Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 151 (2015) 174–183

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

The effect of ascorbic acid on the photophysical properties and photodynamic therapy activities of zinc phthalocyanine-single walled carbon nanotube conjugate on MCF-7 cancer cells

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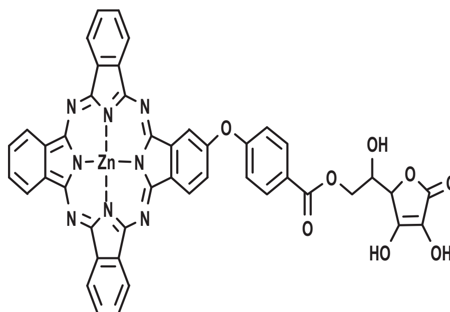
HIGHLIGHTS

- Zinc mono carboxy phenoxy phthalocyanine is coordinated to ascorbic acid.
- The conjugate shows improved photophysical behavior.
- However ascorbic acid suppresses the photodynamic therapy activity.

GRAPHICAL ABSTRACT

Zinc mono carboxy phenoxy phthalocyanine was linked to ascorbic acid with improved photophysical properties. Ascorbic acid was however found to suppress the photodynamic therapy of cancer activity of the phthalocyanine.



ARTICLE INFO

Article history:
Received 7 January 2015
Received in revised form 17 June 2015
Accepted 18 June 2015
Available online 20 June 2015

Keywords:
Singlet oxygen quantum yield
Single walled carbon nanotubes
Zinc carboxy phenoxy phthalocyanine
Ascorbic acid
Photodynamic therapy

ABSTRACT

Zinc mono carboxy phenoxy phthalocyanine (**1**) was chemical modified with ascorbic acid via an ester bond to give ZnMCPPc-AA (**2**). Complexes **2** and **1** were coordinated to single walled carbon nanotubes via π–π interaction to give ZnMCPPc-AA-SWCNT (**3**) and ZnMCPPc-SWCNT (**4**) respectively. Complexes **2**, **3** and **4** showed better photophysical properties: with improved triplet lifetimes and quantum yields, and singlet oxygen quantum yields when compared to **1** alone. The photodynamic therapy activities of complexes **1**, **2**, **3** and **4** were tested *in vitro* on MCF-7 breast cancer cells. Ascorbic acid suppresses the photodynamic therapy effect of **1**, due to its ability to reduce oxidative DNA damage as a result of its potent reducing properties. The highest phototoxicity was observed for **4** which resulted in 77% decrease in cell viability, followed by **3** which resulted in 67% decrease in cell viability. This shows the importance of combination therapy, where the phthalocyanines are the photodynamic therapy agents and single walled carbon nanotubes are the photothermal therapy agents.

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1. Introduction

Metallophthalocyanines (MPcs) are being explored as potential photosensitizers for photodynamic therapy (PDT) due to their exclusive properties that meet the requirements of an ideal photosensitizer. These include intense absorption between 600 and

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http://dx.doi.org/10.1016/j.saa.2015.06.063
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800 nm where the skin is fairly transparent, low dark toxicity and strong phototoxicity due to their ability to generate cytotoxic reactive oxygen species (ROS), especially singlet oxygen [1–5].

Several MPcs have showed high photodynamic therapy activities (*in vitro*) against different cancers [6–8] and some are in clinical trials for PDT [3,9,10]. However, lack of biocompatibility, tumor cell specificity and low cellular uptake remain as draw-backs for the use of MPcs. Consequently, MPcs with different functionalities have been conjugated to different biomolecules such as vitamins [11], amino acid [12], sugars [13–15] for improved biocompatibility and cellular uptake. Thus, the MPc used in this work was linked to ascorbic acid. The conjugate was further adsorbed on single walled carbon nanotube (SWCNTs) as a drug delivery agent.

Cameron et al. [16–18] showed that patients who received ascorbic acid (AA) survived 300 days longer than controls. In addition, the intravenous administration of ascorbate in pharmacological concentrations can selectively kill cancer cells [19–22] due to its ability to generate hydrogen peroxide (H_2O_2) that can further produce free radicals. However, there have been conflicting reports on the role of AA in cancer therapeutics; Kurbacher et al. [23] reported that AA improves the anti-neoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast cancer cells *in vitro* while studies by Subramani et al. [24] stated that AA suppresses cell death in MCF-7 human breast cancer cells induced by tamoxifen. Ascorbic acid is a well-known antioxidant and would be expected to quench singlet oxygen and other ROS required for PDT. We report on the effect of ascorbic acid on the PDT activity of Pc when the two are linked. The effect of ascorbic acid on the PDT efficiency of phthalocyanines is reported for the first time in this work. We do show in this work that AA improves the triplet state quantum yield of the Pc in organic media.

SWCNTs are potential anticancer drug [25] which kill cancer cells through photothermal effect (PTT) [26,27] as a result of their strong absorption of near infrared light. There have been several reports on the effect of SWCNTs (*in vitro*) on different chemotherapeutic drugs on MCF-7 breast cancer cells. Jeyamohan et al. [27] reported on the accelerated killing of MCF-7 cancer cell by doxorubicin using SWCNTs as PTT and drug delivery agents, while Fu et al. [28] reported on improved therapeutic effect of asparagine-glycine-arginine-SWCNT-Paclitaxel.

In this works, we present a study of combination therapy using a dual modality protocol, in which an MPc (or MPc-AA) conjugates are the PDT agents and SWCNTs are the PTT agents. We investigated the role of AA and SWCNTs on the PDT activities of zinc mono carboxy phenoxy phthalocyanine (ZnMCPPc (**1**), Scheme 1) on MCF-7 cancer cells. AA was conjugated via ester bond to **1** represented as ZnMCPPc-AA (**2**) followed by adsorption of **2** on SWCNTs (through π–π interaction) represented as ZnMCPPc-AA-SWCNT (**3**). Experiments were performed where ZnMCPPc (without AA) was adsorbed on SWCNTs (represented as ZnMCPPc-SWCNT, **4**) and SWCNT-COOH linked to AA (represented as SWCNT-AA).

2. Experimental

2.1. Materials

Cultures of MCF-7 breast cancer cells were obtained from Cellonex®. Dulbecco's phosphate-buffered saline (DPBS) and Dulbecco's modified Eagle's medium (DMEM) were obtained from Lonza®. Heat-inactivated fetal calf serum (FCS, 10% (v/v)), 100 μg/mL-penicillin–100 unit/mL-streptomycin-amphotericin-B-mixture were obtained from Biowest®. Zinc phthalocyanine (ZnPc), ascorbic acid and dimethylaminopyridine (DMAP) were from Sigma Aldrich®. Single-walled carbon nanotubes (SWCNT-COOH, 1–5 nm in diameter and 1–5 μm in length) were obtained from Nanolab. Dimethylsulfoxide (DMSO), hexane, N,N′-dicyclohexylcarbodiimide (DCC), dimethylformamide (DMF), and tetrahydrofuran (THF) were obtained from SAARCHEM. ZnMCPPc (**1**) [29] was synthesized according to literature methods.

2.2. Equipment

Fluorescence lifetimes were measured with a FluoTime 300 'EasyTau' spectrometer (PicoQuant GmbH) using a time correlated single photon counting (TCSPC) technique. The samples were excited at 670 nm with a diode laser (LDH-P-670, 20 MHz repetition rate, 44 ps pulse width, PicoQuant GmbH). The detector employed was a Peltier cooled Photomultiplier (PMA-C 192-M, PicoQuant GmbH).

Absorption spectra were recorded on a Shimadzu UV–Vis 2550 spectrophotometer and fluorescence emission and excitation spectra on a Varian Eclipse spectrofluorimeter using a 360–1100 nm filter. The absorbance ranged between 0.04 and 0.05 at the excitation wavelength for all samples.

Laser flash photolysis experiments were performed to determine the triplet decay kinetics. The excitation pulses were produced by a tunable laser system consisting of an Nd:YAG laser (355 nm, 135 mJ/4–6 ns) pumping an optical parametric oscillator (OPO, 30 mJ/3–5 ns) with a wavelength range of 420–2300 nm (NT-342B, Ekspla). The details have been reported [30]. Triplet life-times were determined by the exponential fitting of the decay curves using Origin-Pro 8 software.

The time resolved phosphorescence of singlet oxygen at 1270 nm was used to determine the singlet oxygen quantum yields of all the complexes in DMSO, details have been described by Modisha et al. [31]. The singlet oxygen phosphorescence signal was compared with that of ZnPc standard.

Photo-irradiation for the PDT effects of the complexes were performed using a general electric quartz lamp (300 W); 600 nm glass (Schott) to filter off ultra-violet radiation. No water filter was used hence the samples were exposed to near infrared region where the SWCNTs absorb. Light intensities were measured with a POWER MAX 5100 (Mole-electron detector incorporated) power meter and were found to be 4.3×10^{15} photons $cm^{-2}\,s^{-1}$. The cultured cells were viewed using a Zeiss AxioVert.A1 fluorescence LED (FL-LED) inverted microscope.

X-ray powder diffraction (XRD) patterns were recorded on a Bruker D8 Discover equipped with a Lynx-Eye Detector, using CuK_α radiation (λ = 1.5405 Å, nickel filter). Data were collected in the range from 10° to 100°, scanning at 1° min^{-1} with a filter time-constant of 2.5 s per step and a slit width of 6.0 mm. Details have been provided [32].

Mass spectra data were collected with a Bruker AutoFLEX III Smart beam TOF/TOF mass spectrometer. The instrument was operated in the positive ion mode using an *m/z* range of 400–3000 amu. The spectra were acquired using alphacyano-4-hydroxycinnamic acid as the MALDI matrix, with a 355 nm Nd:YAG laser as the ionizing source. Infrared spectra were recorded on a Perkin-Elmer Universal ATR Sampling accessory spectrum 100 FT-IR spectrometer. The elemental micro analysis was measured using Vario MICRO cube.

Raman spectra were obtained using a Bruker RAM II spectrometer (equipped with a 1064 nm Nd:YAG laser and a liquid nitrogen cooled germanium detector). Solid samples diluted with KBr were used. Thermogravimetric analysis (TGA) were recorded on a Shimadzu DTG-TG 60H with a gas flow of 120 ml/min and operated under a nitrogen atmosphere at 10 °C/min.

Transmission electron microscopy (TEM) images were obtained using a Zeiss Libra TEM 120 model operated at 90 kV.

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