Formulation of Iron Oxide-Silica Nanocarrier for Doxorubicin Delivery in Liver Cancer Therapy

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Liver cancer is one of the serious diseases that threaten the lives of millions around the globe. It accounts for about 9.1% of all cancer deaths worldwide. Studies regarding the diagnosing and treatment of liver cancer have attracted tremendous attention in the medical field. The common treatments available for liver cancer have been reported to be accompanied by several side effects. Therefore, in an effort to overcome the limitations in liver cancer treatment, the present study aims at developing silica coated magnetic iron oxide nanoparticles (IONP-SiO_2) through a solvothermal method. These nanoparticles will act as carriers of doxorubicin (DOX) drug for the treatment of liver cancer. Core-shell of monodispersed and spherical shaped particle sizes of about 20-50 nm were obtained using the Cryo-TEM. The XANES spectra of the Fe atom in the different samples demonstrated an absorbance feature (Fe = 7112 eV) of a *1s* to *3d* transition. The characteristic peaks at 1085, 800 and 460 cm^{-1} correspond to the stretching, bending and out of plane of Si-O bonds, respectively, indicating the successful coating of SiO_2 on the surface of IONPs. The SANS spectra revealed SiO_2' poor thermo-sensitivity; however, after surface modification with temperature sensitive Pluronic P123, changes in the core-shell structure were observed. SANS studies, help us to predict the changes in the core-shell structure of the nanoparticles as results of drug loading and release. Based on using MTT assay, no significant cell toxicity was observed among the cells (293T, HepG2 and Huh7) treated with different concentrations of IONPs and IONP-SiO_2. Interestingly, MTT test showed that after DOX encapsulation, the IONP-SiO_2-DOX complex was able to induce more cell apoptosis. The in vitro studies reveled that high silica concentration lead to higher drug loading, while as the drug release profile showed a pH-dependent drug release, where more DOX was released under acidic environments than in neutral conditions.

Keywords: Drug delivery, Magnetic iron oxide nanoparticles, Silica oxide, Pluronic P123, Doxorubicin, XANES/EXAFS, SANS, Liver cancer.

Introduction

Cancers are the main cause of mortality and health problem worldwide, and liver cancer (LC) is one of the most common. It is considered as the sixth most common cancer and the second leading cause of cancer deaths around the world [1]. Targeted therapies with the goal of accumulation of drug/gene inside cancer cells lead to more effective treatments with fewer side effects. Advances in nanotechnology, reform drug delivery systems (DDSs) by giving more hands on loading of wide range of drugs, biocompatibility, physiological stability, targeting means, the ability to cross the barriers, and in vivo controlled release [2]. Midst various mesoporous materials, mesoporous silica nanoparticles, MSNs, are a promising class of porous materials with exceptional surface properties including high specific surface area as well as pore size that is beneficial to maximum drug loading. Several types of nanoparticles comprising of magnetic nanoparticles (MNPs) presents extraordinary opportunities for drug/gene delivery [3]. Iron oxide nanoparticles (IONPs) which have magnetic properties possess a promise to transform current imaging,

diagnostic, and therapeutic applications. These IONPs have diameters ranging from 1 and 100 nanometer with the core containing magnetite (Fe_3O_4) or maghemite (Fe_2O_3) or a nonstoichiometric configuration of both [3-4].

Therefore, this study aimed to formulate functionalized IONPs with the ability to affect tumor cell viability. IONPs, both coated with silica shell and bare uncoated, were synthesized and functionalized. Silica was used for its ability to protect the magnetic core from oxidation, to improve the magnetite stability and to tailor the surface reactivity by improving biomolecule grafting [4].

Experiments

2.1. Preparation of Silica and Pluronic P123 coated iron oxide magnetic nanoparticles

The IONPs were prepared by a solvothermal method, whereby, 2.1 g of $FeCl_3.6H_2O$ and $FeCl_2.4H_2O$ with the ratio of Fe^{2+}:Fe^{3+} = 1:2 and 0.5 g sodium citrate were dissolved in 200 mL of deionized (DI) water and resulting solution was stirred for 1 h. TEOS was the used at different concentrations to coat them. The obtained silica coated nanoparticles were then further coated with different concentrations of Pluronic P123 polymer.

Results

In this study, the Small-angle neutron scattering (SANS) is a vital method to investigate details of the local, internal structure of the microgel particles. It can be seen in Pluronic P123, a temperature sensitive polymer was cross–linked with silica to improve its temperature sensitivity. The XANES technique was used to obtain the information of electronic configuration, stereochemistry, and the oxidation states of Fe atoms in the IONPs and Silica coated IONPs (**Fig. 1 a and b**). In comparison with the standard position of Fe K–edge of 7,112 eV, the magnetic carrier yielded produced oxidation valences for Fe and shifted the outstanding peak on the absorption curve to high energy.

Discussion

The prepared nanocarrier may serve as a suitable nanocarrier due to its unique crystal structure of magnetite. The silica shell causes a core-shell structure that is suitable for high drug loading capacity. In comparison with the standard position of Fe K–edge of 7,112 eV, the magnetic carrier yielded produced oxidation valences for Fe and shifted the outstanding peak on the absorption curve to high energy. he main peak of the magnetic nanocarrier is detected between Fe^{2+} and Fe^{3+} iron and the curve with more fitting on Fe_3O_4, and the normalized data through differential processing as shown **Fig. 1(a and b)** in Consequently, it can be confirmed that the magnetic nanocomposites including those coated with silica synthesized in this study is Fe_3O_4 structure. Cancer patients tend to have high fever and it is vital for our nanocarrier to be temperature sensitive. The possibility of affirming this phenomenon by SANS seems promising. However, further *in-situ* experiments are necessary to comprehend the release mechanism of the nanocarrier after its exposure to temperature. It can be inferred from the results **(Fig. 2)** that the IONPs-SiO_2 without the polymer was not temperature sensitive and thus the curve didn't show any major change. In contrast, the nanoparticles with the temperature sensitive polymer showed change. Hence, the prepared nanocarrier was considered safe as a drug nanocarrier or MRI agent to enhance targeted delivery to cancer cells. The prepared nanocarrier exhibited no significant cytotoxicity against treated cells. The cell viability was not affected by the nanoparticles while the drug loaded caused high cancer cell death.

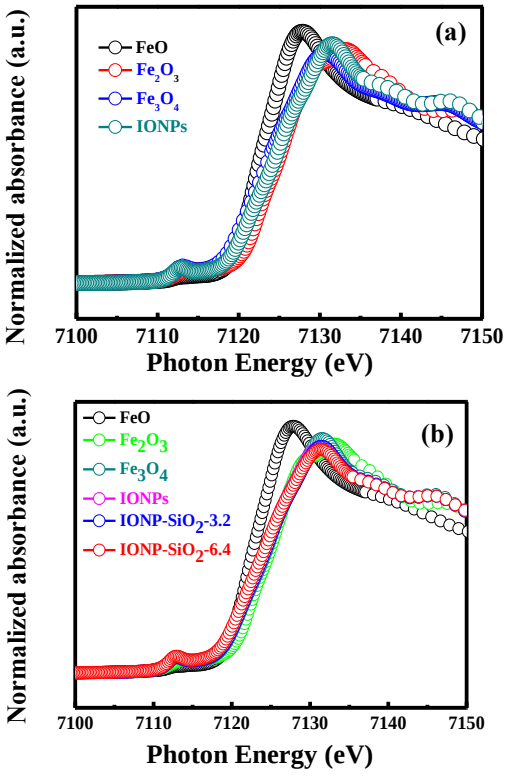

Fig. 1. (a) Fe K–edge XANES spectra of IONPs compared to different iron standards and (b) XANES spectra Fe, FeO, Fe_2O_3, Fe_3O_4 and IONP-SiO_2 at different concentrations of SiO_2.

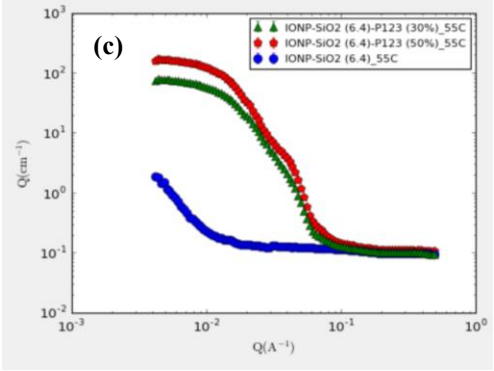

Fig. 2. SANS spectra of IONP-SiO_2, IONP-SiO_2-P123 (30%) and (50%) at 55℃.

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