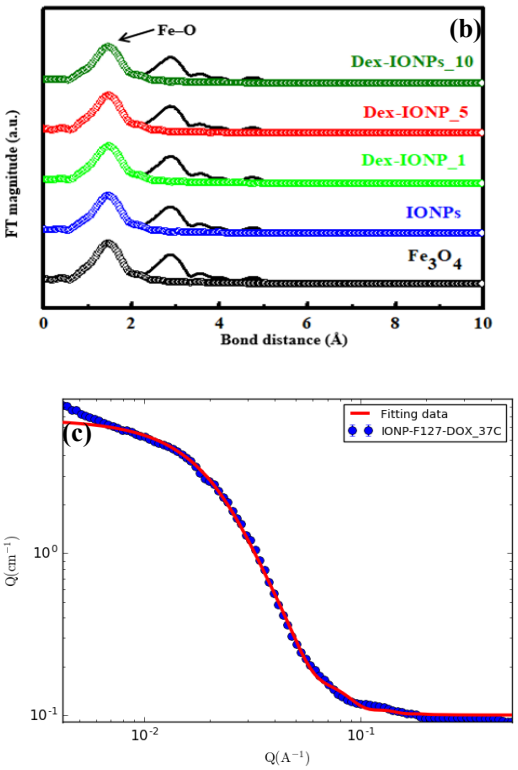


Fig. 1. (a) Fe K–edge derivative XANES spectra of Dex–IONPs samples and iron standards. (b) EXAFS spectra of Dex-IONPs (c) The SANS spectra of IONP–F127-DOX at 37 ℃.

Acknowledgments

The financial support of the Ministry of Science and Technology (MOST), Taiwan, R.O.C. (MOST 105–3113–E–008–003) is gratefully acknowledged. We also thank Dr. Chun-Ming Wu and Dr. Shih-Chun Chung of Taiwan Neutron Team serviced in the Australian Nuclear Science and Technology Organization (ANSTO) for their helps in the SANS experiments.

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