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| Complete List of Authors:    | Yi, Zhigao; Faculty of Material & Photoelectronic Physics, Xiangtan University  
                              | Lu, Wei; Faculty of Applied Science and Textiles The Hong Kong Polytechnic University, Department of Applied Physics  
                              | Qian, Chao; College of Physics and Information Science, Hunan Normal University  
                              | Zeng, Tianmei; College of Physics and Information Science, Hunan Normal University  
                              | Yin, Lingzhen; College of Physics and Information Science, Hunan Normal University  
                              | Wang, Haibo; Faculty of Material & Photoelectronic Physics, Xiangtan University  
                              | Rao, Ling; Faculty of Material & Photoelectronic Physics, Xiangtan University  
                              | Liu, Hongrong; College of Physics and Information Science, Hunan Normal University  
                              | Zeng, Songjun; College of Physics and Information Science, Hunan Normal University;  |
Urchin-like Ce/Tb co-doped GdPO₄ hollow spheres for *in vivo* luminescence/X-ray bioimaging and drug delivery

Zhigao Yi, Wei Lu, Chao Qian, Tianmei Zeng, Lingzhen Yin, Haibo Wang, Ling Rao, Hongrong Liu, Songjun Zeng

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In this paper, we report a self-sacrificing route for fabrication the Ce/Tb co-doped GdPO₄ hollow spheres in the hydrothermal condition using the Gd(OH)CO₃:Ce/Tb precursor as template and NH₄H₂PO₄ as phosphorus source. The X-ray diffraction (XRD) patterns show the amorphous crystal nature of the precursor and pure hexagonal phase of the hollow spheres. The microstructure of the as-prepared precursor and hollow spheres were characterized by transmission electron microscopy (TEM) and scanning TEM (STEM) assays. The results exhibit urchin-like morphology of the solid precursor and hollow spheres. Bright green emissions of the spheres have been detected using an ultraviolet (UV) lamp at 288 nm and the calculated CIE coordinates are (0.289, 0.491). The energy transfer mechanism of Ce and Tb ions in GdPO₄ host has been investigated. The quantum efficiency of the hollow spheres was measured to 61% and the lifetime calculated as 6.94 ms. In addition, the magnetic mass susceptibilities and magnetization of the spheres are found to be 6.39×10⁻⁶ emu/gOe and 1.27 emu g⁻¹ at 20 kOe, respectively. Owing to the excellent downshift luminescence property, the as-prepared GdPO₄:Ce/Tb hollow spheres have been successfully applied in *in vivo* luminescence and X-ray bioimaging for the first time. Moreover, the three-dimensional (3D) *in vivo* X-ray bioimaging of the mouse can provide the accurate location from multiple directions. The high-contrast ratio makes the spheres a promising X-ray contrast agent. Due to the hollow structure, these GdPO₄:Ce/Tb hollow spheres were also used as drug delivery system for doxorubicin (DOX) loading and releasing. The drug loading efficiency is measured to 17% at pH value of 7.4, and the pH-dependent drug release was studied. 47% of the loaded DOX was released within 10 h when pH =5, while there was only 30% in the same time at pH = 7.4 and it took nearly 48 h to reach a comparable level. The different release nature makes these spheres a promising application in targeting therapy of tumor.

1. Introduction

Hollow nano-/micro-materials with controllable size and morphology have attracted increasing research interest in modern chemistry and materials research areas, owing to their outstanding properties, such as, lower density, larger specific area, encapsulation ability and surface permeability. Therefore, these hollow structural materials have promising applications in various fields such as biotechnology, drug delivery, catalysis, fillers, photonic devices, electrochemical cells, and waste removal. With the development of these functional materials, a variety of fabricated methods have been exploited. However, among the various strategies, template route is the most usual and efficient way to obtain hollow structures. Of course, whether on the basis of hard templates (consisting of polystyrene, silica particles and carbon spheres) or building on soft templates (including supramolecules, surfactants and polymer vesicles), all of these strategies have exhibited some shortcomings. According to the former method, a large amount of time is necessary due to the multistep fabrication and removal of the templates. While, there is a huge challenge of controlling the shape and size of the final products through the latter. In addition, hollow spherical nanocrystals can also be obtained by template free routes which make use of the mechanism of the Ostwald ripening process. In comparison to the methods mentioned above, the template route of self-sacrificing gathers their advantages and can receive ideal morphology simultaneously.

Recently, many works have been focused on synthesizing hollow spherical rare-earth (RE) compounds. For instance, as reported, Gd₂O₃ hollow microspheres with uniform morphology and well dispersity have been successfully synthesized using self-sacrificing method and lanthanide ions (Ln³⁺) doped Gd₂O₃ microspheres show excellent luminescence capacities. In addition, Gd₂O₃ hollow spheres were fabricated by homogeneous precipitation method where carbon spheres were utilized as templates and removed by calcination. The as-prepared spheres have been applied as positive T₁ contrast agents for magnetic resonance imaging and drug delivery host carriers for studying...
the drug loading/release properties of these hollow structure spheres as well as their promising therapeutic application. Besides, Gd\(^{3+}\)-based hosts can also act as ideal candidates of contrast agents for X-ray imaging because of the huge K-edge values (Gd\(_{\text{LIII}}\) edge = 50.2 keV) and the large X-ray absorption efficiency of the Gd element (at 80 keV, Gd = 5.57 \(\text{cm}^2\text{g}^{-1}\)).\(^{42,44}\) Therefore, much more efforts have been made to exploit new system of Gd\(^{3+}\)-based host in conjugation with the hollow structure. As represented, GdVO\(_4\):Dy microspheres,\(^{37}\) GdF\(_3\) micro/nano-spheres,\(^{30}\) and Gd\(_2\)O\(_3\):Tb nanocapsules\(^{41}\) have been fabricated and exhibited their unique microstructural and luminescent properties and application in bioimaging and drug loading/release capabilities. Very recently, Eu\(^{3+}\) doped GdPO\(_4\) hollow spheres come into our sight, but the workers have just showed their fluorescent and paramagnetic nature.\(^{50,46}\) However, integration of in vivo bioimaging and drug delivery in a system of Ln\(^{3+}\) doped GdPO\(_4\) hollow spheres have not been exploited. In addition, previous literatures proved the high efficiency of energy transfer between Ce and Tb in phosphors, which inspired us to dope Ce and Tb into GdPO\(_4\) host for intense emissions and further bioimaging.

In this paper, Ce/Tb co-doped GdPO\(_4\) spheres with urchin-like hollow structure were fabricated using a typical self-sacrificing route with some modification. The crystal phase and microstructure of the precursor (Carbonate hydroxide gadolinium, Gd(OH)CO\(_3\)) and final products were studied firstly. Then, the downshift luminescence and paramagnetic properties of the as-prepared spheres were studied in detail. Furthermore, these as-prepared spheres were at the first time used for in vivo luminescence, X-ray, 3D X-ray bioimaging, and drug loading/release investigation. The results indicate that the obtained Ce/Tb co-doped GdPO\(_4\) hollow spheres may be a new generation of biolabels, contrast agents, drug delivery carriers and therapeutic agents.

2. Experimental

2.1 Chemicals and materials

The RE oxides Gd\(_2\)O\(_3\), Ce\(_2\)O\(_3\), and Tb\(_2\)O\(_3\) are all of 99.99\% purity and were purchased from Sigma-Aldrich. The corresponding RE nitrates RE(NO\(_3\))\(_3\) were obtained via dissolving oxides into dilute nitric acid under heating with sequential stirring until the formation of transparent solution. Evaporate the remaining solvent and prepare the final solution with a designed concentration of 0.5 M. The other chemicals (analytical grade) were bought from Sinopharm Chemical Reagent Co., China. All of these reagents were used with no further purification.

2.2 Synthesis of the Gd(OH)CO\(_3\): Ce/Tb Precursor

The urchin-like colloidal Gd(OH)CO\(_3\):Ce/Tb precursor with monodispersity were prepared by a modified homogeneous precipitation method utilizing urea [CO(NH\(_2\))\(_2\)] as precipitator.\(^{47}\) In a typical synthesis, the as-prepared Gd(NO\(_3\))\(_3\), Ce(NO\(_3\))\(_3\), and Tb(NO\(_3\))\(_3\), solution with a total amount of 1 mmol and designed molar ratio of 75:20:5 were dissolved into 50 mL deionized (DI) water. 2.0 g of urea was then added into the former mixture with vigorously stirring. The solution was further stirring for another 2 h at room temperature. The obtained solution was then heated to 80 °C and maintained for 2 h in the oil bath. After the reaction accomplished completely, the milky-white suspension was separated and collected by centrifugation. The impurities were washed with ethanol and DI water three times. The obtained precursor was dispersed into 20 mL of DI water for further use.

2.3 Synthesis of the GdPO\(_4\):Ce/Tb Hollow Spheres

In a typical synthesis, the as-prepared Gd(OH)CO\(_3\):Ce/Tb water solution was labeled as solution A after ultrasonication for 30 min. 0.115 g of NH\(_4\)H\(_2\)PO\(_4\) and 0.1 g of cetyltrimethyl ammonium bromide (CTAB) were added into 20 mL of DI water under stirring to form homogeneous solution B. Solutions A and B were then mixed together with vigorous agitation. Finally, 40 mL of the resultant mixture was transferred into a 50 mL stainless steel autoclave. The system was sealed and maintained at 200 °C for 15 h. After the reaction, the products were cooled to room temperature naturally and the final products were assembled in the bottom of the vessel. The supernatant solution was poured directly and the precipitates were separated and collected via centrifugation. The impurities were removed by washing with ethanol and DI water in sequence. The as-prepared GdPO\(_4\):Ce/Tb hollow spheres were dried in air at 60 °C for 24 h.

2.4 Characterization

The crystal phase of the Gd(OH)CO\(_3\):Ce/Tb precursor and the GdPO\(_4\):Ce/Tb spheres were recorded by powder XRD using a D/max-\(\gamma\)A system X-ray diffractometer at 40 kV and 250 mA with Cu-K\(\alpha\) radiation (\(\lambda = 1.54056 \) Å). The shape and size of these as-synthesized samples were observed using TEM and STEM (JEOL-2100F). Secondary electron image (SEI) at STEM mode was acquired. During the TEM assay, the composed elements of the spheres were detected via the energy-dispersive X-ray spectrum (EDS) affiliated to the TEM. The surface ligands of the samples were detected through Fourier transform infrared spectrum (FTIR) employing a Magna 760 spectrometer ( Nicolet). The luminescence spectra of the samples were recorded by a Zolix Analytical Instrument (fluoroSENS 9000A) equipped with a Xe lamp (400W) at room temperature. After the luminescence assays, the luminescence decay curve of the GdPO\(_4\):Ce/Tb spheres was tested (major parameters: \(\lambda_{ex} = 288\) nm, \(\lambda_{em} = 543\) nm, excitation/emission bandpass: 8 nm, and integrate time: 100 \(\mu\)s). The digital photograph of the water solution containing 1 wt\% of the spheres was taken by a Canon digital camera under the excitation of a UV lamp at 253 nm in the dark. The magnetic property of the as-prepared GdPO\(_4\):Ce/Tb spheres was detected via a vibrating sample magnetometer (VSM, Lake-shore 7410) and the applied field was ranged from -20 to 20 kOe.

2.5 In vivo Luminescence Bioimaging

For the purpose of measuring the feasibility of the in vivo luminescence bioimaging based on the GdPO\(_4\):Ce/Tb spheres, a Kunming mouse was firstly anesthetized via intraperitoneal injection of 100 \(\mu\)L 10 wt\% pentobarbital sodium water solution. Then, the mouse was subcutaneously injected 200 \(\mu\)L of the
GdPO$_4$:Ce/Tb aqueous solution (2 mg/mL). After injection, \textit{in vivo} luminescence bioimaging was observed through an \textit{in vivo} imaging system (Bruker In-Vivo FX PRO). The luminescence bioimaging was captured under the excitation of 470 nm using a band pass filter (600/40 nm) with exposure time of 5 s. All animal procedures comply with the institutional animal use and care regulations, approved by the Laboratory Animal Center of Hunan.

2.6 \textit{In vivo} X-ray Bioimaging

To demonstrate the X-ray bioimaging based on these GdPO$_4$:Ce/Tb spheres, the \textit{in vivo} X-ray bioimaging was carried out. Then, another mouse was subcutaneously injected 200 µL of the GdPO$_4$:Ce/Tb aqueous solution (2 mg/mL) for the X-ray bioimaging at different sites. The X-ray bioimaging was also detected by the \textit{in vivo} imaging system equipped with an X-ray imaging functionality with an operating voltage of 0.45 kVp. The X-ray bioimaging was recorded under the operating voltage of 45 kVp (filter = 0.8 mm and exposure time = 1 min). The 3D X-ray bioimaging was captured by the multimodal animal rotation system (MARS, per 10° ranging from 0 to 360°) and the images were exported as a video at 5 frames per second.

2.7 \textit{In Vitro} Drug Loading and Release

To measure the drug loading capabilities of the GdPO$_4$:Ce/Tb hollow spheres, DOX (Shanghai Ekear Bio&Tech Co., Ltd) loading into the hollow spheres was done by adding 0.5 mg of these powders into 2 mL and 0.1 mg/mL of DOX phosphate buffer solution (PBS, pH = 7.4). The suspension was shaken for 24 h at room temperature for achieving the equilibrium state. The solution was then centrifuged at 12000 rpm for 10 min to collect the DOX-loaded spheres and remove the free DOX. The supernatant was retained and the concentration of DOX loaded on the hollow spheres was measured via the DOX characteristic absorption peak at 480 nm after subtracting the absorbance ascribed to the hollow spheres at the same wavelength. The UV-vis absorbance spectra were detected using a Lambda 750 UV/VIS spectrometer (PerkinElmer Inc.).

To investigate the DOX release kinetics, the obtained DOX loaded GdPO$_4$:Ce/Tb hollow spheres were incubated in PBS with two pH values (5 and 7.4) and soaked all the time. At the designed time interval, DOX released from the hollow spheres was collected by centrifugation and the amounts of released DOX in the supernatant were recorded by the UV-vis absorbance spectrum. All the measurements were done for three times and then took the average value.

3. Results and Discussion

3.1 Structure Characterization

As demonstrated in Scheme 1, the urchin-like Gd(OH)$_2$CO$_3$:Ce/Tb precursor was obtained by homogeneous precipitation method using urea as precipitator. Then, the urchin-like GdPO$_4$:Ce/Tb hollow spheres were prepared via self-sacrificing template route in which the precursor interacted with the added NH$_4$H$_2$PO$_4$ under hydrothermal conditions. The as-prepared spheres have successfully applied in \textit{in vivo} fluorescence, X-ray and 3D X-ray bioimaging. Moreover, the hollow structure of these spheres shows its excellent drug loading and release capabilities.

The crystal phases of the as-prepared samples were first recorded by XRD. Figure 1 shows the XRD results of the Gd(OH)$_2$CO$_3$:Ce/Tb precursor and GdPO$_4$:Ce/Tb hollow spheres. As shown in Figure 1a, the XRD pattern of the precursor exhibits board bands ranging from 15° to 60° indicating the amorphous structure of these precursor. The diffraction peaks of GdPO$_4$:Ce/Tb hollow spheres (Figure 1b) were well indexed to the pure hexagonal phase GdPO$_4$. The crystal phases of the as-prepared samples were first recorded by XRD.
Standards (JCPDS, number 39-0232). The slightly shifting towards lower angle side of the diffraction peak is ascribed to the enlarged unit-cell volume of GdPO$_4$ matrix for the replacement of Gd$^{3+}$ ($r = 1.193$ Å) by Ce$^{3+}$ with relatively larger radius ($r = 1.283$ Å). Moreover, no other peaks of impurity were detected from the XRD pattern which implied the formation of the pure hexagonal phase GdPO$_4$:Ce/Tb.

The shape and size of the as-prepared precursor and final products were characterized by TEM analysis. As shown in panels a and b in Figure 2, typical TEM reveal that the nearly spherical and prickly structures of the both. In addition, SEI acquired at STEM mode (Figure 2c and e) demonstrated that the surface of the precursor was made up by the nanowires and the external of GdPO$_4$:Ce/Tb was composed of nanorods. In comparison with the high-magnification TEM images of these two species, the internal of the precursor shows solid state and the final products were characterized by TEM analysis. As shown in grid of TEM sample.

Figure 2. Morphology and microstructure study: (a) and (b) typical TEM images, (c) and (e) SEI images, and (d) and (f) high-magnification TEM images of Gd(OH)CO$_3$:Ce/Tb and GdPO$_4$:Ce/Tb, respectively; (g) EDS of a sphere in e. The scale bars are all 200 nm for a-f.

3.2 FTIR analysis

As shown in Figure 3, the surface functional groups of the precursor and hollow spheres were identified by FTIR spectra. As demonstrated in Figure 3a, the characteristic peaks at 3393, 1506, 1410, 1077, 843, and 742 cm$^{-1}$ are ascribed to OH (v), CO (ν$_{as}$), CO (ν$_{s}$), CO (δ), and OH (δ), where the v, ν$_{as}$, ν$_{s}$, and δ stand for stretch, asymmetric stretch, symmetric stretch, and deformation, respectively, implying that the composition of the precursor should be Gd(OH)CO$_3$:Ce/Tb. However, the absorption bands at 620 and 543 cm$^{-1}$ and a broad band at 1067 cm$^{-1}$ reveal the presence of phosphate groups (Figure 3b).

![Figure 3. The FTIR spectra of (a) the Gd(OH)CO$_3$:Ce/Tb precursor and (b) the GdPO$_4$:Ce/Tb hollow spheres.](image)

3.3 Photoluminescence (PL) and magnetization properties

The luminescence of Ce/Tb co-doped phosphors and the energy transfer from Ce to Tb ions have been well investigated by previous works. As demonstrated in Figure 4, the energy transfer firstly occurred between Ce$^{3+}$ and Ce$^{4+}$ under the UV irradiation at 288 nm. Then, the energy transferred from Ce$^{3+}$ (5d) to Tb$^{3+}$ (4f$^6$), followed closely by the cross relaxation the Tb$^{3+}$ (5D$_{4}$). The 5D$_{4}$ levels of Tb$^{3+}$ radioactively transferred to the lower energy levels of 7F$_{J}$ (J = 0, 1, 2, 3, 4, 5, 6). Owing to the high efficiency of these energy transfer in Ce/Tb co-doped GdPO$_4$ host, as the inset shown in Figure 5, the digital photograph of the water solution containing 1 wt% GdPO$_4$:Ce/Tb spheres exhibits intense eye-visible green light under the excitation of a 253 nm UV lamp in the dark at room temperature. Figure 5 exhibits the excitation and emission spectra of these hollow spheres. The excitation spectrum (green curve) shows a week band centered at 222 nm and a high and broad band ranging from 250 to 350 nm with a maximum at 288 nm. The former attribute to the 4f$^7$-4f$^6$ transition of Tb$^{3+}$ and the latter are ascribed to the 5d-4f transition of Ce$^{3+}$. The bright and strong emissions of Tb$^{3+}$ (488 nm: 5D$_{4}$-7F$_{6}$, the strongest 543 nm: 5D$_{4}$-7F$_{5}$, 587 nm: 5D$_{4}$-7F$_{4}$, and 596 nm: 5D$_{4}$-7F$_{3}$) are yielded under excitation of 288 nm. A further color coordinates calculation reveals that the luminescence of the GdPO$_4$:Ce/Tb hollow spheres located in the region of green in Commission Internationale de l’Eclairage 1931 chromaticity (CIE 1931) and the calculated coordinates are (0.289, 0.491). In addition, the quantum yield of the GdPO$_4$:Ce/Tb spheres was measured to 61%, further implying energy transfer from Ce$^{3+}$ to Tb$^{3+}$ in GdPO$_4$ host.
Figure 4. Energy transfer mechanism and downshift luminescence emission of the GdPO$_4$:Ce/Tb hollow spheres under the excitation of a UV lamp at 288 nm.

Figure 5. Excitation and emission spectra of the GdPO$_4$:Ce/Tb hollow spheres. Inset is the digital photograph of aqueous solution (1 wt%) under the 253 nm UV lamp irradiation in a sealed room.

Moreover, the decay curve of the as-prepared spheres has been detected. As shown in Figure 6, the square dots represent the experimental data and the red solid line indicates the fitting result. The luminescence lifetime can be estimated by the following formula $I(t) = I_0 \exp(-t/\tau)$, where $\tau$ stands for the lifetime of the emitted lanthanide ions. The lifetime shown by the fitting result via the formula is 6.94 ms.

Figure 6. Decay curve of GdPO$_4$:Ce/Tb hollow spheres.

In addition to the excellent luminescence properties, the GdPO$_4$:Ce/Tb hollow spheres also possess attractive paramagnetic nature which is ascribed to the large magnetic moment of Gd$^{3+}$ (7.94 $\mu_B$) in GdPO$_4$ host. Figure 7 shows the magnetization of the GdPO$_4$:Ce/Tb hollow spheres as a function of applied field ranging from -20 to 20 kOe at room temperature. As demonstrated, these GdPO$_4$:Ce/Tb hollow spheres present paramagnetic property at room temperature. The paramagnetic behavior of the GdPO$_4$:Ce/Tb hollow spheres is primarily ascribed to the seven unpaired inner 4f electrons, which are closely bound to the nucleus and effectively shielded by the outer closed shell electrons from the crystal field. The magnetic mass susceptibility and magnetization of the GdPO$_4$:Ce/Tb hollow spheres are at $\sim 6.39 \times 10^{-5}$ emu/gOe and $\sim 1.27$ emu/g at 20 kOe, respectively. The results indicate that the GdPO$_4$:Ce/Tb hollow spheres can act as contrast agents for magnetic resonance imaging.

Figure 7. Magnetization based on applied field for the GdPO$_4$:Ce/Tb hollow spheres at room temperature.

3.4 In Vivo Luminescence Bioimaging

The toxicity and biocompatibility of the hollow spheres in the same GdPO$_4$ host lattice have been studied by previous work, in which the GdPO$_4$:Eu spheres show well biocompatibility and have been proved as non-toxic materials for biomedical applications. To measure the feasibility of the GdPO$_4$:Ce/Tb hollow spheres for in vivo luminescence bioimaging, a Kunming mouse was subcutaneously injected with 200 µL of the aqueous solution of GdPO$_4$:Ce/Tb hollow spheres (2 mg/mL). After 5 min injection, the mouse was observed for in vivo luminescence bioimaging using a multi-modal in vivo imaging system (Bruker In-Vivo FX PRO) under the excitation of a 400 W Xenon lamp at 470 nm. Figure 8a and 8b show the in vivo whole-body images of the mouse without and with subcutaneous injection of the GdPO$_4$:Ce/Tb hollow spheres, respectively. The high-contrast luminescence signal in the mouse injected with spheres was observed (labeled by red-dotted circles). Figure 8c shows the overlay image, where the luminescence signals are matched well with the whole body of the mouse. Of course, the autofluorescence of the mouse and the lower penetration of UV wavelengths are inevitable shortcomings, limiting the application in in vivo whole-body luminescence bioimaging of these downshifting nanocrystals.
3.5 In Vivo X-ray Bioimaging

Apart from in vivo luminescence bioimaging, the GdPO₄:Ce/Tb hollow spheres can be used as X-ray bioimaging contrast agents due to the large K-edge values and X-ray absorption coefficient of the Gd element. To reveal the in vivo X-ray bioimaging of these spheres, a Kunming mouse was subcutaneously injected with PBS containing these spheres. After 5 min injection, in vivo X-ray bioimaging was performed using a multifunctional in vivo imaging system under voltage of 45 kVp. Figure 9 shows the in vivo X-ray bioimaging in a Kunming mouse. As observed in Figure 9a, there are no X-ray signals detected in the untreated mouse. The high-contrast X-ray absorption contrasts indicated by the red-dotted circles (Figure 9b) are observed after subcutaneous injection with spheres. Moreover, the 3D in vivo X-ray bioimaging of the mouse (in the supporting information, Movie S1) was captured using the protocol model in the multifunctional in vivo imaging system and an image of which is shown in Figure 3c. These 3D X-ray bioimaging can demonstrate the accurate location of the spheres from multiple directions and have a promising application in clinical treatment.

3.6 Drug Loading and Release

Owing to the hollow structure of the spheres, efforts have been made to utilizing the as-prepared hollow spheres as drug host carriers. As demonstrated by former FTIR result, large amounts of hydroxyl groups are on the surface of the GdPO₄:Ce/Tb hollow spheres after hydrothermal reaction. Therefore, the obtained spheres with negative charges of hydroxyl groups can easily interact with the positively charged DOX molecules with protonated primary amine group in a neutral condition. Thus, the electrostatic interaction aforementioned provides the main driving force for DOX loading. In addition, the size distribution of the as-prepared hollow spheres in PBS (0.25 mg/mL) was tested by dynamic light scattering. As shown in Figure S1, the diameter of the spheres was measured to be 865.6 ± 40.25 nm. To qualitatively study the loading efficiency of DOX, the solution containing the spheres and DOX with designed molar ratio was measured by centrifugation and then sonication. As shown in left panel of Figure 10a, in comparison with the free DOX, the mixture of the spheres and DOX exhibits a weaker red color. In addition, reddish precipitate and nearly transparent liquid were observed after centrifugation indicating the binding of DOX on the spheres. As a comparison in upper panel of Figure 10a, the free DOX shows no obvious color change and precipitate. The latter quantified assay of DOX loading efficiency is based on UV-vis spectra according to the characteristic adsorption peak of DOX at 480 nm, due to the linear relation between the amounts of DOX and the intensity of adsorption peak at 480 nm. The DOX loading efficiency of the spheres was calculated to 17%.

Figure 8. In vivo luminescence bioimaging of a Kunming mouse: (a) the X-ray image before injection, (b) the luminescence image after injecting the as-prepared spheres, (c) the overlay of a and b.

Figure 9. In vivo X-ray bioimaging: (a) without injection and (b) with subcutaneous injection with the as-prepared spheres in two regions of a Kunming mouse, (c) an image of the 3D in vivo X-ray bioimaging.

Figure 10. Preparation and characterization of the DOX-loaded spheres: (a) photographs of free DOX and DOX-loaded spheres after centrifugation and sonication, (b) UV-vis absorbance spectra of free DOX, and (c) DOX release from the spheres over time in PBS at pH = 5 and 7.4. Error bars are standard deviations based on triplicated samples.

The accumulated DOX release of the DOX-loaded
GdPO₄:Ce/Tb hollow spheres were detected in PBS with two pH values (5 and 7.4). As shown in Figure 10c, at pH = 5, 47% of the loaded DOX was released within 10 h, whereas at pH = 7.4, there was only 30% in the same time and it took nearly 48 h to reach a comparable level (47%). In addition, to assess the stability of the particles, the solution of these particles after drug release was used for FE-SEM analysis (shown in Figure S2). It can be seen that the particles are still urchin-like and the structure is maintained without any damage. The electrostatic interaction aforementioned is weaker in acidic condition than that in neutral which is the major factor of rapid release at pH=5. These different release nature indicates that the release rate of physically bounded DOX is faster in tumor areas (mild acidic conditions) than that in the blood (neutral environments), which makes the DOX-loaded hollow spheres a promising application in targeting therapy of tumor.

4. Conclusion

In summary, the hexagonal phase Ce/Tb co-doped GdPO₄ spheres with urchin-like hollow structure have been fabricated by self-sacrificing route. The obtained spheres exhibit bright green emissions under the excitation of 288 nm and paramagnetic properties (the magnetic mass susceptibility: 6.39×10⁻⁹ emu/g and magnetization: 1.27 emu/g at 20 Koe). The as-prepared spheres have been successfully applied in vivo luminescence, X-ray, and 3D X-ray bioimaging. The loading efficiency are measured to 17% at pH = 7.4 and the release ratio was calculated to 47% within 10 h (pH = 5). The excellent drug loading and release capabilities make the hollow spheres ideal candidate for targeted therapy.

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Notes and references