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Effects of Pluronic F127 micelles as delivering agents on the *vitro* dark toxicity and photodynamic therapy activity of carboxy and pyrene substituted porphyrins

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ABSTRACT

Metal free, Zn and ClGa containing carboxyphenoxy and phenoxy groups (complexes **1**) and pyrene groups (complexes **2**) were synthesized and embedded into Pluronic F127 micelles (represented as F127). Dark toxicity and photodynamic therapy activities of the embedded porphyrins were successfully studied on MCF-7 breast cancer cells. Dark toxicity showed more than 80% cell viability for all complexes. It was found that **1**-Zn + F127 showed better photodynamic therapy activity compared to **1**-H_2 + F127, and **1**-ClGa + F127, corresponding to the high partition coefficient for the Zn porphyrin derivatives. The same applies to **2**-Zn + F127 compared to **2**-H_2 + F127, **2**-ClGa + F127. **1**-ClGa and **1**-Zn were also linked to Pluronic F127 silica nanoparticles. PDT activities for embedded **1**-ClGa + F127 and **1**-Zn + F127 were much higher than when linked to Pluronic silica nanoparticles (PluS NPs), showing the importance of loading of porphyrins into Pluronic F127 as a drug delivering agent rather than linking. PDT studies at the highest concentration of 60 μg/ml showed decrease in cell viability down to 15.9% for **2**-Zn + F127. The K_p was determined in biphasic octanol and water system.

1. Introduction

Photodynamic therapy (PDT) is a minimally invasive treatment of tumor cells, which requires laser light of appropriate wavelength, a viable photosensitizer, and molecular oxygen [1,2]. The electronically excited photosensitizer (porphyrin) transfers its energy to ground state molecular oxygen to produce excited singlet oxygen, which acts as the chief cytotoxic species resulting in irreversible photo-damage of the tumor cells [1,2].

There has been a strong research focus on synthetic porphyrins for many decades due to a wide range of possible applications, such as in photodynamic therapy (PDT) [2], photodynamic antimicrobial chemotherapy (PACT) [3–5], optoelectronics and biosensing [6].

Porphyrins are well-known photosensitizers for PDT [2,7]. However, they are known to aggregate [8], which affects their photophysical behavior. The driving forces behind the aggregation of porphyrins are the cooperative formation of hydrogen bonds, van-der-Waals forces and the hydrophobic effects [9–11]. Triblock copolymers such as Pluronics reduce the self-aggregation and increase solubility of porphyrins in aqueous media [9,12]. Encapsulation of porphyrins into Pluronic micelles results in water solubility for porphyrins that are not water soluble [13–15].

Pluronics are triblock copolymers which are composed of poly (ethylene oxide) (PEO) and poly(propylene oxide) (PPO) with a PEO-PPO-PEO structure [16–22], Scheme 1. Pluronic triblock copolymer spontaneously forms micelles with an estimated diameter of 30–50 nm at concentrations equal to or above the critical micelle concentration (CMC) [12,23,24]. Several Pluronics have been approved by Food and Drug Administration (FDA) [25–27]. Pluronic F127 triblock-copolymer's biocompatibility and relatively small size help to prevent their micelles from being recognized by proteins and macrophages therefore allowing a greater circulation time [28]. It has been reported that micelles with diameters below 50 nm are able to deeply penetrate tumor tissue in spite of elevated interstitial pressure [29].

5-(4-Carboxyphenoxy)-10,15,20-tris(phenyl)-porphyrin (**1**-H_2) and its ClGa and Zn derivative (**1**-ClGa, **1**-Zn), and metal free 5,10,15,20-tetra(1-pyrenyl) porphyrin (**2**-H_2), and its ClGa (**2**-ClGa) and Zn (**2**-Zn) derivatives (structures are shown in Fig. 1) are embedded into Pluronic F127 micelles in this work. **1**-H_2, **1**-ClGa and **1**-Zn have been linked to Pluronic-silica nanoparticles (PluS NPs) to form **1**-H_2 (PluS, linked), **1**-ClGa (PluS, linked) and **1**-Zn

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