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Full Length Article

Afterglow properties of CaF_2:Tm nanoparticles and its potential application in photodynamic therapy

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ABSTRACT

CaF_2:Tm nanoparticles (NPs) were synthesized by the hydrothermal method. Intense afterglow emission with long life time was found for the produced NPs, so its applicability in photodynamic therapy was investigated. Since the wavelength of the afterglow emission of the NPs fairly matches with the absorption band of the PpIX sensitizer, especially in the red region, the Cystein mediator was used to bond NPs with the PpIX sensitizer. The CaF_2:Tm NPs conjugated with PpIX was exposed to X-ray and by using the Antracene as detector, the production of the singlet oxygen was verified. Therefore, the produced NPs are recommended as a source of energy that improves photodynamic therapy beyond its current limitations.

1. Introduction

Cancer is a malignant type of disease characterized by cells that show uncontrolled growth and have the ability to invade and destroy other tissues. Different traditional treatments for cancer include surgical removal of tumor tissue [1], chemotherapy using compounds that are toxic principally to rapidly growing cells [2] and radiation therapy, where ionizing radiationis directed to the tumor and disrupts the replication of its genetic material [3]. In addition, surgery, chemotherapy and radiotherapy all tend to be immunosuppressive and limit due to risk of cosmetic and functional damage [4]. Photodynamic therapy (PDT) is an emerging alternative to radiation therapy and surgical resection [5]. PDT has been designated as a promising new strategy in the treatment of cancer since the early 1980s [6]. The main advantages of PDT over other techniques are the selectivity of drug accumulation in tumor, the ability to focus the light on the tumor region and the absence of toxicity caused by the drug alone [7]. PDT is a treatment modality that combines a photosensitizing agent with a proper wavelength of light in order to selectively destroy cells. The interaction of photons with photosensitizers in the presence of oxygen molecules, results in the formation of reactive oxygen species (ROS), such as singlet oxygen ($^1O_2$), or free radicals, which can then render apoptotic and necrotic cell death [7,8]. The generation process of ROS has been reviewed in detail [9].The efficiency of PDT is determined by the ROS production which depends on several parameters including the photosensitizer used, light intensity and wavelength and oxygen concentration [10].

During the past few decades, various types of photosensitizer molecules have been synthesized. Many organic dyes, porphyrins and derivatives, flavins and other biomolecules are efficient sensitizers [11]. Porphyrins, chlorines and bacteriochlorins are among the most useful photosensitizers [12]. In 1961 the capacity of Hematoporphyrin derivatives (HpD) to induce a cytotoxic effect in the presence of light with an appropriate wavelength was reported. HpD have been the only photosensitizers used in human clinical studies [13]. Protoporphyrin IX (PpIX) is an efficient hydrophobic sensitizer that is activated by light. The subsequent interaction of activated PpIX with molecular oxygen produces cytotoxic ROS, particularly singlet oxygen ($^1O_2$), that causes irreversible destruction of the target tissue [14–16].

Despite the advantage of PDT over some other techniques, there are two important limitations on PDT, the first one is the side effects of the photosensitizers, and the second is the lack of penetration of visible light in tissues. Therefore, it seems logic to look for new modalities in order to decrease undesired side effects, and at the same time to increase the depth of treatment [17]. To solve the problem of light penetration and enhance the PDT treatment for deep cancers, afterglow NPs has been used. The advent of nanosciences opened up new possibilities for PDT

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[18,19], where NPs were used as highly sophisticated, multifunctional medicines. Theoretically, NPs have potential to improve PDT beyond its current limitations [20].

Afterglow or long-lasting phosphors are doped materials, particularly rare earth-doped materials, with persistent light emission after cessation of excitation [21,22].The afterglow mechanism is related to electron traps, so afterglow luminescence remains from several seconds to hours or is required to overlaps with the absorption wavelength of the photosensitizer [23]. Recently, afterglow NPs such as CaF_2:Eu, ZnO, CdS, ZnS:Cu, Co and LaF_3:Tb were suggested as light source for PDT activation [24–26]. CaF_2:Tm NPs have unique luminescence characteristics which render to use for PDT. In this work, a new PDT mediated by CaF_2:Tm afterglow NPs is designed for the first time in which the light is generated by NPs with attached photosensitizers.

2. Materials and methods

The raw materials used for synthesis of CaF_2:Tm NPs were Ca$(NO_3)_2$ (of 99.95% purity), NH_4F (of 99.9% purity), $Tm(NO_3)_3$ (of 99.99% purity), Brij 35 (of 99.9% purity) and distilled deionized water, ethanol and methanol (all from Merck Chemicals). Protoporphyrin (PpIX) and L-Cystein were produced from Sigma-Aldrich, Germany and EDC (ethyl dimethylaminopropyl carbodiimide), NHS (N-Hydroxy succinimide), DMSO and Anthracen from Fluka, Switzerland. The hydrothermal method was used for preparation of CaF_2:TmNPs based on following reaction [27].

$$Ca(NO_3)_2+2NH_4F\rightarrow CaF_2+2NH_4(NO_3)$$

The solution of Brij 35 surfactant and calcium nitrate were prepared by mixing them slowly while was placed on a stirrer. Thulium nitrate and L-cysteine were added to the above solution and finally the ammonium fluoride was included very slowly while stirred. The final mixture was placed in an autoclave at 200 °C for 12 h, followed by cooling. The solid part was collected by centrifuging the product mixture and was washed with deionized water for several times. The obtained nanostructures were dried in an oven for 2 h at 150 °C. Then the solution of EDC was added to protoporphyrin (PpIX) in DMSO drop by drop while stirring and after 10 min, NHS was added slowly. Then the solution of CaF_2:Tm NPs conjugated to L-Cystein, were added to the last solution of PpIX and EDC dropwise. The stirring was continued for 24 h. Finally, the conjugates of CaF_2:Tm NPs with PpIX were separated by centrifuging and purified by washing with ethanol.

3. Characterization

The structural characterization of the synthesized sample was supported by X-ray diffraction (XRD) with RigakuD-maxcIII diffractometer using CuK_α radiations. SEM images were obtained using a scanning electron microscope model Philips XL-30 ESEM equipped with energy dispersive spectrometer (EDS). UV–visible absorption spectroscopic measurements were recorded by Shimadzu UV1700 spectrometer. In addition, infrared measurements were recorded on a Buck 100 instrument using KBr pellets at room temperature. Photoluminescence (PL) spectrum was recorded using a Perkin-Elmer spectrometer model LS55 with photo multiplier tube and Xenon lamp at room temperature. For afterglow measurements, a 20 W UV lamp from Nitride Semiconductors Co., with an irradiation peak at 250 nm and a100 kVp, 80 mA X-ray facilities with 1 Gy/min irradiation dose rate were used as excitation sources. Afterglow emission spectra and decay curves were detected using a cooled electro-optic spectrometer (Thermo-Electric cooled and regulated CCD, Avantec Co., NL-6961 RB Eerbeek, the Netherlands). The Ava Spect-2048 × 14 Fiber Optic Spectrometer was a back-thinned type CCD spectrometer with high quantum efficiency and high UV sensitivity.

4. Results and discussion

As stated in Section 2, the synthesis procedure and characterization of CaF_2:Tm NPs has been reported earlier by our team [27]. X-ray diffraction (XRD) pattern of CaF_2:Tm NPs is shown in Fig. 1. XRD analysis of the NPs showed a cubic lattice structure in correspondence with the ICSD collection code no. 060368 which is observed below the figure.

The broad peak in low angle region is due to the glass which was used as cell in XPD process.The crystalline size of CaF_2:Tm NPs was estimated using the Scherer's formula which was calculated to be approximately 40 nm. In order to further reveal the size and the shape of the prepared CaF_2:Tm NPs, the SEM images were utilized

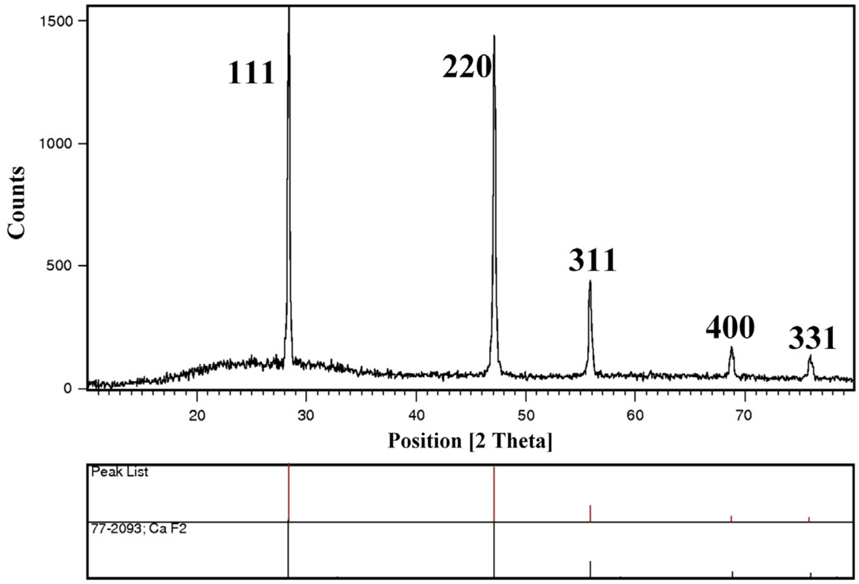

Fig. 1. X-ray diffraction (XRD) pattern of CaF_2:Tm NPs. The position of XRD peaks of the bulk CaF_2 crystalline are shown at the below.