

β -NaYbF₄: Gd/Ce/Tm@CaF₂-PVP Core–Shell Nanoparticles for Enhanced NIR-II Photothermal Therapy

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β -NaYbF₄: Gd/Ce/Tm@CaF₂-PVP Core–Shell Nanoparticles for Enhanced NIR-II Photothermal Therapy

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Abstract

Photothermal therapy (PTT) has emerged as a promising approach for tumor treatment due to its non-invasive nature and high spatiotemporal controllability. Rare earth-doped inorganic nanomaterials exhibit unique advantages in near-infrared-II (NIR-II) imaging-guided PTT. However, conventional rare earth nanoparticles often suffer from low fluorescence efficiency caused by surface defects and concentration quenching, which limits their biomedical applications. Here, we propose a design strategy of “inert shell synergy with biocompatibility”: an epitaxially grown CaF₂ shell of approximately 1.6 nm thickness is coated onto β -NaYbF₄: 5%Tm³⁺, 30%Gd³⁺, 2%Ce³⁺ core nanoparticles, which effectively suppresses surface quenching and concentration quenching, leading to a greatly enhanced NIR-II photoluminescence intensity. Notably, calcium and fluorine in CaF₂ are natural constituents of human bone, endowing the nanoparticles with excellent biocompatibility—a distinct advantage over conventional shell materials based on heavy metals or inert oxides. Subsequent surface modification with NOBF₄ and polyvinylpyrrolidone (PVP) yields NTF-PVP nanoparticles with good aqueous dispersibility and low cytotoxicity. Both in vitro and in vivo experiments demonstrate that NTF-PVP exhibits efficient photothermal conversion performance under near-infrared laser irradiation, and in situ intratumoral injection achieves outstanding photothermal therapeutic efficacy in 4T1 tumor-bearing nude mice. Collectively, this study for the first time combines the fluorescence-enhancing effect of an inert CaF₂ shell with the inherent biocompatibility of its constituent elements, providing a new paradigm for designing high-performance, low-toxicity rare earth-based PTT agents, and holds potential application value in cancer therapy.

Keywords: rare earth doped inorganic nanoparticles, photothermal treatment (PTT)

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1. Introduce

In recent years, rare-earth-doped nanoparticles have attracted considerable interest in bioimaging and therapy due to their unique optical properties [1, 2]. Their applications in tumor fluorescence imaging and photothermal therapy (PTT) have expanded rapidly [3, 4]. Extensive reviews have summarized the development of these materials and their photothermal applications [5, 6, 8]. Among various treatment strategies, PTT based on photothermal conversion has emerged as a promising branch because of its non-invasiveness and high controllability [7]. Rare-earth-doped inorganic nanoparticles can convert excitation energy into heat through non-radiative relaxation, serving as efficient PTT agents [7, 9]. Moreover, combining them with other photothermal materials such as CuS, Bi₂S₃, and gold (Au) can further enhance the photothermal effect synergistically [9, 10].

Following this concept, several multifunctional rare-earth-based photothermal platforms have been developed. For example, Sha et al. synthesized a core-shell nanomaterial NaYF₄: Er³⁺/Yb³⁺@NaYF₄: Sm³⁺/Yb³⁺ capable of simultaneous photothermal conversion and temperature detection: part of the absorbed excitation light is converted into a temperature-sensing signal, while another part is converted into heat for cancer therapy. Notably, its photothermal conversion ability increases with the Yb³⁺ concentration in the shell and the power of the 980 nm laser, demonstrating good controllability [11, 12]. Chu et al. designed NaYF₄: Yb/Er/Nd@NaYF₄: Nd@AgBiS₂ core-shell nanomaterials. By utilizing an efficient cross-relaxation pathway between Nd³⁺ and AgBiS₂, the photothermal conversion efficiency could be tuned from 14.7% to 45.0% [13]. Under 808 nm laser excitation, the product also generates strong up conversion luminescence that activates the AgBiS₂ shell to produce reactive oxygen species for photodynamic therapy (PDT) [14]. The cross-relaxation mechanism was further elucidated in related studies [15, 16]. In vitro and in vivo experiments confirmed that the combined PTT/PDT treatment achieved satisfactory therapeutic outcomes [13, 14].

In contrast to the above works, this study focuses on a different material system and treatment modality. Specifically, we selected β -NaYbF₄:5% Tm³⁺, 30% Gd³⁺, 2% Ce³⁺ as the core, which exhibits strong near-infrared II (NIR-II) emission and a small particle size. The advantage of this core lies in its NIR-II emission, which facilitates deep-tissue imaging, and the co-doping of Gd³⁺ and Ce³⁺ is expected to synergistically

regulate energy transfer pathways [17, 18, 19]. Furthermore, we introduced a CaF_2 epitaxial shell. Since Ca and F are intrinsic components of human bone, this shell significantly improves the biocompatibility of the nanoparticles [20, 21]. Meanwhile, the inert CaF_2 layer effectively passivates surface defects, and the investigation of its influence on the core's fluorescence properties has been well documented [22, 23]. Specifically, systematic studies have confirmed that such an inert shell can suppress both surface quenching and concentration quenching, thereby enhancing the NIR-II emission [24-26]. The protective role of inert shells has been further emphasized in recent works [27, 28]. To render the hydrophobic NTF nanoparticles water-soluble, a ligand exchange procedure using NOBF_4 was first performed to replace the original oleate ligands [29, 30]. Subsequently, polyvinylpyrrolidone (PVP) was introduced as a hydrophilic capping agent, which not only ensures excellent aqueous dispersibility but also provides good colloidal stability [31, 32]. In addition, various ligand exchange and surface modification protocols have been established to improve the biocompatibility and dispersion of hydrophobic nanoparticles [35-40]. The good biocompatibility of PVP-modified nanoparticles has been widely verified in biomedical applications [33, 34]. Finally, the $\beta\text{-NaYbF}_4\text{:}5\% \text{ Tm}^{3+}, 30\% \text{ Gd}^{3+}, 2\% \text{ Ce}^{3+}@\text{CaF}_2$ (NTF) core-shell nanoparticles were surface-modified with PVP to obtain NTF-PVP with good water solubility and biocompatibility [29-34]. The photothermal performance of NTF-PVP was systematically evaluated through vitro and in vivo experiments, and photothermal therapy was performed on 4T1 tumor-bearing nude mice by in situ injection of NTF-PVP. This work provides a new design concept and inorganic rare-earth-doped nanoparticles in the field of photothermal therapy, distinct from previously reported combination therapy or temperature-sensing platforms, highlighting the potential of a single material system for safe and efficient photothermal conversion.

2. EXPERIMENTS

2.1 Experiments section

Nitrosyl tetrafluoroborate (NOBF_4), trifluoroacetic acid (TFA), oleic acid (OA), and 1-octadecene (ODE) were purchased from Energy Chemical. Toluene, acetone, polyvinylpyrrolidone (PVP), dichloromethane, and anhydrous ethanol were purchased from Sinopharm Chemical Reagent. Calcium oxide (CaO), N, N-dimethylformamide (DMF), and cyclohexane were purchased from Macklin.

2.2 Experiments section

2.2.1 Preparation of $\text{NaYbF}_4\text{:} \text{Tm}^{3+}, \text{Gd}^{3+}, \text{Ce}^{3+}$

Synthesized according to Reference [41]. Weigh $\text{YbCl}_3\cdot 6\text{H}_2\text{O}$, TmCl_3 , $\text{GdCl}_3\cdot 6\text{H}_2\text{O}$, $\text{CeCl}_3\cdot 7\text{H}_2\text{O}$ into the reaction bottle and add 6 mL OA and 15 mL ODE. Maintain a uniform speed

and heat up to 150 °C under vacuum to remove excess water, air, and other impurities, then stop heating and let the reaction cool down and maintain at 50 °C. Accurately weigh NaOH and NH₄F dissolved in 10 mL methanol solution, add to the reaction bottle and then stir the mixed solution at a uniform speed for 30 minutes. After that, the temperature rises to 120 °C, and vacuum is applied to remove the excess impurities. Under the protection of N₂, the reaction solution is heated to 290 °C and stirred at a constant speed for 2 hours. Then let the reaction solution naturally cool to room temperature, add ethanol to precipitate nanocrystals, and wash it many times with ethanol and cyclohexane. Finally, the obtained NaYbF₄: Tm³⁺, Gd³⁺, Ce³⁺ nanoparticles are dispersed in 10 mL of cyclohexane as the core reserve solution.

2.2.2 NaYbF₄: 2%Tm³⁺, 30%Gd³⁺, 2%Ce³⁺@CaF₂ synthesis

Synthesized according to Reference [42]. Weigh CaO (0.5 mmol) added to the reaction bottle and add 5 mL deionized water and 5 mL TFA. After that, the mixed solution is heated to 90 °C to maintain a high-speed stirring reaction for 1 h, and then N₂ is put into the reaction bottle to remove the reaction solvent to obtain calcium trifluoroacetate Ca(CF₃COO)₂ shell precursor. Then add 10 mL OA, 10 mL ODE and the above prepared core reserve solution (5 mL) to the reaction bottle. Stir the mixed solution at a uniform speed, heat it to 120 °C to vacuum to remove excess water, air, and other impurities, and then put N₂ into the round-bottom flask. Then heat the reaction solution to 300 °C under the protection of N₂ to maintain the stirring reaction for 30 minutes. After that, let the reaction solution naturally cool to room temperature, add ethanol to precipitate nanocrystals, transfer the mixed solution to a 50 mL centrifuge tube, wash it many times with ethanol and cyclohexane, and finally disperse NTF nanoparticles in 10 mL cyclohexane for later use.

2.2.3 NaYbF₄: 2%Tm³⁺, 30%Gd³⁺, 2%Ce³⁺@CaF₂@PVP (NTF-PVP) Synthesis

Synthesized according to Reference [43]. Accurately weigh NOBF₄ (0.05 mmol) to a 50 mL flask and then add 5 mL dichloromethane solution. Then add 10 mL of NTF cyclohexane solution to the flask and shake the flask gently until flocculent precipitation is observed. After that, the mixed solution is transferred to a 50 mL centrifuge tube and put it into the centrifuge for 30 minutes at a rotation speed of 11,000 rpm and then remove the upper liquid in the centrifuge tube to retain the solid products at the bottom. Then add 5 mL toluene and 5 mL cyclohexane to the centrifuge tube to disperse the solid products and ultrasonicate for 3 min to ensure that they are mixed evenly. Then put the centrifuge tube into the centrifuge at a speed of 11,000 rpm for 30 min and then remove the upper liquid to retain the solid products at the bottom. Add 5 mL DMF to redisperse the above solid

products and then transfer the mixed solution to a 50 mL flask. Accurately weigh 250 mg PVP, add it to the flask and add a magnet to keep it stirring vigorously at room temperature for 30 minutes. Finally, add acetone to precipitate the nanocrystals, and then put them into the centrifuge for 30 minutes at a rotation speed of 11,000 rpm. After centrifugation, remove the upper liquid to retain the solid product at the bottom.

2.3 Characterization

Measure the crystal structure of the product using an X-ray powder diffractometer (XRD, Rigaku Mini Flex 300). Use scanning electron microscopy (SEM, JEOL JSM-7800F) and test the morphology of the product. Photoluminescence in Edinburgh steady-state/transient fluorescence spectrometer (FLS-1000).

2.4 Photothermal Performance Measurement

NTF-PVP and NaYbF₄: Tm/Gd/Ce nanoparticles were separately dispersed in PBS to prepare stock solutions of equal concentration (after 10-fold dilution, the absorbance at 980 nm was measured to be $A_{980} \approx 0.47$, corresponding to an original concentration of approximately 18 mg/mL). Aliquots of 1 mL of each solution were transferred into a 1-cm path-length quartz cuvette. A 980 nm continuous-wave laser (output power 3.2 W) was used as the excitation source, vertically irradiating the solution in the cuvette until the temperature reached a plateau (approximately 9 min), ensuring thermal equilibrium. The laser was then immediately turned off, and the solution was allowed to cool naturally to room temperature for 650 s. An equal volume of pure PBS was subjected to the same laser irradiation as a blank control.

The temperature changes during the entire process were recorded in real time using an infrared thermal camera. According to Newton's law of cooling ($\ln(\Delta T) = -t/\tau_s + C$), the cooling curve data within the first 84 s after laser shut-off were fitted with a single-exponential function to obtain the system time constant τ_s . The overall heat

transfer coefficient hS was then calculated from $hS = mC/\tau_s$, where m is the mass of the solution (1 g) and C is the specific heat capacity of water ($4.2 \text{ J}\cdot\text{g}^{-1}\cdot^\circ\text{C}^{-1}$).

The photothermal conversion efficiency (η) was calculated using the Roper model:

$$\eta = \frac{hS \times (T_{\max} - T_{\text{surr}}) - Q_{\text{dis}}}{I \times (1 - 10^{-A_{980}})}$$

where $T_{\max}$ is the maximum temperature of the sample at thermal equilibrium, T_{surr} is the ambient temperature, Q_{dis} is the heat generated by the PBS solvent itself under laser irradiation ($Q_{\text{dis}} = hS \times \Delta T_{\text{PBS}}$), I is the laser power (3.2 W), and A_{980} is the absorbance at 980 nm. For the original stock solutions, the absorbance exceeded 4, thus $1 - 10^{-A_{980}} \approx 1$, meaning the absorbed laser power was essentially equal to I .

2.5 In Vitro Cytotoxicity Evaluation

The in vitro cytotoxicity of NTF-PVP nanoparticles against 4T1 murine breast cancer cells was evaluated using the standard Cell Counting Kit-8 (CCK-8) assay. 4T1 cells were seeded into 96-well plates at a density of 1×10^4 cells per well and incubated at 37°C in a 5% CO_2 atmosphere for 12 h to allow cell attachment.

For the concentration-dependent cytotoxicity assay, the culture medium was replaced with fresh medium containing NTF-PVP at various concentrations (0, 3.125, 6.25, 12.5, 25, 50, 100, and 200 $\mu\text{g/mL}$), and the cells were incubated for 1 h. For the time-dependent cytotoxicity assay, cells were incubated with NTF-PVP at a fixed concentration of 200 $\mu\text{g/mL}$ for different time intervals (1, 3, 6, 12, 24, and 48 h). After the respective treatments, the medium was removed, and the cells were washed twice with PBS. Then, 100 μL of fresh medium containing 10% CCK-8 reagent was added to each well, followed by further incubation at 37°C for 2 h. The absorbance of each well was recorded at 450 nm using a microplate reader.

Cells cultured with complete medium without any treatment served as the control group (100% viability), and wells containing only medium and CCK-8 reagent without cells served as the blank background. Each experiment was performed in triplicate, and the cell viability (%) was calculated as:

$$\text{Cell viability (\%)} = \frac{A_{\text{sample}} - A_{\text{blank}}}{A_{\text{control}} - A_{\text{blank}}} \times 100\%$$

Where A_{sample} is the absorbance of the treated wells, A_{control} is the absorbance of the untreated control wells, and A_{blank} is the absorbance of the blank wells.

3. RESULTS AND DISCUSSION

3.1. NaYbF₄: 2% Tm³⁺, 30% Gd³⁺, 2% Ce³⁺@CaF₂ Synthesis and

Characterization of Core-Shell Structure

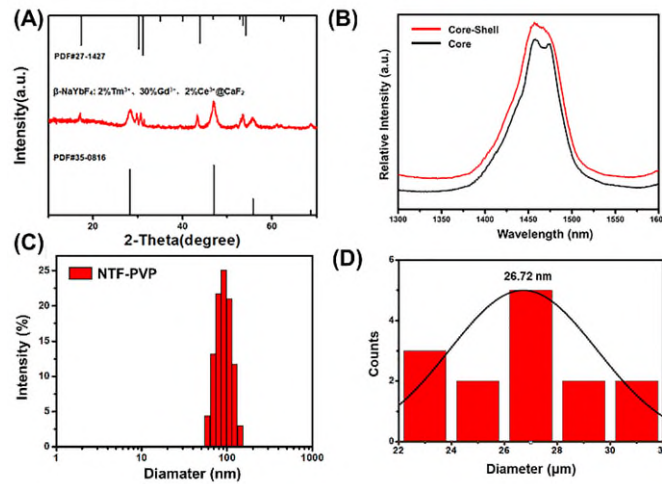


Fig. 1(a) XRD spectrum of $\beta\text{-NaYbF}_4$: 2% Tm³⁺, 30% Gd³⁺, 2% Ce³⁺@CaF₂, and XRD standard spectrum of β -phase NaYbF₄ (JCPDS 27-1427), XRD standard spectrum of CaF₂ (JCPDS 35-0816). (c) The particle size distribution graph of NTF-PVP in deionized water solution. (d) Particle size distribution of $\beta\text{-NaYbF}_4$: 2% Tm³⁺, 30% Gd³⁺, 2% Ce³⁺@CaF₂.

As shown in Fig. 1A, the XRD spectrum of the product is consistent with the standard hexagonal phase NaYbF₄ spectrum of JCPDS 27-1427 and the standard CaF₂ spectrum of JCPDS 35-0816, proving that the product is NaYbF₄: 2% Tm³⁺, 30% Gd³⁺, 2% Ce³⁺@CaF₂ core shell mechanism.

Fig. 1B shows the luminescence intensity of the materials in the near-infrared (NIR) region. An obvious emission peak is observed around 1450–1500 nm, which falls within the second near-infrared window (NIR-II). Notably, after coating with a CaF₂ shell (red line), the relative luminescence intensity is higher than that of the bare core (black line). In photothermal therapy, NIR-II luminescence is typically used for bioimaging and

tracking. The shell coating effectively suppresses energy quenching caused by surface defects, thereby enhancing the luminescence performance.

Fig. 1C presents the hydrodynamic diameters of NTF-PVP nanoparticles in aqueous solution (or in a solution containing the surfactant PVP). The particle sizes are centered around 100 nm, with a very narrow and concentrated distribution. This size is highly desirable because nanoparticles smaller than 200 nm can achieve passive targeting and accumulation at tumor sites via the enhanced permeability and retention (EPR) effect, which is a prerequisite for efficient photothermal therapy.

Fig. 1D displays the size distribution of β -NaYbF₄: 2% Tm³⁺, 30% Gd³⁺, 2% Ce³⁺@CaF₂ particles, where the red line represents the histogram and the black line is the fitted distribution curve. From the peak of the curve, the particle size is extremely small, with an average diameter of 26.72 nm, which is favorable for overcoming biological barriers and achieving deep tumor penetration.

3.2. NaYbF₄: 2% Tm³⁺, 30% Gd³⁺, 2% Ce³⁺@CaF₂ water soluble improvement

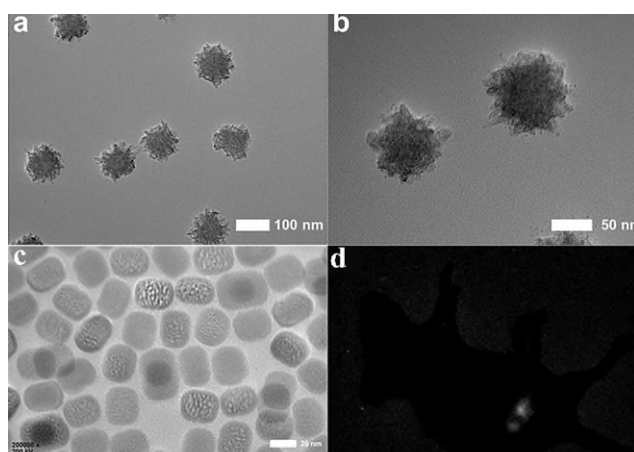


Fig. 2 (a, d) TEM picture of NTF-PVP; (c) TEM characterization of β -NaYbF₄: 2% Tm³⁺, 30% Gd³⁺, 2% Ce³⁺@CaF₂ (scale bar: 20 nm) (d) Fluorescence image of nude mouse tumor after tumor in-situ injection of NTF-PVP.

It is prepared by thermal decomposition method and reacts with high boiling point organic solvent oleic acid (OA). The nanoparticles of the core-shell are oil-soluble, which limits their further application in the biological field. To improve the hydrophobicity of the product, we use NOBF₄ to treat the surface of nanoparticles and replace the original organic ligands on the surface with BF₄⁻ anions [29, 30]. Due to the

weak affinity between the surface of BF_4^- anion and nanoparticles, we use PVP to further modify the surface of nanoparticles to make the nanoparticles water-soluble [31, 32]. Then we characterized the morphology of the sample through TEM (Fig. 2a, b).

It is known that CaF_2 has high optical transparency and high stability in the water environment, so we chose CaF_2 as the epitaxial shell of the product to construct the core-shell structure [20-26]. The TEM diagram of the product is shown in Fig. 2c, which is like a regular rectangular plate with good monodispersity and an average particle size of less than 50 nm.

Then we dissolve NTF-PVP nanoparticles in PBS and configure it into an 18 mg/mL solution and take out 200 μL of the above solution and inject it into the 4T1 tumor in the nude mouse tumor through in-situ injection. The UniNano NIR-II small animal real-time imaging system is used to observe the fluorescence imaging distribution of samples in nude mice and record them through the NIR CCD camera. As shown in Fig. 2d, obvious fluorescence brightness can be observed at the nude mouse tumor, which proves that NTF-PVP nanoparticles have been enriched at the tumor site.

3.3. Characterization of photothermal properties

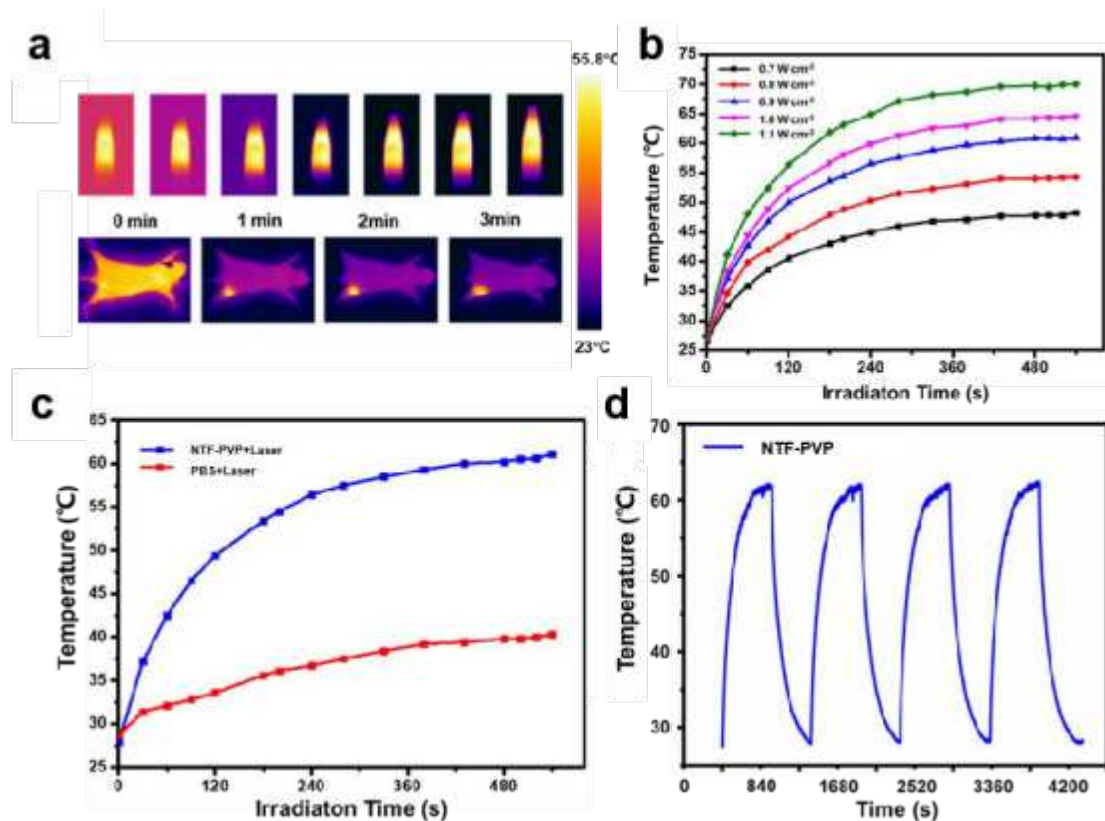


Fig. 3(a) Infrared thermal image at different time intervals after injecting NTF-PVP at the nude mouse tumor (b) Temperature change of 980 nm laser irradiation NTF-PVP solution with different power density (c) Temperature change of NTF-PVP solution and PBS control group under 980 nm laser irradiation (d) Heating/cooling curve after 4 times of NTF-PVP solution under repeated on/off 980 nm laser irradiation.

To verify the photothermal performance of NTF-PVP nanoparticles in vivo, we took out 200 μ L NTF-PVP solution and injected it into the tumor site of 4T1 nude mice through tumor in-situ injection. Use a 980 nm laser to continuously irradiate the centrifuge tube equipped with a certain solution and continue to irradiate the tumor site of the nude mouse for 3 minutes. Observe the temperature change of the solution in the centrifuge tube by tracking the thermal signal under the infrared thermal imager and observe the temperature change of NTF-PVP nanoparticles in its body by tracking the thermal signal of the 4T1 tumor-bearing mouse under the infrared thermal imager [7, 9].

As shown in Fig. 3a, with the passage of 980 nm laser irradiation time, the temperature of the solution in the centrifuge tube containing NTF-PVP solution continues to increase. With the passage of 980 nm laser irradiation, the temperature of the tumor site of the nude mouse rises rapidly, eventually reaching about 55 °C, which can kill tumor cells and effectively inhibit their malignant proliferation.

We irradiate the NTF-PVP solution with a 980 nm laser with different power densities and use an infrared thermal imager to monitor the temperature change of the sample. As shown in Fig. 3b, with the increase of the excitation power of the laser, the maximum temperature that the NTF-PVP solution can reach after irradiation increases significantly, which proves that NTF-PVP has obvious power dependence and controllability. To test the in vitro photothermal performance of NTF-PVP, as shown in Fig. 3c, the temperature of the NTF-PVP solution rises from 27 °C to about 60 °C after being continuously irradiated by a 980 nm laser. The temperature of the centrifuge tube with the same volume as PBS is relatively slow to rise after continuous irradiation by a 980 nm laser, which proves that NTF-PVP has an excellent photothermal effect. Finally, we tested the photothermal stability of NTF-PVP nanoparticles, set the same power 980 nm laser to irradiate NTF-PVP solution, and studied the photothermal stability of NTF-PVP nanoparticles through four on/off cycles of 980 nm laser. As shown in Fig. 3d, after 4 cycles, the photothermal effect of NTF-PVP nanoparticles has not significantly fluctuated, highlighting their excellent photothermal stability [11, 12, 13].

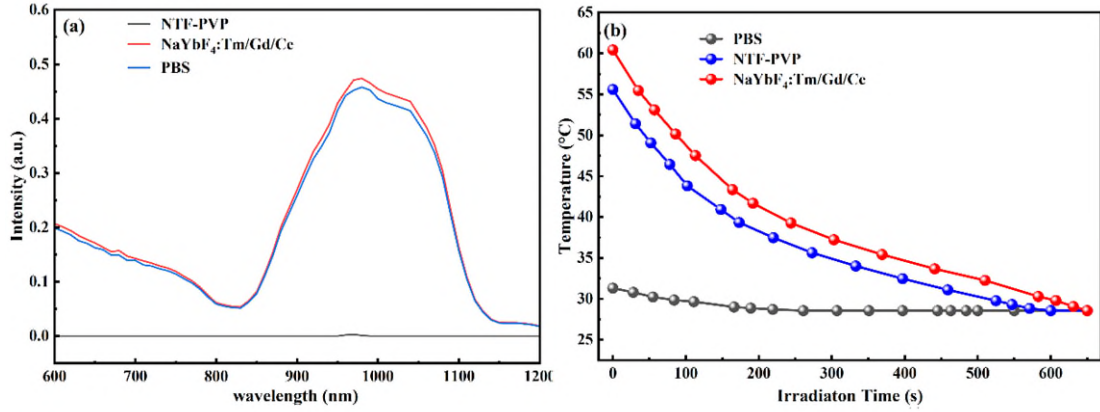


Fig. 4 (a) UV-vis-NIR absorption spectra of NaYbF₄: Tm/Gd/Ce and NTF-PVP; (b) Photothermal heating and cooling curves of NaYbF₄: Tm/Gd/Ce and NTF-PVP under 980 nm laser irradiation (3.2 W).

Fig. 4 presents the optical absorption spectra and photothermal heating/cooling curves of the as-prepared samples. As shown in **Fig. 4(a)**, the PBS control exhibits a nearly flat baseline across the 600–1200 nm range, indicating negligible light absorption at 980 nm. In contrast, both NTF-PVP and NaYbF₄:Tm/Gd/Ce nanoparticles display distinct absorption peaks around 980 nm, confirming their strong capability to harvest NIR laser energy. Notably, the absorbance intensity of NTF-PVP ($A_{980} = 0.47088$) is slightly higher than that of the uncoated core ($A_{980} = 0.45224$), suggesting an enhanced light-harvesting efficiency after CaF₂ shell coating, which correlates well with its superior photothermal performance observed in subsequent experiments.

Fig. 4(b) illustrates the temperature evolution of the samples under 980 nm laser irradiation (3.2 W) over time. Upon laser exposure, the temperature of the PBS control increases only marginally, reaching a maximum of approximately 31 °C, which confirms that the solvent's intrinsic photothermal contribution (Q_{dis}) is negligibly small. In sharp contrast, the NTF-PVP dispersion exhibits a rapid temperature elevation to 60.43 °C, corresponding to a temperature rise (ΔT) of 31.87 °C. Meanwhile, the NaYbF₄:Tm/Gd/Ce core reaches a maximum temperature of 55.59 °C with a ΔT of 27.04 °C. These results unequivocally demonstrate that both materials possess efficient photothermal conversion capabilities under 980 nm excitation, with the NTF-PVP showing superior performance due to its enhanced absorbance and reduced surface quenching.

After the laser is turned off (at approximately 400 s), all samples undergo natural cooling and eventually return to ambient temperature (28.56 °C) within 650 s. The cooling segments of these curves were further analyzed to quantify the photothermal conversion efficiencies (η) using the Roper model. The initial 84 s of the cooling phase were selected for fitting because this period exhibits the largest temperature difference and the fastest cooling rate, thereby providing the most accurate reflection of the system's heat dissipation characteristics. The calculated η values are **34.4%** for NTF-PVP and **28.7%** for NaYbF₄:Tm/Gd/Ce, respectively. These values are among the most competitive reported for rare-earth-based photothermal agents in the NIR-II region and highlight the beneficial role of the CaF₂ inert shell in enhancing photothermal performance.

Taken together, **Fig. 4(a) and (b)** establish a clear structure–property relationship: the enhanced NIR absorbance enabled by the CaF₂ shell (Fig. 4a) directly translates into superior photothermal heating (Fig. 4b), ultimately yielding a high photothermal conversion efficiency. This integrated dataset provides robust evidence for the potential of NTF-PVP as an effective agent for NIR laser-induced photothermal therapy.

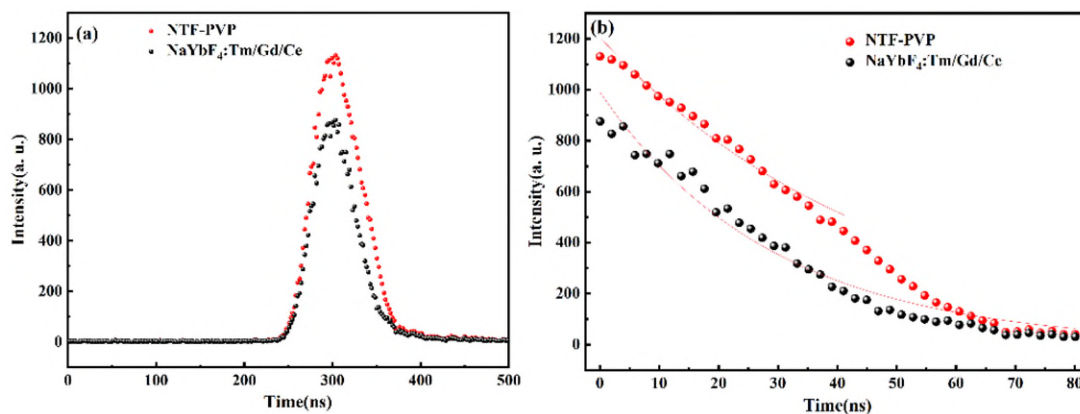


Fig. 5 (a) Raw time-resolved photoluminescence (TRPL) decay curves of NaYbF₄:Tm/Gd/Ce core and NTF-PVP core–shell nanoparticles under pulsed laser excitation; (b) Normalized TRPL decay curves after time-zero correction (peak shifted to 0 ns) with single-exponential fitting (solid lines). The fitted lifetimes are 29.2 ns for the bare core and 47.6 ns for NTF-PVP.

Fig. 5 presents the time-resolved photoluminescence (TRPL) decay spectra of NaYbF₄:Tm/Gd/Ce core and NTF-PVP core–shell nanoparticles. As shown in Figure 5(a), the raw decay curves display a complete evolution of luminescence intensity following the excitation pulse centered at approximately 300 ns. The rising edges reflect the instrument response

function (IRF) and the laser pulse profile, while the falling edges represent the intrinsic luminescence decay dynamics of the materials. Notably, the NTF-PVP sample (red) exhibits a significantly higher peak intensity (approximately 1150 a.u.) compared to the bare core (black, approximately 850 a.u.), indicating that the CaF_2 shell coating substantially enhances the emission efficiency by suppressing surface-related nonradiative recombination.

Fig. 5(b) shows the normalized decay curves after time-zero correction, where the peak maximum at ~ 300 ns in Fig. 5(a) was shifted to 0 ns, and only the initial 0–80 ns decay segment is displayed to exclude the tail noise. The scattered symbols represent the experimental data, and the solid lines correspond to single-exponential (ExpDec1) fitting. The fitting results reveal that the bare core exhibits a short lifetime of approximately 29.2 ns, whereas the NTF-PVP sample shows a markedly prolonged lifetime of approximately 47.6 ns. This significant enhancement in lifetime (approximately 63% increase) directly demonstrates that the epitaxial CaF_2 shell effectively passivates surface defects and inhibits nonradiative energy dissipation channels [24, 25, 26]. The prolonged lifetime, combined with the enhanced emission intensity, unambiguously confirms the superior photoluminescence performance of the core-shell architecture, making it highly promising for NIR-II bioimaging applications.

The prolonged lifetime observed in NTF-PVP is fully consistent with the enhanced NIR-II photoluminescence intensity (Fig. 1B) and the superior photothermal conversion efficiency (Fig. 4), collectively demonstrating that the CaF_2 inert shell not only suppresses surface quenching but also channels the absorbed energy into both radiative and thermal pathways more efficiently.

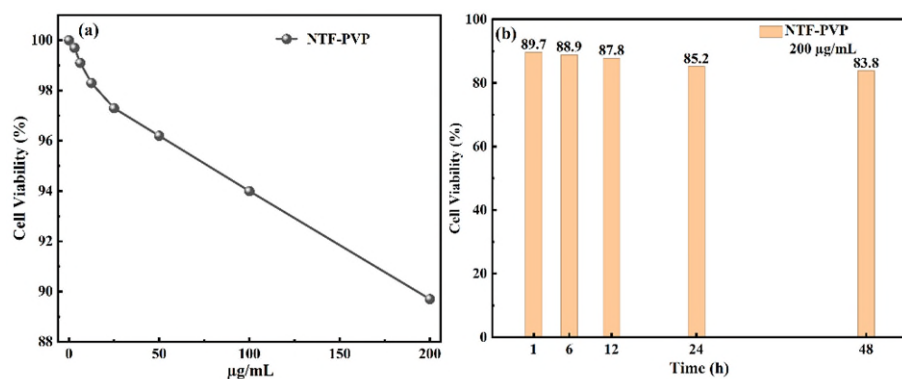


Fig. 6 (a) Concentration-dependent cell viability of 4T1 cells after 1 h incubation with NTF-PVP at various concentrations (0–200 $\mu\text{g/mL}$); (b) Time-dependent cell viability of 4T1 cells incubated with NTF-PVP at a fixed concentration of 200 $\mu\text{g/mL}$ for 1–48 h.

Fig. 6 presents the in vitro cytotoxicity of NTF-PVP against 4T1 cells evaluated by the standard CCK-8 assay. The consistently high cell viability (>80%) across all tested conditions confirms the excellent biocompatibility of NTF-PVP, which is attributed to the PVP surface modification and the intrinsic biocompatibility of the CaF₂ shell components [33, 34]. As shown in Fig. 5(a), the cell viability exhibited a gradual concentration-dependent decrease upon exposure to NTF-PVP at concentrations ranging from 0 to 200 µg/mL for 1 h. Remarkably, even at the highest tested concentration of 200 µg/mL, the cell viability remained above 90%, indicating exceptionally low intrinsic cytotoxicity within the entire tested concentration range under short-term exposure.

Fig. 6(b) illustrates the time-dependent cytotoxicity of NTF-PVP at a fixed concentration of 200 µg/mL over an extended incubation period from 1 h to 48 h. The cell viability showed only a modest decline from 89.7% (at 1 h) to 83.8% (at 48 h), still maintaining a high level above 83% even after prolonged incubation.

Collectively, these results unequivocally demonstrate that NTF-PVP possesses excellent biocompatibility, with cell viability consistently exceeding 80% under all tested conditions, including high concentration (200 µg/mL) and prolonged incubation (up to 48 h). This low cytotoxicity renders NTF-PVP highly suitable for further biomedical applications, particularly in the context of in vivo photothermal therapy.

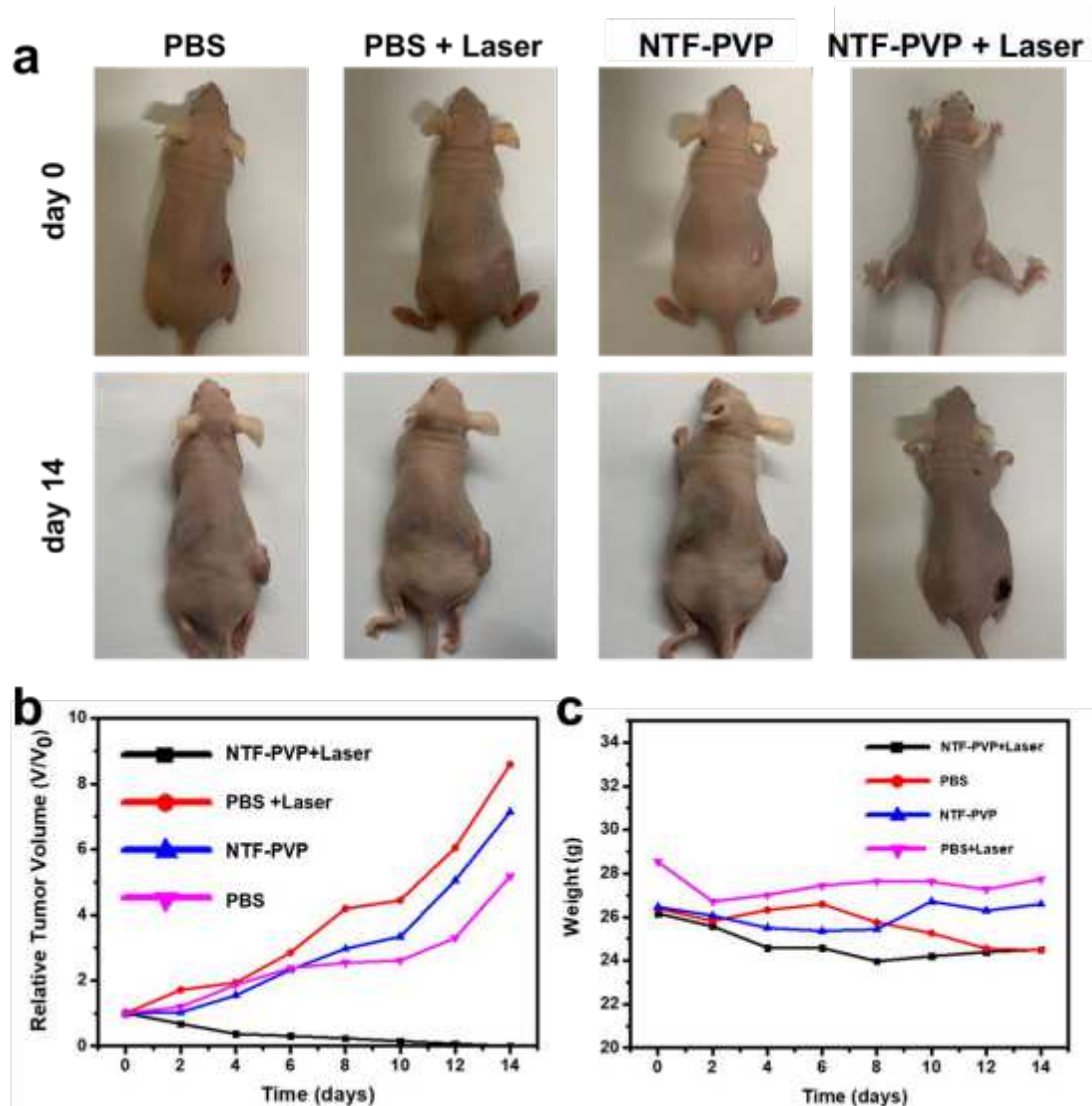


Fig. 7(a) Photos of tumor changes on days 0 and 14 in the injection NTF-PVP photothermal treatment group and other control groups (b) Relative growth curve of tumors in the injection NTF-PVP photothermal treatment group and other control groups (c) Weight change curve in NTF-PVP photothermal treatment group and other control groups.

The 4T1 tumor-harned nude mice were divided into four groups: (1) tumor-retaining nude mice injected with PBS in stituto; (2) tumor-in-site injection of PBS + tumor-in-site nude mice irradiated by 980 nm laser; (3) tumor-injecting nude mice with NTF-PVP solution of the same volume; (4) tumor-in-place Inject the same volume of NTF-PVP solution + tumor-in-computed naked mice with 980 nm laser irradiation at the tumor. After that, the corresponding laser irradiation treatment and observation were carried out on each group of nude mice every other day for 14 days.

As shown in Fig. 7a, by comparing the tumor change photos of each group of nude mice on days 0 and 14, it can be found that except for the fourth group, the tumors of the nude mice in the control group continued to grow. At the same time, it is obvious that the tumors of the fourth group of nude mice were eliminated, leaving only black scars in the original tumor site, which proves that the tumors of the fourth group of nude mice have been effectively treated. It is well known that within 14 days of PTT, changes in tumor volume and weight of nude mice can reflect the therapeutic effect and safety. The corresponding curve of the relative volume change of the tumor of each group of tumor-restrained naked mice is shown in Fig. 7b, and the tumor growth of the fourth group of tumor-loaded naked mice is continuously inhibited. In contrast, the tumors of the other groups of tumor-borne nude mice were in a state of continuous growth. As shown in Fig. 7c, during photothermal treatment, the weight of each group of nude mice remained stable, which proves that the use of NTF-PVP nanoparticles for PTT is highly safe.

4. CONCLUSIONS

The synthesized NTF-PVP nanoparticles have a good photothermal effect. In 14 days of treatment, it can have a very good effect on clearing tumor cells. Therefore, NTF-PVP nanoparticles have good potential in tumor treatment, which is consistent with the general advantages of rare-earth-based photothermal agents reported previously [7, 9]. Overall, our findings align with the general principles of energy transfer regulation in rare-earth doped core-shell systems [44].

We investigated the fluorescence performance change of β -NaYbF₄: 5%Tm³⁺, 30%Gd³⁺, 2%Ce³⁺ nanoparticles after epitaxial growth of a CaF₂ shell. The epitaxially grown CaF₂ shell has a thickness of approximately 1.6 nm, which can effectively reduce the surface quenching and concentration quenching effects of the β -NaYbF₄: 5%Tm³⁺, 30%Gd³⁺, 2%Ce³⁺ core nanoparticles, leading to an enhancement of the NIR-II PL intensity of the product [20, 22-26]. Moreover, calcium and fluorine in CaF₂ are constituent elements of human bone, which can greatly improve the biocompatibility of nanoparticles [20, 21]. Finally, surface modification of the NTF nanoparticles with NOBF₄ and PVP endows the nanoparticles with high biocompatibility [29-34]. Meanwhile, both in vitro and in vivo experiments demonstrate that NTF-PVP nanoparticles achieve satisfactory therapeutic effects when used for PTT. In conclusion, NTF-PVP nanoparticles represent an excellent PTT agent with potential application value in cancer therapy.

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