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Inhibition of Neuroblastoma cancer cells viability by ferromagnetic Mn doped CeO_2 monodisperse nanoparticles mediated through reactive oxygen species

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HIGHLIGHTS

- Mn doped CeO_2 nanoparticles with cubic fluorite structure were synthesized.
- Mn dopant significantly tailored the band gap of CeO_2 nanoparticles.
- The synthesized nanoparticles exhibited room temperature ferromagnetic behavior.
- The cytotoxicity of these nanoparticles was reported for the first time.
- The synthesized nanoparticles exhibited differential cytotoxicity.

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ABSTRACT

Here we report the Mn doping induced effects on structural, Raman, optical, magnetic and anticancer properties of CeO_2 nanoparticles prepared via soft chemical route. Structural and microstructural results infer that the synthesized nanoparticles have single phase cubic fluorite structure of CeO_2 and that Mn doping results in enhancement of the structural defects. Scanning electron microscopy results reveal the formation of monodisperse nanoparticles having average particle size ranging from 30 to 41 nm. The optical absorbance spectroscopy analysis discloses the band gap energy tailoring of CeO_2 nanoparticles via Mn doping. Room temperature ferromagnetism (RTFM) has been found in both as-prepared and Mn doped CeO_2 nanoparticles. This RTFM of the synthesized nanoparticles have been attributed to the Mn ions and surface defects such as oxygen vacancies. Finally, the influence of Mn dopant on the cell viability and reactive oxygen species (ROS) generation levels of CeO_2 nanoparticles in the presence of healthy and cancerous cells have been studied. It has been observed that the differential cytotoxicity of the synthesized nanoparticles is strongly correlated with level of ROS generation.

1. Introduction

Being an important oxide catalyst, ceria (CeO_2) is widely used from a long time as a three way catalyst such as photocatalytic degradation catalyst for environmental and biological hazards and catalyst supports [1–3]. The catalytic characteristics of CeO_2 are instigated from its exceptional properties such as redox reactions, structural defects like oxygen vacancies, high surface area, high oxygen storage capacity and revelation of exceedingly reactive facets during catalysis [4,5]. The catalytic activity of CeO_2 can be efficiently enhanced by controlling the above mentioned factors via doping some transition ion (for instance, Mn^{3+}) [6]. It has been reported that scaling down the CeO_2 into nanoscale lead to enhanced catalytic activity due to higher structural defects and larger surface area [7]. The catalytic activity of CeO_2 nanomaterials can be further enhanced by either loading noble metal on it or selective metal doping [8–10]. Selective metal doping into the host matrix is an easy and effective approach in order to control the properties of metal oxides nanostructures [11,12]. Doping CeO_2 nanomaterials with different ionic states can enhanced its catalytic activity remarkably because dopant can distort the lattice structure

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and create large number of structural defects such as oxygen vacancies due to replacement of Ce^{4+} [13]. For instance, Fe doped CeO_2 nanoparticles have been reported to have greater photocatalytic activity as compared to undoped nanoparticles which is assigned to narrowing of band gap and larger surface area of doped nanoparticles [14]. N. Sabari Arul et al. have reported that the surface area and morphology play important role in the enhanced photocatalytic activity of Co doped CeO_2 nanorods [15]. Manganese (Mn) being one of the most common transition metal is considered to be the best dopant for CeO_2 because of its smaller ionic radii as compared to Ce ions [6]. Hence, Mn doped CeO_2 nanomaterial may solve the problems in the photocatalytic activity of CeO_2 based catalysts. In the literature, it has been reported that Mn dopant can cause the formation of large amount of defects in CeO_2 crystal structure which led to remarkably higher catalytic performance [16]. It is well established fact that reactive oxygen species (ROS) play vital role in the inhibition of cancerous cells by metal oxides nanomaterials which in return depends on the defects states in the system [17]. Hence, it is believed that Mn doping can lead to enhanced anticancer activity of CeO_2 nanoparticles. Till date, to the best of our knowledge no article is published on the anticancer activity of Mn doped CeO_2. Keeping this in view, Mn dopant induced effects on the ferromagnetic and cytotoxicity of the CeO_2 nanoparticles synthesized by facile chemical method has been studied.

2. Experimental procedure

2.1. Synthesis of monodisperse nanoparticles

Co-precipitation method was used to synthesize undoped and Mn doped CeO_2 monodisperse nanoparticles. Cerium nitrate ($CeNO_3.6H_2O$) and Manganese chloride ($MnCl_2.4H_2O$) were used as precursors. Different molar solutions of $CeNO_3.6H_2O$ and $MnCl_2.4H_2O$ were prepared in distilled water in order to synthesize 0, 1, 3, 5 and 7 at% Mn doped CeO_2 nanoparticles. These solutions were then placed on hot plate for magnetic stirring at 90 °C and 500 rpm. 2 mL acetic acid was added to the above solution as a capping agent and 1M NaOH basic solution was supplemented drop by drop until pH value reaches up to 10. Now the solution was stirred for 1 h at 90 °C and 500 rpm. After cooling, the precipitates were collected and washed with distilled water via centrifugation. Finally, the synthesized samples were calcined for 2 h at 300 °C with heating rate of 10 °C per minute. The calcined samples were characterized for different physical properties using X-ray diffraction (XRD), Raman spectroscopy, Scanning electron microscopy (SEM), Ultra Violet (UV)-visible absorption spectroscopy and Vibrating sample Magnetometer(VSM) techniques.

2.2. Anticancer activity and cytotoxicity determination

In this course of study, the SH-SY5Y are cancerous while HEK-293 are healthy human cell lines and were purchased from American Type Culture Collection (Manassas, VA, USA). Both type of cells were maintained in Dulbecco's Modified Eagle's Medium (DMEM) (Sigma–Aldrich) supplemented with 10% fatal bovine serum (FBS) and grown at 37 °C in a humidified environment with 5% CO_2 plus 95% air separately. Both type of cells were seeded in 96 well plates and allowed to attach for 48 h. The suspensions of undoped and Mn doped CeO_2 nanoparticles (0, 1, 3, 5, and 7 at %) were applied to both type of cells. The cells treated without nanoparticles were used as control in these experiments. A fluorescence microscope (Hitachi, Tokyo, Japan) was used for cell viability assay. ROS detection was carried out by flow cytometry.

3. Results and discussions

3.1. Structural analysis

XRD characterization has been employed to investigate the phase purity and average crystallite sizes of the synthesized samples. As shown in Fig. 1(a), all the diffraction peaks in the XRD patterns of the synthesized samples are well indexed to the single phase cubic fluorite structure of CeO_2. The absence of impurity phases indicates that cubic fluorite structure is the only phase present in undoped and Mn doped CeO_2 synthesized samples. Furthermore, the position of the main peak (111) has been shifted towards higher angles as shown in Fig. 1(b) which assures the successful doping of Mn ions in the CeO_2 crystal structure demonstrating the formation of homogeneous Ce–Mn–O solid solution [18]. This shift is associated with lattice contraction and distortion due the replacement of Ce^{4+} ions by smaller ionic radii trivalent Mn^{3+} ions [12,19]. The average crystallite sizes been calculated by Scherer formula given by;

$$D = \frac{0.89\lambda}{\beta cos\theta}$$

Where D represents average crystallite size, λ is wavelength of the incident x-rays, β is full width at half maximum (FWHM) in radians and θ is diffraction angle of the (111) peak. The calculated average crystallite size of undoped CeO_2 sample has been found to be 8 nm which is decreased down to 6 nm with Mn doping.

Raman spectroscopy has been used to further validate the phase purity of the synthesized samples. Raman spectroscopy is an effective technique to detect the possible secondary phases which can easily flee from the detection limits of XRD. Furthermore it gives information about structural defects caused by the dopants which lead to the shift in Raman peaks. Fig. 2 depicts the Raman spectra of undoped and Mn doped CeO_2 synthesized samples. A well defined Raman band is observed at 443 cm^{-1} which corresponds to the first order F_{2g} Raman active mode of the cubic fluorite structure of CeO_2. The observed Raman band has a huge shift of 22 cm^{-1} from the Raman active F_{2g} mode of bulk CeO_2. This F_{2g} mode is very sensitive to any disorder/defects in the oxygen sublattice [20]. Hence, this huge shift in F_{2g} mode may be linked with the presence of Ce^{3+} ions and oxygen vacancies in the system [20–22]. The only difference between the Raman spectra of undoped CeO_2 and that of Mn doped CeO_2 is the reduction in the

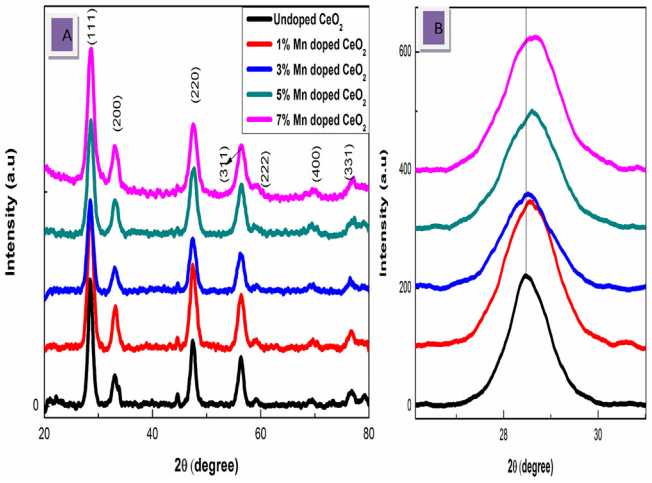

Fig. 1. A. XRD patterns of the prepared samples and B. Shift in the (111) peak with Mn doping.