

Assembled magnetic nanoparticles for photosensitive nitric oxide release and turn-on fluorescence detection *in situ*



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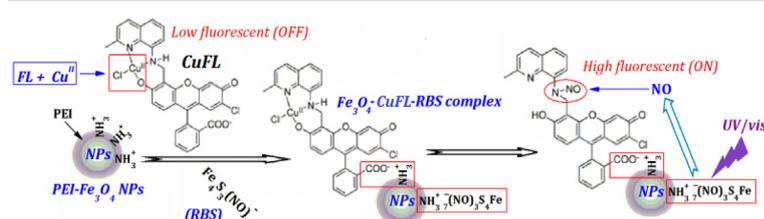
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HIGHLIGHTS

- Non-fluorescent Fe₃O₄–CuFL–RBS nanocomposites were facily prepared by electrostatic interactions.
- The nanocomposites enabled releasing NO upon visible light irradiation.
- The released NO could be detected *in situ* based on selective fluorescence turn-on response of nanocomposites to NO.

GRAPHICAL ABSTRACT



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ABSTRACT

Under electrostatic interactions, polyethylenimine-stabilized Fe₃O₄ magnetic nanoparticles were assembled with photosensitive nitric oxide (NO) donors (Fe₃S₃(NO₇⁻), RBS) and CuFL complex consisting of fluorescein derivatives (FL) and Cu^{II} to prepare Fe₃O₄–CuFL–RBS nanocomposites. The as-prepared nanocomposites exhibited weak fluorescence and hardly any release of NO upon light irradiation of 480 nm. The nanocomposites enabled NO release due to RBS photolysis under 365 nm light irradiation, while the released NO could *in situ* conjugate with CuFL to form FL–NO complex based on N-nitrosate reaction, which was verified by fluorescence increase responses of FL–NO (excited at 480 nm). Thus, Fe₃O₄–CuFL–RBS nanocomposites realized light-triggered NO release and turn-on fluorescence detection of NO *in situ*.

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1. Introduction

As a free radical molecule, nitric oxide (NO) is produced in endothelial cells from L-arginine by different forms of NO synthase, and possesses important functions in biological systems [1]. NO is commonly used for a signal and bio-regulatory molecule to mediate multiple biological events (e.g., tumor growth and suppression), or

used for a γ -radiation sensitizer to enhance the selectivity of killing neoplastic tissues [2,3]. So far, great efforts have focused on the synthesis of composites that can serve as the NO source to store NO [4]. Especially, the photoactive NO delivery systems surpassing other NO sources and precursors have generated much interests as they can conduct highly controllable release of NO and specific delivery of NO to targeting sites [5]. Photochemical triggered precursors with UV–visible light can be precisely controlled by photoexcitation, thereby facilitating the timed, located and dosage-controllable administration of drugs or agents [6].

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Earlier researches have revealed that NO donors and NO probes are separated usually, and they barely present in the same system simultaneously [7,8]. Nevertheless, NO donor complex that can release NO and *in situ* detect NO would be promising especially for its biomedical applications. Quantum dots-carboxymethyl chitosan (CMC)-based NO donors were prepared and enabled the spontaneous release of NO in physiological environments [7]. Researchers adopted fluorescence decrease/quenching mode (turn-off) to detect NO released *in situ*. By contrast, the “turn-on” mode (fluorescence enhancement) is preferable due to the reduced changes of false positives [9]. The CMC-folic acid (FA) complex has been assembled with photosensitive donors of NO, ($\text{Fe}_4\text{S}_3(\text{NO}_7^-)$) (abbreviated as RBS) to fabricate CMC-FA-RBS nanoconjugates, which realized light-triggered release of NO without the detection of NO *in situ* [10]. In addition, Tan et al. developed a CuFL-chitosan diazeniumdiolate system that could perform spontaneous NO release in buffer solutions and real-time fluorescence increase (“turn-on” mode) detection of NO *in situ* [8].

2-[2-Chloro-6-hydroxy-5-[(2-(methylcarboxy) quinolin-8-ylamino) methyl]-3-oxo-3H-xanthen-9-yl] (abbreviated as FL) is one of fluorescein derivatives that can form a 1:1 complex with Cu^{II} (CuFL) [11,12]. CuFL reacts with NO and causes remarkable fluorescence increase *via* nitrosation of secondary amine on ligands [12]. CuFL responds to NO selectively and yields *N*-nitrosated ligand (FL-NO). CuFL is responsible for fluorescence turn-off response and could be developed toward a probe of NO, together with combined advantages including water-solubility, nontoxicity, cell-membrane-permeation and high biocompatibility [13–15]. In the past decade, similar organic and inorganic fluorescence probes have been reported extensively [16–24].

As established, superparamagnetic nanocomposites have become a favorite topic due to their promising targeted/site-specific capacities, high magnetization, good biocompatibility and reduced side-effect [25–28]. In this regard, we developed a new nanocomposite system (Fe_3O_4 -CuFL-RBS) that could perform light-triggered NO release, *in situ* fluorescence turn-on detection of NO and potential magnetism-targeted delivery when used as a smart carrier. Herein, superparamagnetic Fe_3O_4 nanoparticles (NPs) were assembled with CuFL to form Fe_3O_4 -CuFL nanocomplex, which was used for a fluorescence “turn-on” probe of NO [29]. The expected Fe_3O_4 -CuFL-RBS were newly developed based on good results from Fe_3O_4 -CuFL studies. In terms of the advantages of Fe_3O_4 -CuFL-RBS nanocomposites, they could be further developed for biomedical applications, especially in targeting drug delivery, photo-controlled drug release and *in vivo* tracking related to fluorescence signal amplifying.

2. Material and methods

Polyethylenimine (PEI)-stabilized Fe_3O_4 NPs were prepared based on the reported method [29], and the details are available (Part S1 in Supplementary Data). Under ultrasonication and agitation, 2.5 mL of CuFL aqueous solution (10 μM , with Cu: FL molar ratio of 1: 1) was dropwisely added into the aqueous suspension of PEI- Fe_3O_4 NPs (1 mg mL^{-1} , 20 mL), followed by the addition of 2.5 mL of RBS aqueous solution (1 wt%, Na^+ salts of RBS [30]) to prepare Fe_3O_4 -CuFL-RBS nanocomposites. Other chemicals with analytical grade were purchased from Shanghai Chemical Reagent Corp. Phosphate buffered saline (PBS, 10 mM) and deionized water was utilized in all experiments.

Transmission electron microscope (TEM) images were acquired by a JEOL JEM-1400 TEM operating at 120 kV of acceleration voltage. Vibrating sample magnetization (VSM) curves were recorded by a vibrating-sample PPM-9 magnetometer at 305 K. X-ray diffraction (XRD) patterns were measured by a D5005 X-ray powder diffractometer equipped with $\text{Cu K}\alpha$ radiation. The NO concentrations were detected using colorimetric Griess reaction (Part S2 in Supplementary Data). Emission spectra were obtained with a FLSP 920 fluorescence spectrophotometer.

3. Results and discussion

Under electrostatic interactions, Fe_3O_4 -CuFL-RBS nanocomposites were prepared and showed the potential for NO release and *in situ* fluorescence turn-on detection of NO (Fig. 1). In view of the paramagnetic Cu^{II} center and photoinduced electron transfer, fluorescent FL becomes low/non-fluorescent (OFF) after conjugation with Cu^{II} to form CuFL complex [8,29]. Upon excitation with 365 nm light (the maximum absorption peak of RBS) [10], NO was released from nanocomposites due to RBS photolysis. The released NO could *in situ* conjugate with CuFL to form a new FL-NO complex *via* *N*-nitrosate reaction, which resulted in fluorescence increase (turn-on) [8].

As shown in Fig. 2a, the prepared PEI- Fe_3O_4 NPs have a uniform, discrete and spherical shape. By analyzing the diameter distribution of 200 particles in TEM visual field, Fig. 2b displays an average diameter of 8.7 ± 0.6 nm. Fig. 2c shows the nearly zero coercivity and remanence, which reveal the superparamagnetism features of Fe_3O_4 NPs and Fe_3O_4 -CuFL-RBS nanocomposites. The saturation magnetization of Fe_3O_4 NPs is ~ 3.4 emu g^{-1} , but it decreases to ~ 2.3 emu g^{-1} for the Fe_3O_4 -CuFL-RBS. This might result from the combination of CuFL and RBS around the surface of Fe_3O_4 NPs, which quenches the magnetic moment [31,32]. In Fig. 2d, Fe_3O_4 is the dominant phase in the two samples and five characteristic peaks for Fe_3O_4 NPs were observed, implying that the binding

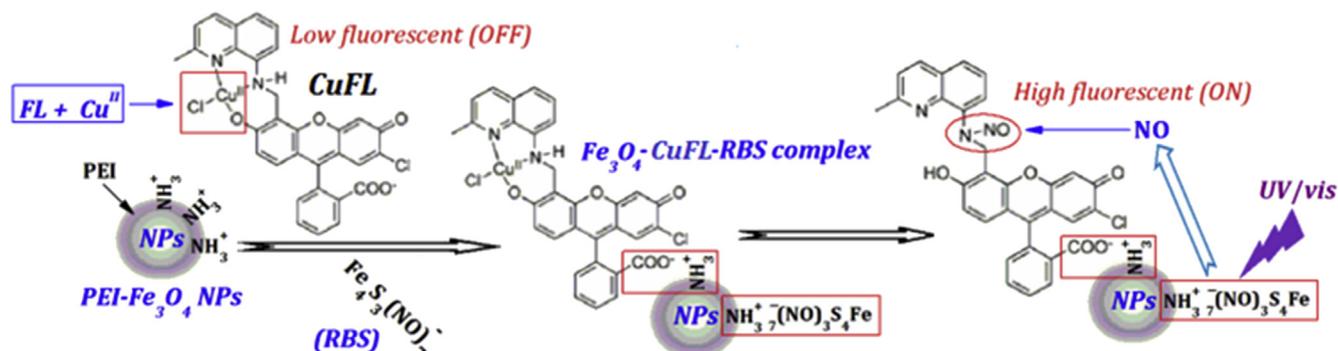


Fig. 1. Schematic illustration of the synthetic procedures and properties of Fe_3O_4 -CuFL-RBS nanocomposites.

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