[Article]

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聚丙烯酸功能化高效发光的 $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ 纳米晶合成及细胞成像

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摘要: 采用水热合成一锅法制备了聚丙烯酸功能化单分散的 $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ 纳米颗粒 ($\text{La}_{1-x}\text{Eu}_x\text{F}_3\text{@PAA}$ NPs)。利用透射电子显微镜(TEM)、X射线衍射(XRD)、傅里叶变换红外光谱(FTIR)和光致发光光谱(PL)对样品的形貌、结构、组成和荧光性能进行表征。该纳米颗粒平均粒径为 (7 ± 3) nm, 具有较好的分散性、稳定性与生物相容性。将纳米颗粒与HeLa癌细胞共同孵育, 体外成像结果表明材料对HeLa癌细胞显示出低细胞毒性。用水热法制备的 $\text{La}_{1-x}\text{Eu}_x\text{F}_3\text{@PAA}$ 纳米颗粒可以作为光学荧光探针用于细胞成像, 在生物医学领域表现出巨大的潜力。

关键词: 稀土纳米颗粒; 水热法; 水分散液; 高效发光; 生物成像

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Synthesis of Poly(acrylic acid)-Functionalized $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ Nanocrystals with High Photoluminescence for Cellular Imaging

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Abstract: Monodisperse $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ nanoparticles (NPs) were functionalized by poly(acrylic acid) (PAA) via a one-pot modified hydrothermal method. The morphology, crystal structure, surface groups, and luminescence properties of the as-produced $\text{La}_{1-x}\text{Eu}_x\text{F}_3\text{@PAA}$ NPs were characterized by transmission electron microscopy (TEM), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), and photoluminescence (PL) spectroscopy. The produced nanoparticles were (7 ± 3) nm in size, water soluble, and buffer stable, with good photostability and biocompatibility. *In vitro* imaging revealed the low cytotoxicity of the as-synthesized NPs incubated with HeLa cancer cells. Thus, the colloidal $\text{La}_{1-x}\text{Eu}_x\text{F}_3\text{@PAA}$ NPs exhibit great potential for use as optical imaging probes in biological applications.

Key Words: Lanthanide nanoparticle; Hydrothermal; Aqueous dispersion; Efficient luminescence; Bioimaging

1 Introduction

With the tremendous developments of fluorophores in the past decades, fluorescent bioimaging has been emerging as an important technique in diagnosis and treatment of a variety of

diseases¹⁻⁴. Organic dyes and quantum dots (QDs) are most intensively investigated optical probes in clinical diagnostic applications due to their bright fluorescence while both of them have certain limitations⁵⁻⁷. For example, organic dyes are easily

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subject to photo-bleaching and luminescence blinking in view of the mutability of conjugating π -electrons^{8,9}. The heavy metal ions in QDs (e.g., Cd_3As_2 , PbSe and so on) possess serious toxicity though they show superior photostability and high resistance to photobleaching^{10,11}. Hence, finding an appropriate substitute for the existing biological probes is still under active exploration.

Recently, lanthanide nanoparticles (Ln NPs) have stood out from the competition in the field of fluorescent bioimaging owing to their remarkable features: (1) high photochemical stability and high PL quantum yield (QY); (2) long luminescence lifetimes (microsecond to millisecond); and (3) low toxicity^{12–15}.

Aqueous dispersity of nanomaterials is a prerequisite for biomedical applications, so are the lanthanide luminescent bioprobes^{3,16,17}. Nonetheless, most as-prepared nanoparticles cannot suspend in water steadily¹⁰. Recently, Mimun *et al.*¹⁸ studied the stability of $\text{GdF}_3:\text{Nd}^{3+}$ nanophosphor suspension in the deionized (DI) water, but aggregation appeared in two days. Inorganic or organic surface modification can be applied to transform the hydrophobic of Ln NPs to the hydrophilic and stabilize the dispersion¹⁹. For example, a SiO_2 layer was coated on NdF_3 NPs to obtain biocompatible and highly-efficient fluorescent core-shell $\text{NdF}_3/\text{SiO}_2$ NPs²⁰. Chitosan/ $\text{LaF}_3:\text{Eu}^{3+}$ nanoparticles (NPs) with excellent dispersity in aqueous solution were prepared using a one-pot method²¹. Nevertheless, these surface modifying methods either need complex procedure²², or lead to low QY that impacts greatly on high-contrast between bioimaging and fluorescence background^{12,13}, or have limited stability¹⁸. A facile synthetic procedure to obtain stable and highly luminescent Ln NP aqueous dispersion is needed urgently.

Herein, we report on a simple preparation of stable $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ NP aqueous dispersion with polyacrylic acid (PAA) as a surface modifying agent with a one-pot hydrothermal synthesis. The optimum PAA-functionalized $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ nanospheres present a high stability not only in DI water, but also in phosphate buffer solution (PBS), which is one of the most frequently used biological buffers. In addition, we incubate $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@\text{PAA}$ NPs with HeLa cancer cells at different concentrations and hours to study the cellular toxicity and cell uptake of $\text{La}_{1-x}\text{Eu}_x\text{F}_3@\text{PAA}$ NPs.

2 Experimental and computational section

2.1 Materials

All starting materials were obtained from commercial supplies and used as received. $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (99.9%), $\text{Eu}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ (99.9%), and NH_4F (96%) were purchased from Alfa Aesar. Polyacrylic acid (PAA, $M_w = 3000$) was obtained from Aladdin Chemistry Co., Ltd. Ethyl alcohol was supplied from Yasheng Chemical Co., Ltd. DI water was throughout.

2.2 Characterization

The transmission electron microscopy (TEM) and the selected area electron diffraction (SAED) rings were carried out on a JEM-2100F emission transmission electron microscope. The X-ray powder diffraction (XRD) patterns were measured on a Bruker D8 Advance X-ray powder diffractometer. The emission spectra were measured by full-featured steady state/transient fluorescence spectrometer FLS920 from Edinburgh Instruments. Digital photographs of the NP dispersion were taken by a digital camera (Sony T7) without image processing. The fluorescence micrographs were observed under a con-focal laser scanning microscope (Olympus FluoView™ FV1000) made in Japan. All the photoluminescence studies were carried out at room temperature.

2.3 Synthesis of $\text{La}_{1-x}\text{Eu}_x\text{F}_3@\text{PAA}$

The $\text{La}_{1-x}\text{Eu}_x\text{F}_3@\text{PAA}$ NPs were synthesized using a hydrothermal method. In a typical procedure^{23,24}, weighted amount of $\text{La}(\text{NO}_3)_3$ and $\text{Eu}(\text{NO}_3)_3$ were dissolved in deionized water (19 mL) and ethyl alcohol (45 mL) under magnetic stirring, and the total rare earth ion molar concentration was 0.5 mmol. Then 125 mg PAA was added to the Ln-containing solution under magnetic stirring at 80 °C to form a clear solution. After that, 2 mmol NH_4F was added and stirred for 10 min. The mixture was transferred into a 100 mL Teflon-lined autoclave, and elevated up to 160 °C for 12 h. The as-prepared NPs were separated by centrifugation for 15 min at $1.05 \times 10^4 \text{ r} \cdot \text{min}^{-1}$ and re-dispersed in water for several times, and then were finally dispersed in DI water.

2.4 Photoluminescence bioimaging *in vitro*

To evaluate the capability of *in-vitro* PL optical bioimaging of $\text{La}_{1-x}\text{Eu}_x\text{F}_3@\text{PAA}$ NPs, HeLa cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum, 1% penicillin and streptomycin at 37 °C and 5% CO_2 . The biological imaging was evaluated by utilizing the confocal laser scanning microscope. All $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@\text{PAA}$ NP aqueous solutions to the cells experiment were dispersed in PBS.

3 Results and discussion

3.1 Synthesis and characterization of $\text{La}_{1-x}\text{Eu}_x\text{F}_3@\text{PAA}$

In the one-pot green hydrothermal process (Fig.1), a coordinative polymer (PAA) was introduced to mediate the precipitation and the crystallization process of the $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ NPs to prevent the rapid precipitation of Ln fluorides in water²⁵.

During the process of the growth of $\text{La}_{1-x}\text{Eu}_x\text{F}_3@\text{PAA}$ NPs, an almost constant cation concentration was maintained by the equilibrium between coordination and precipitation. In addition, PAA also encapsulated the NPs without further aggregation²⁰. Finally, the crude NPs underwent recrystallization into nanosized single-crystal in hydrothermal treatment, as verified by high resolution TEM (Fig.2C).

Fig.1 Schematic illustration of $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ NPs surface with PAA coating.
R represents PAA.

Fig.2A and C show the TEM images of the as-prepared NPs, the monodispersed $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@PAA$ NPs are irregular plate-like in shape, with an average diameter of (7 ± 3) nm (Fig.2B). Notably, NPs smaller than 10 nm could be excreted more efficient in human body, and allow the use of higher dose of imaging agents^{26,27}. The SAED rings in Fig.2D reflect the random orientation of nano-crystalline particles, and the SAED patterns agree well with the diffractions from the (111), (112), and (113) planes of the hexagonal LaF_3 .

The XRD patterns of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@PAA$ NPs and the standard diffraction lines of the hexagonal LaF_3 crystal (JCPDS No. 32-0483) are shown in Fig.3A. The diffraction peaks of the $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@PAA$ NPs (the curve) match the pure hexagonal LaF_3 phase (the vertical lines) very well, which is in accordance with the SAED analysis. Additionally, no trace of characteristic peak for impurity phase was observed, indicating a pure phase of LaF_3 NPs prepared with the feasible one-step synthesis route. The compositional distribution of the

Fig.2 TEM particle size distribution and SAED patterns of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@PAA$ NPs.

(A, C) TEM; (B) particle size distribution; (D) SAED.

Fig.3 XRD and EDS patterns of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@PAA$ nanoparticles.

(A) XRD patterns; (B) EDS patterns

$\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@PAA$ nanocrystals was obtained by energy dispersive spectrometer (EDS) analysis (Fig.3B). From the EDS pattern, the EDS signals of La, F, C, O, and Eu can be clearly observed across the region of the nanocrystals.

By attaching onto the surface of the nanoparticles, hydrophilic polymer, PAA, endows the $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@PAA$ nanocrystals with excellent dispersibility in aqueous solution, as required in biomedical imaging and cancer therapy. In order to confirm that the surface of nanoparticles was modified by

Fig.4 FT-IR spectra and thermogravimetric curve of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@PAA$ NPs.

(A) FT-IR spectra; (B) thermogravimetric curve. (a) $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@PAA$ NPs;

(b) $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3$ NPs; (c) pure PAA.

PAA, the FT-IR spectra of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3$ nanoparticles, $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3$ @PAA nanoparticles, and pure PAA were measured. As shown in Fig.4A(a) and (b), two characteristic bands resulting from the asymmetric and symmetric stretching vibrations of the C—O in COOH group can be observed at 1452 and 1416 cm^{-1} respectively. The band at 2944 cm^{-1} was assigned to the stretching vibration of the methylene(CH_2) in the long alkyl chain of PAA, and another peak corresponding to the stretching modes of C=O in COOH group was also observed at 1723 cm^{-1} . However, these four characteristic absorption peaks of PAA could not be observed in Fig.4A(c), except the distinguishable band at 1642 cm^{-1} resulting from the La-O vibration in impurities caused by the presence of H_2O during the reaction²⁸. The result clearly indicated that a large amount of PAA capped on the surface of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3$ nanoparticles. For investigating the content of PAA, the thermogravimetric analysis was done. As shown in Fig.4B, the weight loss induced by the decomposition of PAA reached ~14% (w) from 200 to 600 °C, consistent with previous reports²⁹. At the same time, the mass losses further confirm the surface functionalization of PAA on $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3$ nanoparticles.

3.2 Photoluminescence properties

In order to study the effect of Eu^{3+} concentration on the photoluminescence properties of $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ @PAA nanocrystals aqueous dispersion, the emission spectra and

Fig.5 Emission spectra and the decay curve of the $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ @PAA NPs.

(A) emission spectra; (B) decay curve.

the luminescent decay curves of $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ @PAA nanocrystals aqueous dispersion with different Eu^{3+} ions concentration were recorded at room temperature (Fig.5). Fig.5A exhibits the emission spectra of $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ NPs aqueous dispersions under 393 nm excitation with x values of 0.01, 0.25, 0.5, 0.75, 1.0 respectively. Four fluorescence peaks corresponding to the transitions from 5D_0 to 7F_J ($J = 0, 1, 2, 4$) of Eu^{3+} ions were clearly observed. Increasing Eu^{3+} concentration, the fluorescent intensity increased for low concentration and then decreased when x value is greater than 0.5. The cross-relaxation dominated the electron transition and thus decreased the luminescent intensity at high Eu^{3+} concentration ($x > 0.5$). Fig.5B illustrates the fluorescence decay curves of $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ @PAA NP aqueous dispersion by monitoring the $^5D_0 \rightarrow ^7F_2$ at 613 nm under 393nm excitation. The lifetimes of $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ @PAA NPs in aqueous solution were calculated by fitting the decay curves with a single exponential decay. The lifetimes were about 4.57, 2.58, 1.93, 1.17, and 0.60 ms for x value of 0.01, 0.25, 0.5, 0.75, 1.0, respectively. The increasing Eu^{3+} concentration shortened the NPs' lifetime, which was caused by "concentration quenching effect", in good agreement with

Fig.6 QY spectra of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3$ @PAA NP aqueous dispersion.

Fig.7 PL intensity of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3$ @PAA NPs dispersed in DI water at different time.

The inset shows photograph (right) of aqueous solution of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3$ @PAA NPs and PL photograph (left) of the aqueous solution under irradiation at 365nm with a 4W hand-held UV lamp.

the change of fluorescence intensity.

The absolute QY for $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@\text{PAA}$ NP aqueous dispersion was estimated to be as high as 66%, which meets the requirements of ideal photoluminescent probes for *in vitro* and *in vivo* imaging. The QY can be represented simply in the following formula:

$$\text{QY} = \int E_{\text{emission}} / (\int E_{\text{solvent}} - \int E_{\text{sample}})$$

where $\int E_{\text{emission}}$ is the integration of the luminescence emission spectrum of the sample; $\int E_{\text{sample}}$ is the integration of the spectrum of the light used to excite the sample ($E_{\text{NP aqueous dispersion}}$ in our case); $\int E_{\text{solvent}}$ is the integration of the spectrum of the light used for excitation with the solvent only ($E_{\text{H}_2\text{O}}$ in our case). The QY spectra of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@\text{PAA}$ NP aqueous dispersion are shown in Fig.6.

To confirm the photostability of $\text{La}_{1-x}\text{Eu}_x\text{F}_3@\text{PAA}$ NPs aqueous dispersion, we acquired the fluorescence spectra of $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@\text{PAA}$ nanocrystals dispersed in DI water for

extended periods of time (Fig.7). Even after two months, the fluorescence intensity almost remained unchanged. As shown in below inset (left) of Fig.7, bright red luminescence under irradiation of a 4 W hand-held UV lamp (365 nm) was observed. High photostability and efficient red-light emission suggested that $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@\text{PAA}$ nanocrystals were a type of attractive luminescent probes because these nanocrystals emitting in the red and near-infrared regions are preferred for *in vivo* biological imaging.

3.3 *In vitro* photoluminescence imaging of HeLa cancer cells

To evaluate the capability of $\text{La}_{1-x}\text{Eu}_x\text{F}_3@\text{PAA}$ as a nanoprobe for optical bioimaging, PL imaging *in vitro* of HeLa cancer cells incubation with $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@\text{PAA}$ was investigated by utilizing a con-focal laser scanning microscope equipped with excitation at 515 nm, PL signals were collected at 600–650 nm. Besides, a cell control was

Fig.8 Confocal fluorescent microscopy images of HeLa cancer cells incubated with $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@\text{PAA}$ NPs at a concentrations of $500 \mu\text{g}\cdot\text{mL}^{-1}$ for different time. Each series shows a bright-field image, luminescent image, and the overlay.

(A) the control group; (B) 1 h; (C) 2 h; (D) 3 h; (E) 4 h; (F) 6 h.

Fig.9 Confocal fluorescent microscopy images of washed HeLa cancer cells incubated with $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3@\text{PAA}$ NPs at a concentrations of $500 \mu\text{g}\cdot\text{mL}^{-1}$ for different time.

Each series shows a bright-field image, luminescent image, and the overlay.

(A) the control group; (B) 1 h; (C) 2 h; (D) 3 h; (E) 4 h; (F) 6 h.

Fig.10 Confocal fluorescent microscopy images of HeLa cancer cells incubated with $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3\text{@PAA}$ NPs for 4 hours at different concentrations from 500 to 3000 $\mu\text{g}\cdot\text{mL}^{-1}$.

Each series shows a bright-field image, luminescent image, and the overlay.

(A) the control group; (B) 500; (C) 1000; (D) 1500; (E) 2000;

(F) 3000 $\mu\text{g}\cdot\text{mL}^{-1}$.

also investigated. With the prolonging of incubation time, as shown in Fig.8, the luminescence intensity in HeLa cells enhanced obviously, suggesting that an increasing number of NPs were taken up by the HeLa cells. Moreover, the bright field images of the cells were also observed for comparison to the confocal fluorescent microscopy images, which indicates that the bright-field images of the cells significantly overlapped with the confocal images. In addition, the HeLa cells still maintain good morphology after 6 hours' incubation except few dead cells, which means that the best incubation time of HeLa cells with $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3\text{@PAA}$ NPs at a concentrations of 500 $\mu\text{g}\cdot\text{mL}^{-1}$ to keep good morphology is about 4 hours.

After each incubation time, the HeLa cells were washed twice by PBS to remove the NPs which were on the surfaces of the cells, so as to confirm that the red luminescence came from the interior of the cells. Fig.9 shows the confocal

fluorescent microscopy images of the washed HeLa cells. An obviously increasing visible luminescence signal can be detected over the course of time, implying that $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3\text{@PAA}$ NPs indeed gone inside the cells rather than adhered to the cell surface.

In order to determine the impact of NPs concentration on HeLa cells morphology, the fluorescence microscopy images of HeLa cancer cells incubated with $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3\text{@PAA}$ NPs for 4 h at 37 °C for different concentrations from 500 to 3000 $\mu\text{g}\cdot\text{mL}^{-1}$ were taken, as shown in Fig.10. With the incubation concentration increasing, the luminescence intensity strengthened clearly except minor difference for higher concentration above 1000 $\mu\text{g}\cdot\text{mL}^{-1}$. Besides, the morphology became coarser when the concentration reached 1500 $\mu\text{g}\cdot\text{mL}^{-1}$. Therefore, the ideal incubation concentration is 1000 $\mu\text{g}\cdot\text{mL}^{-1}$.

4 Conclusions

In conclusion, monodisperse $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ NPs functionalized by PAA have been prepared through one-step facile hydrothermal approach. It is found that these NPs were fluorescent and had an average size of (7 ± 3) nm. PAA was applied to cap the nanoparticles during the synthesis process, which rendered them water soluble and provided functional chemical groups, such as amino groups on the nanoparticles. These nanoparticles exhibited absolute QY of 66% with x value of 0.5, and showed great dispersion stability and photoluminescence stability within a time period of at least two months. Meanwhile, no measurable cytotoxicity was observed in HeLa cells for the $\text{La}_{0.5}\text{Eu}_{0.5}\text{F}_3\text{@PAA}$ NPs concentration up to 3000 $\mu\text{g}\cdot\text{mL}^{-1}$. Therefore, the generality of one-pot method can be extended to synthesis of $\text{La}_{1-x}\text{Eu}_x\text{F}_3$ NPs with FA and other functional ligands with a carboxyl group, which opens up a new perspective for preparing surface-functionalized ligands for biolabelling and targeted imaging.

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