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Nanostructures of an amphiphilic zinc phthalocyanine polymer conjugate for photodynamic therapy of psoriasis

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ABSTRACT

Psoriasis is a chronic inflammatory skin disease affecting 2–5% of the population worldwide and it severely affects patient quality of life. In this study, an amphiphilic zinc phthalocyanine polymer conjugate (ZPB) was synthesized, in which zinc phthalocyanine (ZnPc) was conjugated with the poly(ethylene glycol) (PEG) chain of Brij 58. ZPB showed two maximum UV–vis absorption wavelengths, 348 nm and 678 nm. A monomolecular micelle of ZPB formed in water with a mean size of 25 nm and zeta potential of −15 mV. The nanostructures aggregated into cloudy precipitates, which were easily dispersed. The nanostructure showed the shell–core structure with the ZnPc segments as the core and the PEG chains as the shell. The anti-psoriasis effect of the ZPB nanostructure was explored using a guinea pig psoriasis model. After comparing the anti-psoriasis effects of saline, light alone, ZPB alone, and the combination of light and ZPB, the combination of light and ZPB showed the best photodynamic therapy of psoriasis based on the light excitation of the photosensitizer ZPB and the psoriasis was nearly cured according to the histopathological investigation. The ZPB nanostructure is a promising anti-psoriasis nanomedicine based on photodynamic therapy.

1. Introduction

Psoriasis is a chronic inflammatory skin disease that affects 2–5% of the population worldwide [1,2]. It is characterized by an excessive growth and abnormal differentiation of keratinocytes in skin lesions, which can moderately or severely affect patient quality of life [3]. Three methods are clinically used for psoriasis treatment, including topical therapy, phototherapy and systemic therapy. However, none of these strategies is ideal and safe [2]. Recently, one kind of silver nanoparticles was tried to treat psoriasis by topical application [4]. In conventional phototherapy, photosensitizers are injected into the circulation and phototherapy begins after a specific time period. However, systemically administered photosensitizers and long-term exposure of ultraviolet A (320–400 nm) or B (290–320 nm) radiation could result in severe side effects, such as hepatotoxicity, renal toxicity, hypertension, hyperlipidemia, and skin cancer [5]. Aminolevulinic acid (5-ALA) is currently used in the clinic via an oral route for the phototherapy of psoriasis. It is also used topically to treat psoriasis under red light in some reports, although pain and limited therapeutic efficiency are reported to occur [6].

An important mechanism of photodynamic therapy (PDT) is the oxidation of biomacromolecules by singlet oxygen ($^1O_2$), which is generated via energy transfer from the excited photosensitizer to molecular oxygen. Phthalocyanine is a second-generation photosensitizer. Compared to the first-generation photosensitizer (e.g., 5-ALA), phthalocyanine occupies a better safety and efficacy profile. More importantly, the excitation wavelength of phthalocyanine is long and falls within the range of 600–800 nm [7]. It is well known that the light of longer wavelengths readily penetrates more deeply into the skin [8,9]. Phthalocyanine is highly water-insoluble, resulting in the inconvenience of its use in the systemic or topical applications. The water-soluble derivatives of phthalocyanine were synthesized and they could be applied for intravenous administration [10]. However, the membrane permeability of water-soluble molecules is weak, particularly for the thick lesions of psoriasis. The lipid derivatives of phthalocyanine and two octa-substituted phthalocyanines were prepared and investigated for topical treatment of psoriasis [11]. However, the tetrahydrofuranazone formulations had to be applied due to the strong hydrophobic property of the lipid derivatives. The topical application of organic solvents likely results in severe skin stimulation and side effects.

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Moreover, some novel inorganic and hybrid nanoscale photosensitizers take new therapeutic opportunities [12–14].

In this study, we designed an amphiphilic zinc phthalocyanine polymer conjugate, in which zinc phthalocyanine (ZnPc) was the core and a biocompatible amphiphilic polymer, Brij 58,was the shell. It has been reported that nanocarriers have good skin permeability and can deliver cargos to the deep tissues of the skin, particularly favoring the treatment of psoriasis [2,15,16]. Brij-type surfactants have been reported to have the ability overcoming the multidrug resistance of cancer cells [17]. We prepared the ZnPc-contained amphiphilic polymer conjugate and the formed nanostructures were further explored for the PDT of psoriasis.

2. Materials and methods

2.1. Materials

4-Nitrophthalonitrile was purchased from Beijing Beshine Chemical Co., Ltd., China. Polyoxyethylene (20) cetyl ether (Brij 58) was obtained from Sigma (St. Louis, MO, USA). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was obtained from Beijing Ouhe Technology Co., Ltd., China. Organic solvents were of analytical grade, and other chemicals were of reagent grade. 9,10-dimethylanthracene (DMA) was from TCI (Tokyo, Japan). Zinc phthalocyanine (ZnPc) from TCI was used as the control in the determination of singlet oxygen quantum yield. Azone was purchased from Beijing Chemical Reagent Company. Polyvinylpyrrolidone (PVP K30) was obtained from Shanghai Well-Tong Material Technology Co., Ltd. Propranolol Hydrochloride Tablets were purchased from Shanxi Yunpeng Pharmaceutical Co., Ltd. Purified water was prepared using the Heal Force Super NW Water System (Shanghai Canrex Analytic Instrument Co., Ltd., China) and used throughout the study. Ultraviolet–visible (UV–vis) spectra, infrared (IR) spectra, nuclear magnetic resonance (^{1}H NMR, 400 MHz) spectra and mass spectra were recorded on a TU-1901 UV-vis spectrophotometer (Beijing Purkinje General Instrument Co., Ltd., China), Bio-Rad FTS-65A infrared ray spectrometer (Bio-Rad Laboratories Inc., CA, USA), JNM-ECA-400 NMR spectrometer (JEOL Ltd., Tokyo, Japan) and MALDI–TOF mass spectrometer (Bruker, Germany), respectively. A microscope (BDS200-FL, Chongqing Optec Instrument Co., Ltd., China) and dual-light He–Ne laser instrument (JK-3, Beijing Institute of Radiation Medicine, China) were used.

2.2. Animals

Healthy male guinea pigs (weight, 180–220 g) were obtained from the Laboratory Animal Center of Beijing Institute of Radiation Medicine (BIRM). Food and water were freely supplied. All of the protocols for animal experiments were approved by the Animal Care and Use Committee of BIRM and performed according to the Guide for the Care and Use of Laboratory Animals. The animals were sacrificed to obtain tissues. All of the studies were performed according to the DECLARATION of Helsinki.

2.3. Synthesis of the amphiphilic zinc phthalocyanine polymer conjugate

Three steps were performed in the synthesis of the amphiphilic ZnPc derivative, i.e., the ZnPc-Brij 58 conjugate (ZPB). The preparation details are shown in Fig. 1. 4-Nitrophthalonitrile (1.72 g, 10 mmol) was dissolved in dimethyl sulfoxide (DMSO, 50 ml). 4-Hydroxyl benzoic acid (1.66 g, 12 mmol) was added and stirred until dissolved. Next, K_2CO_3 (17 g) was added, and the reaction proceeded for 72 h at room temperature. The reaction was terminated by pouring the solution into ice-cold water followed by adjusting the pH to 1.0 with hydrochloride acid. A large amount of precipitates were formed, which were further maintained for 12 h at room temperature. The precipitates were filtered and washed with water until neutral. The solid was recrystallized from methanol three times and a white crystal of 4-(4-carboxyl benzyloxyl)phthalocyanitrile was obtained with a yield of 84%.

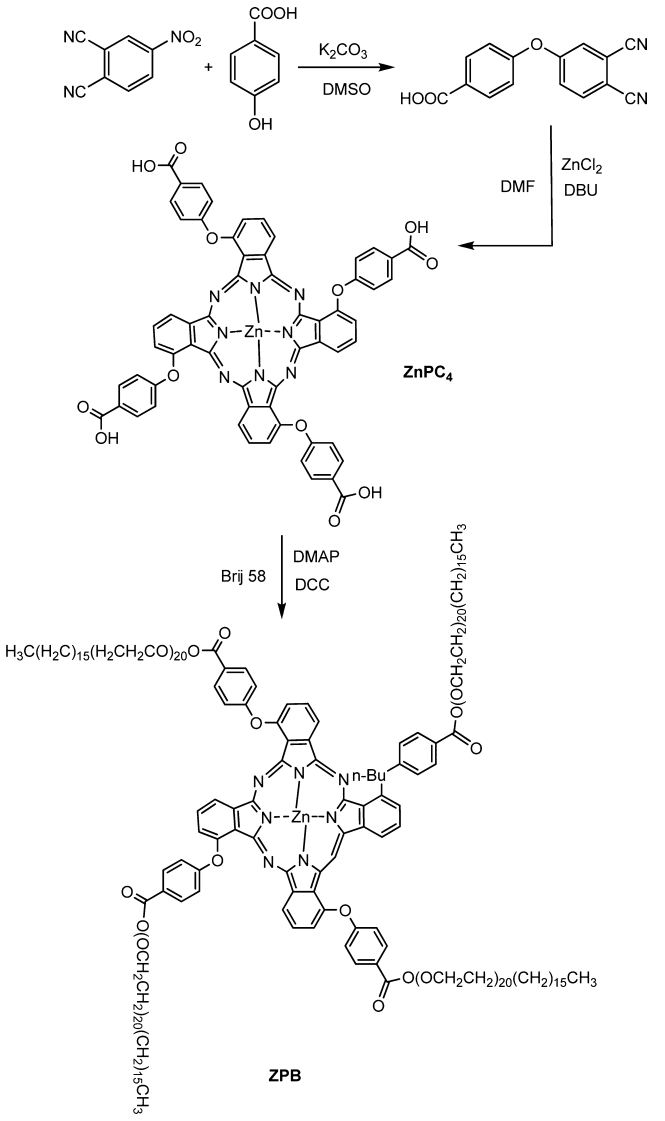

Fig. 1. Synthetic route of the zinc phthalocyanine Brij 58 conjugate (ZPB).

The second step is the synthesis of zinc β-tetra-(4-carboxyl benzyloxyl)phthalocyanine ($ZnPC_4$) [18,19]. 4-(4-Carboxyl benzyloxyl)phthalocyanitrile (1.06 g, 4 mmol) was dissolved in N,N′-dimethylformamide (DMF, 30 ml) and heated to 60 °C in a bath. $ZnCl_2$ (0.53 g, 4 mmol) was added under a nitrogen atmosphere and dissolved. DBU (1 ml) was added. The solution was quickly heated to 200 °C and refluxed for 12 h. The reaction was terminated by pouring the solution into an aqueous solution of 2 M HCl followed by overnight storage. The precipitates were filtered and washed with water to a neutral pH. The precipitates were dried and purified using a silica column with tetrahydrofuran (THF) as the eluent until no green liquids flowed. The filtrates were collected and the solvent was removed to obtain a green solid of $ZnPC_4$ ($C_{60}H_{32}N_8O_{12}Zn$) with a yield of 42%. TLC: cyclohexane/methanol, 1:5, v/v, R_f = 0.7; UV (THF): λ_{max} = 354, 674 nm; IR (KBr) ν_{max} (cm^{-1}): 748.1 (Zn—N), 1095.6, 1504.6, 1599.2, 1678.9 (phthalocyanine), 1237.4 (Ar—O—Ar), 1716.0 (—CO—), 2955.8, 3070.9,