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Water-soluble ferrocene complexes (WFCs) functionalized silica nanospheres for WFC delivery in HepG2 tumor therapy

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ABSTRACT

Silica-encapsulated nanospheres of water-soluble ferrocene complexes WFCs@SiO_2 and WFCs@SiO_2@glutaraldehyde (GA) were first synthesized by a facile inverse-microemulsion method. The surface functional groups, particle size, and morphologies of nanospheres were characterized by IR spectra, UV–vis absorption spectra, dynamic light scattering (DLS) and SEM images. Single-crystal X-ray diffraction was used to confirm the molecular structure of free ferrocenyl-pyrazol ligand (**L**) and three WFCs, namely, $[Ni(C_{22}H_{14}F_6FeN_4O_4)(H_2O)_4]$ (**5a**), $[Mg(C_{22}H_{14}F_6FeN_4O_4)(H_2O)_4]\cdot 3H_2O$ (**5b**), and $[Ba(C_{22}H_{14}F_6FeN_4O_4)(H_2O)_3]$ (**5c**). The electrochemical properties of **5a–5c** were explored by cyclic voltammetry. The WFCs-loading capacities of **5a–5c** in WFCs@SiO_2 were found to be 38.4, 38.2, and 38.1 μg/mg, respectively. Cell studies under two drug delivery modes (free diffusion and endocytosis) were carried out by MTT cell-survival assays and morphological observation of HepG2 cells. It's interesting that the cytotoxicity of WFCs against HepG2 was increased by applying silica nanocarriers. Compared to WFCs@SiO_2, the modification of GA on the spherical surface provided not only the better water-dispersity but also additional functional groups for further modification of other pharmacophores. The novel nanocarrier system for WFC delivery present a novel concept-of-proof method to protect varieties of affordable metal-based anticancer agents in physiological conditions and provided experimental basis for future studies focusing on drug delivery of other WFCs.

1. Introduction

Nowadays, although the overall mortality of cancer declines due to remarkable breakthroughs made in diagnosis and treatment, cancer is still one of the leading causes of death with a high rate [1]. In addition to radiation and surgical intervention, current cancer treatments rely heavily on cisplatin-based chemotherapy, which has been used for more than 30 years [2,3]. However, the inefficiency on platinum-resistant tumors and severe side effects of these costly cisplatin-based treatments has become a considerable challenge for cancer therapy. In this situation, alternative metal-based anticancer medicines should be developed. Among the non-platinum antitumor agents, ferrocene complexes have recently received increasing attention due to their advantages of hypotoxicity, ease of modification and good redox properties [4,5]. A large number of therapeutic agents which incorporate ferrocene as pharmacophore on the scaffold of biologically active molecule have been found to be one of the most promising antitumor candidates [6–8]. In 2016, Hussain's group designed a ferrocenyl neodymium(III) complex, which shows remarkable photocytotoxicity in cancer cells superior to those without the ferrocenyl moiety [9]. Arambula and coworkers reported a series of ferrocenylated *N*-heterocyclic carbene supported gold(I) complexes as potential anticancer agents in A549 lung cancer cells [10]. Two main anticancer mechanisms were suggested for the notable anticancer advances exhibited by these ferrocene complexes. The first mechanism is that ferrocene unit undergoes a fast and reversible oxidation process and turns into corresponding ferrocenium cation ($Fc^{2+} \rightarrow Fc^{3+}$). This oxidation process can catalyze the production of reactive oxygen species (ROS) and generate oxidative DNA damage [11]. The second mechanism is that ferrocene unit can disturb the normal functioning of the mechanism compromising cell viability and induce tumor cell cycle arrest in some phases and subsequent apoptosis [12]. Nevertheless, further clinical applications of ferrocene complexes in cancer therapy have been hindered by the low solubility and low stability in physiological conditions, which are common problems facing by most metal complexes [13,14]. Much attention should be given to explore more novel water-soluble ferrocene complexes-based drugs with good biocompatibility.

Recent advances in nanocarriers, as significant application of

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nanotechnology, offer an alternative approach to resolve many of challenges in developing metal-based anticancer medicines with high drug-loading ability, low toxicity, and controlled-release properties [1,15]. Additionally, nanocarriers can protect metal complexes drugs from adverse environments, enhance permeability and retention (EPR) effect, improve the delivery of poorly soluble drugs, and lead specific accumulation in targeted cells/tissues, thereby achieving high treatment efficiency with low side effects [14,16]. The development of multifunctional nanocarriers for drug delivery with enhanced anticancer effects has been in the forefront of current cancer therapies and drug formulations. To date, various materials such as micelles, polymers, metal particles, carbon nanotubes, and silica nanoparticles have been used to fabricate the nanocarriers for drug delivery [17–22]. Among these materials, encapsulation with silica to protect metal complexes drugs from adverse environments in physiological conditions has been well developed because of the high biocompatibility, chemical stability, tunable functionalization and low-toxicity degradation pathways of silica material [23,24]. In 2016, Lin and coworkers reported a multifunctional nanocarrier system based on mesoporous silica for targeted delivery of a ruthenium(II) complex, whose further clinical application is limited by low aqueous solubility and great cytotoxicity to normal cell lines [25]. This system dramatically enhanced the anticancer efficacy of ruthenium(II) *N*-heterocyclic carbene complex and decreased its cytotoxicity to normal cells.

Inspired by the recent contributions on ferrocene complexes and silica nanocarriers for cancer therapy, we firstly designed and synthesized one ferrocenyl-pyrazol ligand (L) with acetic acid moiety. Subsequently, corresponding water-soluble ferrocene complexes (WFCs) were prepared by solvent evaporation. Single-crystal X-ray diffraction was used to confirm the molecular structure of free ligand **L** and three synthesized ferrocene complexes (5a–5c). The electrochemical properties of 5a–5c were explored by cyclic voltammetry. Importantly, three WFCs acted as potential anticancer agents were further encapsulated in silica to form the multifunctional nanospheres (WFCs@SiO_2 and WFCs@SiO_2@glutaraldehyde (GA)) through a facile inverse-microemulsion method (Fig. 1). The positive charge of the surface and spherical morphology of silica-encapsulated nanospheres can partly enhance the selective uptake by endocytosis in cancer cells and thereby improve their anticancer efficacy. In particular, the obtained WFCs@SiO_2 nanospheres were further cross-linked by GA to increase water-dispersity and provide additional functional groups on the spherical surface for further modification of other pharmacophores. Finally, a series of cell studies under two different drug delivery modes (free diffusion and endocytosis) was carried out on their cytotoxicity by both MTT cell-survival assays and morphological observation of HepG2 cells. With the use of this presented strategy on investigating nanocarriers for WFC delivery, other metal-based antitumor agents can also be encapsulated in silica nanospheres and undergo further modification to achieve higher anticancer efficacy.

2. Experimental section

2.1. Materials and general methods

All reagents and solvents were obtained from commercial sources and used without further purification unless specified. Elemental analyses (C, H and N) were performed on a Vario MACRO cube elemental analyzer. NMR spectra were recorded on a Bruker AVANCE III 500 MHz spectrometer using the deuterated solvent of $CDCl_3$ and d_6-DMSO as internal standard. IR spectra were recorded in the range 4000–400 cm^{-1} using KBr pellets on a BRUKER TENSOR 27 spectrophotometer. Thermogravimetric analysis (TGA) was operated on SHIMADZU TA-60ws under N_2 conditions from room temperature to 1000 °C with a heating rate of 10 °C·min^{-1}. UV–vis absorption spectra of solutions were recorded from 300 to 800 nm at room temperature with a Shimadzu UV-1750 spectrophotometer. The zeta potential and particle size of nanospheres was analyzed on a Delsa™ Nano system (Beckman Coulter). Scanning electron microscopy (SEM) images were obtained using an S-4800 instrument (Hitachi Ltd.) with the accelerating voltage of 10.0 kV.

2.2. Preparation of the ligand L

The ligand **L** was synthesized according to the procedure described in Fig. 2.

(i) The synthesis of compound **1** and **2** was performed according to the reported literature [26].

(ii) Synthesis of compound **3**: To a solution of **2** (460.0 mg, 1.0 mmol) in 20 mL ethanol, hydrazine hydrate (0.146 mL, 3.0 mmol) was added dropwise over 15 min and then the mixture was refluxed for 6 h. After the reaction mixture was cooled to room temperature, excess hydrazine hydrate and solvent was removed under reduced pressure. The product was obtained as an orange powder after purification by column chromatography over silica gel with eluents of petroleum ether/ethyl acetate (4:1). Yield: 32% (145.3 mg). Found: ^{1}H NMR (500 MHz, DMSO): δ = 13.45 (s, 2H, NH), 6.54 (s, 2H, CCHC), 4.77 (s, 4H, CH_{Fc}), 4.33 (s, 4H, CH_{Fc}).

(iii) Synthesis of compound **4**: Powdered **3** (454.0 mg, 1.0 mmol) and t-BuOK (280.5 mg, 2.5 mmol) was dissolved in CH_3CN (25 mL) and then ethyl bromoacetate (0.333 mL, 3 mmol) was added dropwise. The mixture was stirred and refluxed for 6 h. Then the solvent was removed under reduced pressure. Pure compound, as reddish-orange oil, was obtained by column chromatography with eluents of petroleum ether/ethyl acetate (6:1). Yield: 54% (338.0 mg). Found: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.55 (s, 2H, CCHC), 4.92 (s, 4H, CCH_2N), 4.42 (t, 4H, CH_{Fc}), 4.38 (t, 4H, CH_{Fc}), 4.22 (m, 4H, CH_3CH_2OOC), 1.26 (t, 6H, CH_3CH_2OOC).

(iv) Synthesis of compound **5** (**L**): The above-mentioned ester **4** (0.626 g, 1.0 mmol) was dissolved in H_2O (15 mL), and then NaOH (0.12 g, 3 mmol) was added. The mixture was stirred and refluxed for 5 h in dark. The obtained suspension was cooled down to room temperature and the black precipitate was removed by filtration. Then, the aqueous solution was acidified by the addition of 1 M HCl solution under vigorous stirring. The precipitated brown product was obtained by filtration. Yield: 80% (456.0 mg). Found: ^{1}H NMR (500 MHz, DMSO): δ = 6.79 (s, 2H, CCHC), 5.04 (s, 4H, CCH_2N), 4.69 (s, 4H, CH_{Fc}), 4.42 (s, 4H, CH_{Fc}). IR (cm^{-1}): 3421 (m), 1726 (vs), 1633 (m), 1405 (s), 1079 (s), 936 (s), 814 (vs), 461 (s).

2.3. Preparation of the complex 5a–5c

2.3.1. $[Ni(C_{22}H_{14}F_6FeN_4O_4)(H_2O)_4]$ 5a

Ligand **L** (285.0 mg, 0.5 mmol) and NaOH (40.0 mg, 1.0 mmol) were dissolved in 10 mL distillated water with stirring until absolutely dissolved, and then mixed with a solution of $NiCl_2{\cdot}6H_2O$ (118.8 mg, 0.5 mmol) in H_2O (10 mL). Finally, the reaction mixture was adjusted to pH 7 with 0.1 mol·L^{-1} NaOH solution and heated to 90 °C for 10 h. After cooled to room temperature, the suspension was filtered to remove any undissolved reactants and the obtained filtrate was left to slowly evaporate water in dark at room temperature. Orange transparent crystals suitable for X-ray crystallographic analysis could be obtained after a period of about one month. Yield: 84% (293.6 mg). Found: ^{1}H NMR (500 MHz, DMSO): δ = 6.56 (s, 2H, CCHC), 4.74 (s, 4H, CCH_2N), 4.57 (s, 4H, CH_{Fc}), 4.27 (s, 4H, CH_{Fc}). IR (cm^{-1}): 3417 (vs), 1624 (s), 1513 (m), 1387 (m), 1131 (s), 1081 (s), 979 (m), 810 (m), 466 (s). Anal. calcd for $C_{22}H_{22}F_6NiFeN_4O_8$ (699.0): C, 37.77; H, 3.15; N, 8.01; Found: C, 37.82; H, 3.34; N, 8.09%.

2.3.2. $[Mg(C_{22}H_{14}F_6FeN_4O_4)(H_2O)_4]{\cdot}3H_2O$ 5b

The synthetic procedure was similar to that of **5a** except that

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