Phase transformation in Mn-doped titania hollow spheres and their biocompatibility studies

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Abstract Mn-doped titania hollow nanospheres were prepared via sacrificial core templating method at room temperature, using carbon spheres as the sacrificial core and template. X-ray diffraction and thermal studies showed the phase transformation of titania from anatase to rutile at temperature as low as 550 °C, when the dopant (i.e., Mn) concentration was increased from 1 to 6 mol % (with respect to Ti). Fourier transform infra red spectroscopic studies have been carried out to determine the surface functional groups, while the spherical and hollow morphology of the titania nanostructures have been confirmed through scanning electron microscopic as well as transmission electron microscopic studies. The chemical composition of the samples has been determined through X-ray photoelectron spectroscopic studies, while their magnetic properties have been studied using superconducting quantum interference device analysis. The biocompatibility and suitability of the nanospheres for intracellular applications has been tested through conventional MTT assay using MDA-MB 231 human breast cancer cell lines.

Keywords Mn-doped · Titania · Hollow spheres · Anatase · Rutile · Biocompatibility

Introduction

Recently, there has been a surge of research interest in developing appropriate inorganic nanostructures for different biomedical applications. Various nanostructures of hydroxyapatite (Andronesu et al. 2013; Venkatesan et al. 2011; Wang et al. 2009), magnetite (Daumann et al. 2014; Dorniani et al. 2013), zirconia (Batra et al. 2013; Tang et al. 2010), titania (Hou et al. 2014; Aw et al. 2012), silica (Bernal et al. 2014; Xu et al. 2013) etc., have already gained attention due to their efficacy in the fabrication of biosensors and nanocarriers for targeted delivery of drugs as well as substrates for immobilization of biomolecules. Among the various inorganic materials, titania (TiO₂) holds great promise in biomedical applications owing to its wide availability, biological as well as chemical inertness and have so far been reported in various morphological forms such as nanoparticles (Liang et al. 2013), nanorods (Pang et al. 2013), nanowires (Sun and Wu 2013), nanosheets (Liu et al. 2013), nanotubes (Pandikumar and Ramaraj 2013), mesopores (Mascolo 2013), and hollow spheres (Zhao and Middelberg 2013). However, all literature reports on biomedical applications using titania based nanomaterials have been performed using titania (TiO₂) films (Kim et al. 2010), mesoporous nanoparticles (Wu et al. 2011), and nanotubes (Aw et al. 2012; Gulati et al. 2012). The hollow nanostructured titania (or, doped titania), which have the potential to create a whole new generation in host–guest chemistry because of their low density, high surface area, tunable pore structure and good surface

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permeability, have not been much explored for biomedical applications till date, according to the best of our knowledge. In an attempt to contribute in this area, we report a novel methodology for the synthesis of hollow nanospheres of TiO_2 which have been tested for their biocompatibility.

From literature reports, it is evident that titania nanostructures can either be functionalized or new properties can be introduced by doping the host material with appropriate dopants. For instance, Ao et al. (2010) investigated the photocatalytic activity of N-doped titania hollow spheres for degradation of reactive Brilliant Red dye X-3B. Xu et al. (2006) investigated the ferromagnetic property evoked in Mn-doped TiO_2 thin films and related the structural phase transition of TiO_2 to the annealing temperature of the films, while Saponjic et al. (2006) studied the effect of Mn-dopant on the charge separation and surface reconstruction in Mn-doped titania nanoparticles. In the present study, titania hollow spheres have also been doped with Mn(II) to induce magnetic property in the material. The magnetic character developed on doping with manganese is expected to enable the magnetic field induced navigation of the titania nanospheres during biomedical application such as in targeted delivery of drugs. Further, cytotoxicity studies of the synthesized Mn-doped hollow nanospheres of TiO_2 have been performed by conventional MTT assay using MDA-MB 231 cells for testing their biocompatibility.

The hollow nanospheres of titania have been prepared under ambient condition by sacrificial core templating method, where carbon spheres were used as the sacrificial core templates, while samples with different doped-Mn concentrations were obtained by varying the mole percent of Mn (i.e., 1, 2, 4, and 6 mol % with respect to Ti). The Mn-doped hollow nanospheres of TiO_2 , obtained on calcination of the respective precursors at 550 °C, have been characterized in detail.

Experimental

Chemicals and materials

Titanium tetraisopropoxide was purchased from Spectrochem Pvt Ltd (India), while manganese(II) acetate tetrahydrate and anhydrous dextrose (GR) were purchased from Merck (India). 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was obtained from Sigma-Aldrich. Human breast cancer cell lines (MDA-MB-231) were obtained from the National Center for Cell Science (NCCS), Pune (India). Absolute ethanol and milli-Q water were used throughout the study.

Preparation of carbon spheres

A 0.7 M aqueous solution of dextrose was hydrothermally treated at 170 °C for 6 h in a Teflon lined autoclave under autogenous pressure. The blackish residue obtained was centrifuged, washed with water and ethanol and finally dried at 60 °C for 12 h to obtain the carbon spheres.

Preparation of hollow Mn-doped titania nanospheres

Initially, undoped titania hollow spheres were prepared as follows: 20 mmol of titanium tetraisopropoxide was added to 40 mL ethanol. This was then mixed with 0.08 g of freshly prepared carbon spheres and the mixture was sonicated for 30 min. After 6 h of undisturbed standing, the solution mixture was centrifuged and the collected solids were washed with ethanol, dried at 60 °C for 12 h, and finally calcined at 550 °C for 4 h in air. These samples have been named as HT in the text. For preparing the Mn-doped nanospheres, the procedure was repeated with the addition of the required amount of manganese(II) acetate tetrahydrate in the starting solution mixture of titanium tetraisopropoxide and carbon spheres. Four different samples with different dopant (i.e., Mn) concentrations were prepared by changing the mole percentage of Mn (i.e., 1, 2, 4, and 6 mol % with respect to Ti) in the samples. The dried Mn-doped titania samples, containing 1, 2, 4 and 6 % mole percent of Mn were calcined at 550 °C for 4 h in air and were indexed as HMT-1, HMT-2, HMT-4, and HMT-6, respectively, in the text.

Procedure for the cytotoxicity studies

The cytotoxicity of the prepared titania nanospheres were determined through conventional MTT [3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. MDA-MB 231 cells were seeded in 96-well plate at a density of 2,000 cells per well in DMEM (Dulbecco's Modified Eagle's medium) complete medium. The cells were incubated for 16 h for adhesion and growth. After incubation, the complete DMEM medium was replaced by incomplete DMEM medium and the cells were treated with different concentrations of the prepared hollow nanospheres. For comparison, control wells were treated with only DMEM medium. After 48 h of incubation, the medium (containing the hollow nanospheres) were discarded, replaced with 100 μL of MTT solution (1 mg/mL) and further incubated for 4 h for the reduction of MTT to formazan crystals by the viable cells. The unreduced MTT solution was then discarded and 100 μL of DMSO (dimethyl sulfoxide) was added to each well of the 96-well plate to dissolve the formazan crystals formed by the viable

cells. Finally, the plates were shaken and the absorbance of formazan dye was measured at 550 nm using a bench-mark microplate reader. The assay was performed in triplicate. The cytotoxic effect in each of the treatments was expressed as percentage of cell viability relative to the untreated control cells (% control) and expressed as follows:

$$\text{Cytotoxic effect (\%)} = \left(\frac{[\text{OD of treated cells}]_{550 \text{ nm}}}{[\text{OD of control cells}]_{550 \text{ nm}}} \right) \times 100 \quad (1)$$

where, OD represents the optical density of the respective solution measured at 550 nm.

Characterization

X-ray diffraction (XRD) was employed for the crystalline phase identification of the prepared hollow spheres using Cu-K α radiation over 2θ range of 10° – 70° at a scan rate of 3° min^{-1} and with a sampling interval of 0.05 at 40 mA and 40 kV by using Bruker AXS Diffractometer D8 Powder XRD. The functional group analysis was done by Fourier transform infrared (FT-IR) spectroscopy using Perkin-Elmer Spectrum RXI instrument, within the scan range $4,000$ – 400 cm^{-1} . The thermogravimetric analysis (TGA) was performed using Netzsch STA 409 PC Luxx (Germany). The morphology of prepared hollow spheres were analysed by scanning electron microscopy (SEM) using SUPRA 40 Field Emission Scanning Electron Microscope (Carl Zeiss SMT AG, Germany) and transmission electron microscopy (TEM) using JEM-2100 HRTEM (JEOL, Japan) operating at 200 kV. The chemical composition of the samples were determined by X-ray photoelectron spectroscopy (XPS), carried out on PHI 5000 VersaProbe II Scanning XPS Microprobe (Φ ULVAC-PHI, INC.) using monochromatic AlK α radiations (1,486 eV). The carbon 1 s peak at a standard value of 284.5 eV has been used to calibrate the binding-energy scale for the XPS measurements. Magnetic measurements were carried out using EverCool SQUID VSM DC magnetometer (Quantum Design, USA).

Results and discussion

Crystalline phase analysis

X-ray powder diffraction (XRD) studies were carried out for all the synthesized hollow nanospheres to ascertain their crystalline phase and purity. The observed XRD patterns of the samples were shown in Fig. 1. The HT sample (i.e., undoped titania) exhibits the characteristic

Fig. 1 XRD patterns of the prepared samples after calcining at 550°C

peaks of anatase phase of titania (JCPDS file No. 86–1157). From XRD analysis, it is apparent that with increase in the dopant (i.e., Mn) concentration, the intensity of the characteristic diffraction lines corresponding to the anatase phase of titania decreases and is gradually replaced by the characteristic diffraction lines corresponding to the rutile phase. The rutile phase (JCPDS file No. 76–0317) was eventually achieved in HMT-6, which contained 6 mol % of Mn with respect to Ti. It can thus be inferred that the doped Mn ions gets incorporated into the titania crystal lattice and facilitates the phase transformation from anatase to rutile, when the dopant concentration is increased up to 6 mol %. For pure/undoped titania, the anatase to rutile phase transformation generally occurs on heating the samples at temperatures between 600 and 700°C (Suresh et al. 1998), but it is apparent from our study that this phase transformation could be achieved at a lower temperature ($\sim 550^\circ \text{C}$) when titania is doped with up to 6 mol % of Mn. The absence of any additional peaks in the XRD patterns of the prepared samples indicate the absence of any impurity and infers the proper doping of Mn ions into the crystal lattice of titania.

Functional group analysis

Fourier transform infra-red (FT-IR) spectroscopy has been carried out to analyze the functional groups present in as-prepared carbon spheres, as-prepared HMT-2 as well as calcined HMT-2 samples (calcined at 450 and 550°C), and the spectra are depicted in Fig. 2. The observed broad band around $3,420 \text{ cm}^{-1}$ in the spectrum of carbon spheres (Fig. 2a) corresponds to O–H stretching of the carboxylic bonds (Zhang et al. 2012) formed during the dehydration process of dextrose. The band at $1,635 \text{ cm}^{-1}$ can be

Fig. 2 FT-IR spectra of as-prepared carbon spheres (a), as-prepared HMT-2 (b), HMT-2 calcined at 450 °C (c) and 550 °C (d)

attributed to C=C stretching vibration, while the bands in the region 1,000–1,500 cm^{-1} indicates the existence of large amounts of residual hydroxyl groups as well as trace

carbonyl groups in the prepared carbon spheres (Li et al. 2010). The FT-IR spectrum of the as-prepared HMT-2 sample, depicted in Fig. 2b, shows lowering of intensity of the organic functional groups as well as the O–H stretching band at 3,420 cm^{-1} present in the carbon spheres. This lowering in intensity of the functional groups present in the carbon spheres in the as-prepared HMT-2 sample, may be due to the surface coating of carbon spheres with 2 mol % Mn-doped titania. The calcined samples of HMT-2, depicted in spectra ‘c’ and ‘d’ of Fig. 2, shows further weakening and eventual disappearance of the bands associated with the carbon spheres when the calcination temperature was increased from 450 to 550 °C. This could be due to the complete removal of the carbon spheres from HMT-2 samples during calcination. However, the calcined samples of HMT-2 depicted a new broad band centred at around 530 cm^{-1} , which became prominent with increase in the calcination temperature from 450 to 550 °C. This band could be attributed to the Ti–O bending vibrations, which could be associated with the crystallization of titania phase in the samples upon calcination.

Fig. 3 TGA curves for as-prepared samples of HT and HMT-6 (a), DTA curves for HT (b) and HMT-6 (c)

Thermal studies

TGA-DTA studies were carried out for the as-prepared samples of HT and HMT-6 for determining the calcination temperature required for the complete removal of the carbon core and the formation of crystalline titania. The thermal studies were performed by heating the samples in alumina crucibles from room temperature to 1,000 °C in air at a heating rate of 10 °C/min. The TGA curves for both the samples, shown in Fig. 3a, reveal four regions of significant weight loss below 450 °C. The first weight loss from room temperature (29 °C) to 140 °C corresponds to the loss of physically adsorbed water, while the second weight loss from 140 to around 235 °C attributes to the loss of crystallization water. The third weight loss between 235 and 395 °C represents the loss of the carbon core through combustion and the fourth weight loss from 395 to 445 °C corresponds to the crystallization of amorphous state to anatase phase of titania for both the samples (i.e., HT and

HMT-6). Beyond 450 °C, the TGA curves for both the samples show no significant weight loss, indicating the formation of thermally stable titania phase. The DTA curves for the two samples, represented in Fig. 3b, c, shows an endothermic peak at about 100 °C for both the samples, corresponding to the removal of water moieties from the samples, while two exothermic peaks centred at 290 and 430 °C for HT and at 280 and 409 °C for HMT-6 samples are observed. The first exothermic peak corresponds to the removal of carbon core, while the second peak represents the crystallization of amorphous state to anatase phase of titania. A third exothermic peak starts appearing at 610 and 468 °C for HT and HMT-6, respectively, that represent the temperature for phase transformation from anatase to rutile phase of titania. It is visible that on doping titania with 6 mol % Mn, the phase transformation temperature is lowered from 610 °C in HT (undoped titania) to 468 °C in HMT-6 samples, consistent with the XRD patterns of the samples analysed after calcining at 550 °C.

Fig. 4 SEM images of as-prepared carbon spheres (a), HT (b), and HMT-1 (c), calcined HMT-1 (d), broken spheres of HMT-1 (e) and HMT-2 (f), hollow three-dimensional network structure of HT (g), HMT-1 (h), and HMT-2 (i)

Morphological analysis

The morphological characteristic of the as-prepared carbon spheres as well as the as-prepared and calcined Mn-doped samples of titania were determined by scanning electron microscopic (SEM) studies. Spherical shape with smooth surface and almost uniform diameters of the as-prepared carbon spheres is evident from their SEM

images shown in Fig. 4a. The as-prepared samples of HT and HMT-1, obtained on surface coating of carbon spheres with titania and 1 mol % Mn-doped titania, respectively, also possesses smooth surface and spherical shapes as apparent from their SEM images shown in Fig. 4b, c, respectively. After calcining the samples at 550 °C, the surfaces become a bit rough due to the contraction of titania precursor associated with the removal

Fig. 5 TEM images of HT (a) and HMT-1 (b) (inset their corresponding SAED patterns)

Fig. 6 XPS spectra of Ti 2p core levels (a), O 1s core levels (b), and Mn 2p core levels (c) for HMT-1 and HMT-6

of carbon core, possessing a diameter of about 400 nm, as represented by the SEM image of HMT-1 in Fig. 4d. The hollow nature of the calcined samples with wall thickness of around 40 nm may be inferred from the ruptured spheres seen in the SEM images of HMT-1 and HMT-2 in Fig. 4e, f, respectively. In addition, the SEM images shown in Fig. 4g–i infers that the hollow spheres get

interlinked on calcination to generate a three-dimensional network structure.

Spherical shape and hollow nature of the calcined (at 550 °C) undoped and Mn-doped titania samples are also evident from transmission electron microscopic (TEM) studies. The bright field TEM images of calcined HT and HMT-1 samples are shown in Fig. 5 as typical

Fig. 7 $M(H)$ curves for HMT-6 and HMT-2 (a), hysteresis loops for HMT-2 (b) and HMT-6 (c)

Fig. 8 ZFC- FC curves for HMT-2 and HMT-6

representatives, while their corresponding SAED patterns are shown as inset in their respective bright field TEM images in Fig. 5a, b, respectively.

XPS analysis

X-ray photoelectron spectroscopy (XPS) was employed on HMT-1 and HMT-6 samples to determine their chemical structure and the results were shown in Fig. 6. The XPS spectra of Ti 2p core levels (Fig. 6a) for HMT-1 shows binding energy peaks for Ti 2p_{3/2} and Ti 2p_{1/2} at 458.05 and 463.79 eV, respectively, while the binding energy peaks of Ti 2p_{3/2} and Ti 2p_{1/2} peaks for HMT-6 were observed at 458.1 and 463.8 eV, respectively. The corresponding Ti 2p doublet separation for HMT-1 and HMT-6 was 5.72 and 5.7 eV, respectively. The position of the Ti 2p doublet peaks and the separation value between 5.7 and 6 eV indicates the presence of Ti⁴⁺ state in the prepared spheres (Liu et al. 2007).

The XPS spectra of O 1s core level for HMT-1 and HMT-6 are shown in Fig. 6b. The binding energy peak for O 1s was observed at 529.29 and 529.4 eV for HMT-1 and HMT-6, respectively. These binding energy values correspond to the normal lattice sites in the titania (TiO₂) structure with oxygen in O²⁻ state in the hollow spheres.

The XPS spectra of Mn 2p core levels for the samples were shown in Fig. 6c. The binding energy peaks corresponding to Mn 2p_{3/2} and Mn 2p_{1/2} peaks were observed at 641.3 and 652.9 eV, respectively, for HMT-1 and 641.7 and 653.4 eV, respectively, for HMT-6 with a doublet separation of 11.6 and 11.7 eV for HMT-1 and HMT-6, respectively. The peak position and doublet separation values for the samples correspond to the presence of Mn²⁺ state in the prepared spheres. In addition, it was observed that the binding energy peaks shows a positive shift for all the three elements in HMT-6 as compared to HMT-1, which indicates the more positive charged surface of HMT-6 which is due to the high concentration of dopant (i.e., Mn) ions in HMT-6 as compared to HMT-1.

Magnetic measurements

Magnetic measurements of the prepared HMT-2 and HMT-6 samples were performed with superconducting quantum interference device (SQUID). The field-dependent magnetization M(H) curves of the samples at room temperature (300 K), shown in Fig. 7a, reveals that the saturation magnetization of HMT-6 is higher as compared to HMT-2, suggesting the increase in magnetization with increase in Mn content. The coercive field and saturation magnetization for HMT-2 and HMT-6 were found to be 34.7 Oe; 0.037 emu/g and 183.7 Oe; 0.048 emu/g, respectively. The hysteresis loops of the samples at 300 K, shown in Fig. 7b,

c, shows that both the samples exhibit room temperature ferromagnetism. The observed ferromagnetism in the samples (at 300 K) is due to the incorporation of Mn ions into the titania crystal lattice. Any possible contribution from manganese oxides and/or Ti/Mn binary oxides can be ruled out, since they are ferromagnetic only at 100 K or less (Tian et al. 2008).

The temperature dependent magnetization in HMT-2 and HMT-6 have been shown by the zero-field-cooled (ZFC) and field-cooled (FC) magnetization curves carried out between 5 and 380 K under an applied field of 100 Oe. The ZFC and FC magnetization curves for HMT-2 and HMT-6, shown in Fig. 8, reveals the absence of blocking temperature for both the samples. In addition, the divergence of the FC and ZFC curves at temperatures well above 300 K indicates that the T_C (Curie temperature) of both the samples is above 300 K and both the samples exhibit ferromagnetism at room temperature.

Cytotoxicity studies

To determine the safety and toxicological level of the prepared nanospheres for intracellular applications, the cytotoxicity of the prepared spheres were examined by MTT assay using human breast cancer cell line (MDA-MB 231) treated with various concentrations of the spheres. The plot of concentration versus percentage of cell viability (shown in Fig. 9) for the various nanospheres reveals that the cell viability is more than 50 % (i.e., half maximal inhibitory concentration, IC₅₀) even when their dosage is as high as 200 µg/mL. The IC₅₀ value for HT, HMT-1, HMT-2, HMT-4, and HMT-6 was found to be 293.9, 246.7, 280, 202.3, and 243.4 µg/mL, respectively. For all the prepared nanospheres, the IC₅₀ values indicate that they are all biocompatible and could be used for intracellular applications.

Fig. 9 MTT assay for the prepared samples

Fig. 10 Optical microscopic images of the cells after 48 h of incubation with the prepared hollow spheres

The observations from MTT assay was further substantiated through optical microscopic images of the cell lines taken after 48 h of incubation with different concentrations of the prepared nanospheres. The optical microscopic images displaying the amount of viable cells left on the wells of the 96-well plate is shown in Fig. 10.

Conclusions

In conclusion, Mn-doped titania hollow spheres have been successfully prepared through sacrificial core templating method using carbon spheres as the sacrificial core templates. The hollow spherical structures of the calcined samples, with diameters of about 400 nm and wall thickness of 40 nm, were confirmed through SEM and TEM studies. XRD studies revealed the anatase phase for undoped titania sample which got transformed into the rutile phase with increase in the dopant (i.e., Mn) concentration at temperature as low as 550 °C. XPS studies shows the presence of Ti^{4+} state for Ti, O^{2-} state for O, and Mn^{2+} state for Mn. Magnetic studies confirmed the presence of room temperature ferromagnetism in the Mn-doped samples. Further, the samples were found to be biocompatible with IC_{50} values higher than 200 $\mu g/mL$ for all the samples, thereby validating their applicability for different biomedical applications.

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