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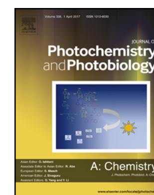

5,10,15,20-Tetrakis (4-carboxyphenyl) porphin-conjugated poly(l-lactic) acid/polyethylene oxide nanofiber membranes for photodynamic therapy

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This article is dedicated to Professor Dr. Chen-Ho Tung's eightieth birthday.

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ABSTRACT

In this work, a poly(l-lactic) acid (PLLA)/polyethylene oxide (PEO) nanofiber membrane was prepared by electrospinning as a carrier for the photosensitizer 5,10,15,20-tetrakis (4-carboxyphenyl) porphin (TCPP) to study the effects of singlet oxygen ($^1O_2$) on tumor cells. Scanning electron microscopy and confocal laser scanning microscopy images showed that the fiber surface was smooth and that TCPP was evenly dispersed in the nanofibers. TCPP, PLLA, and PEO were mixed with nanofibers without the formation of new chemical bonds, as shown by Fourier transform infrared spectroscopy. The addition of PEO improved the hydrophilicity of the nanofibers, making the contact angle of the PLLA nanofiber membrane change from 93.3° to near 0° and resulting in good cell compatibility. The sustained release experiment showed that when the amount of TCPP was 3%, the cumulative release concentration after 72 h was close to saturation in the test system. Electron spin resonance spectroscopy confirmed that TCPP produced $^1O_2$ at light irradiation (532 nm). The results of in vitro cell experiments showed that TCPP@PLLA/PEO nanofiber membranes did not affect the normal growth of HeLa cells but had cytotoxic effects on cancer cells under light irradiation.

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1. Introduction

Photodynamic therapy (PDT) is a targeted treatment that uses an exogenous photosensitizer (PS), such as hematoporphyrin or dihematoporphyrin ether, which can quickly accumulate in hyperplastic and new tissues, particularly tumor tissues, under the appropriate visible light or near infrared light irradiation, producing singlet oxygen ($^1O_2$) or other reactive oxygen species and causing irreversible damage to the tumor or diseased tissue [1,2]. PDT has two advantages: PS can be selectively accumulated in tumor tissue cells by connecting target molecules or drug carriers, and the light dose and scope can be controlled, allowing PDT to target tumor cells. As a new technique with high efficiency, minimal trauma, low toxicity, and selectivity [3], PDT is being tested in the clinical setting for the treatment of cancers of the head and neck, brain, lung, pancreas, intraperitoneal cavity, breast, prostate, and skin [4].

There are three parameters affecting the clinical application of PDT: PSs, light wavelength, and selective drug delivery [5]. In the selection of a drug carrier, since most PSs have high lipophilicity, it is necessary to select a suitable encapsulation strategy to protect the hydrophobic PS from the aqueous environment. At present, nanospheres, nanocapsules, micelles/liposomes, and polymer particles (nanoparticles and microparticles) are widely used as PDT drug carriers. For example, oil-based micelles using polyoxyethylene castor oil (Tween-80, Cremophor-EL, etc.) enhance drug loading and increase tumor uptake. Moreover, liposomal formulations can improve the efficacy and safety of PSs [6,7]. As polymer nanofibers whose physical and chemical properties, structure, and size are adjustable, PSs can simulate the biological microenvironment to varying degrees and can covalently immobilize a variety of tumor targeting molecules; thus, PSs are also valuable drug carries [8,9]. After resection of a tumor, PS-loaded nanofibers can be directly deposited on the wound. By slow release of PSs from fibers,

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PSs will accumulate in the tumor cells; subsequent irradiation of the cells with a specific wavelength of light will induce PS-dependent $^1O_2$ production to kill the tumor cells directly.

Electrospinning is an important technology for the preparation of polymer nanofibers ranging from submicrometers to nanometers in diameter [10,11]. Nanofibers are laminated to form nanofiber membranes with large surface areas, high porosity, flexibility, and surface functionality [12] to allow use in cell tissue engineering, biosensors, wound materials, and drug release systems [13]. Severyukhina et al. [14] used this technique to prepare a composite membrane of PS and chitosan, demonstrating that PS-loaded nanofibers affected the metabolic activity of T-47D cancer cells, but not MC3T3-E1 noncancer cells. Henke et al. [15] reported the preparation of TMPyP-loaded polystyrene nanofibers exhibiting photooxidative activity against inorganic and organic molecules and antimicrobial activity against Escherichia coli. Additionally, Yoo et al. [16] reported that polyving akohol nanofibers loaded with the PS 5-aminolevulinic acid were prepared by electrospinning and coated on metal scaffolds; they dound that these nanofibers were effective for the treatment of cholangiocarcinoma.

Polylactic acid (PLA) is a medical polymer with good biodegradability and biocompatibility and has been widely used for orthopedic internal fixation, controlled drug release, and tissue engineering [17,18]. However, because PLA lacks a hydrophilic structure, the surface is strongly hydrophobic.; this is conducive to combination with hydrophobic drug molecules but affects the material and cell affinity [19]. Accordingly, it is necessary to modify PLA to increase its hydrophilicity. The currently available methods for improving the hydrophilicity of PLA include copolymerization, grafting, and blending modification. Falconi et al. [20] used PLA and gelatin to prepare novel PLA microspheres with hydrophilic and bioadhesive surfaces using coprecipitation techniques. Ke et al. [21] mixed PLA with starch and polyvinyl alcohol to improve the hydrophilicity of the material and improve the tensile strength of the blend.

In this report, nanofiber membranes containing 5,10,15,20-tetrakis (4-carboxyphenyl) porphin (TCPP), poly(l-lactic) acid (PLLA), and polyethylene oxide (PEO) were prepared by electrospinning, resulting in the formation of a TCPP@PLLA/PEO sustained release system. The effects of PLLA/PEO nanofibers on sustained release of TCPP and cytotoxicity in tumor cells after irradiation at 532 nm were investigated.

2. Materials and methods

2.1. Materials

PLLA (average molecular weight [Mw] of 100,000 Da) was purchased from Jinan Dai Gang Biotechnology Company (Jinan, China). PEO (Mw = 1,000,000 Da) was purchased from Alfa Aesar. Dichloromethane (DCM, AR) and *N,N*-dimethylacetamide (DMAC, AR) were purchased from Beijing Chemical Works. TCPP, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium-bromide (MTT), and 9,10-anthracenediyl-bis(methylene)-dimalonic acid were purchased from Sigma-Aldrich (St. Louis, MO, USA). Phosphate-buffered saline (PBS; 0.1 M, pH 7.2–7.4) was purchased from Solarbio. Dulbecco's modified eagle medium (DMEM) was purchased from Gibco. A Cell Counting Kit-8 (CCK-8) was purchased from Dojindo Laboratories. A live/dead cell imaging kit was purchased from Life-Technology. 2,2,6,6-Tetramethyl piperidine (TEMP) was purchased from J&K Scientific. PLLA and PEO were dried in an oven at 60 °C for 8 h. Other reagents were used without any purification.

2.2. Preparation and methods

2.2.1. Preparation of TCPP-loaded PLLA/PEO nanofibers

According to the parameters listed in Table 1, we weighed a certain amount of TCPP, PLLA, and PEO and added the material to the DCM, with magnetic stirring for 8 h. After being completely dissolved, DMAC was added, and stirring was continued for 30 min to prepare a TCPP/PLLA/PEO mixed solution.

Electrospinning was carried out using electrospinning equipment. The solution was sucked into a syringe, and the flow rate was controlled with a syringe pump. A stainless steel flat-mouthed nozzle with a diameter of 0.32 mm and a stainless steel receiver measuring 20 cm in diameter were used. A high-voltage DC power supply (0–40 kV) was used. The electrospinning parameters were set as follows: flow rate, 1 mL/h; voltage, +8.5 kV; receiving distance, 15 cm; drum speed, 60 rpm. The temperature of the experiments was 25 °C, and the environment humidity was 30%. All processes involved in TCPP were carried out in the dark to prevent degradation of TCPP. The nanofiber membranes obtained by electrospinning were dried in a vacuum oven at 60 °C for 8 h to completely remove the solvent.

2.2.2. Characterization

The obtained nanofiber membranes were observed by scanning electron microscopy (SEM; S-4800; Hitchi, Japan) to determine the surface morphology (acceleration voltage: 10 kV). Prior to testing, all samples were sprayed with an ion sputtering apparatus (Mc1000; Hitachi) with a gold injection parameter of 10 mA for 60 s (particle size: 8–10 nm, film thickness: <5 nm). The fiber diameter was calculated using Nano Measure 1.2 software. Each fiber membrane sample was selected for 100 fibers in a SEM image at 1000 × magnification. Subsequently, the diameter distribution and average diameter were analyzed using Origin (OriginLab Corporation). The characteristics of aggregation of TCPP in nanofibers were imaged by confocal laser scanning microscopy (CLSM; N-C2-SIM, Japan) with an excitation wavelength of 561 nm. The components in the nanofibers were characterized by Fourier transform infrared spectroscopy (FTIR, Excalibur 3100; Varian, USA). The hydrophilicity of the membranes was measured using a

Table 1
TCPP/PLLA/PEO solutions with different ratios.

Serial number	Sample code	Polymer concentration (wt%)	PLLA/PEO (w/w)	DCM/DMAC (w/w)	TCPP/(PLLA/PEO)(wt%)
1	PLLA/PEO 4−0	4	5/1	6/4	0
2	PLLA/PEO 4−1	4	5/1	6/4	1
3	PLLA/PEO 4−2	4	5/1	6/4	2
4	PLLA/PEO 4−3	4	5/1	6/4	3
5	PLLA 4-1	4	/	6/4	1

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