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Development of a promising drug delivery for formononetin: Cyclodextrin-modified single-walled carbon nanotubes

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ABSTRACT

The design of hydroxypropyl-β-cyclodextrin (HP-β-CD) modified carboxylated single-walled carbon nanotubes (CD-SWCNTs) composition was to improve the biocompatibility and reduce the toxicity of carbon nanotubes as the delivery of anticancer drug formononetin (FMN). According to the result of fourier-transform infrared spectrometry (FTIR), HP-β-CD was grafted to carboxylated single-walled carbon nanotubes (SWCNTs-COOH) successfully. The entrapment efficiency and loading capacity of the CD-SWCNTs loading with FMN (CD-SWCNTs-FMN) were evaluated by HPLC experiments, which could reach to (88.66 ± 3.13) % and (8.43 ± 1.11) % respectively. The samples were characterized by x-ray diffractometry (XRD), differential scanning calorimetry (DSC), laser particle size analysis and scanning electron microscopy (SEM). Moreover, the research on drug release kinetics demonstrated a slow and sustained release. The *in vitro* cytotoxicity assay revealed that the antitumor activity of CD-SWCNTs-FMN is stronger than that of the free FMN. In conclusion, CD-SWCNTs synthesized in this study were prospective sustained-release and drug-targeting system for anti-tumor drugs.

1. Introduction

Formononetin (FMN), a isoflavonoid of *T. pratense* L., possesses potent pharmacological activities like strong antiviral, antioxidant, cardioprotective effects and inducing tumor cell apoptosis in some cancer types *in vitro* and *in vivo*. FMN, meanwhile, is a poorly-water-soluble compound, and is difficult to develop as a drug product [1,2]. Therefore, it is essential to explore a drug delivery system to transport FMN. Carbon nanotubes (CNTs) are regarded to a novel class of nano-materials discovered in 1991 via an arc-discharge method, which are another formulation of carbon element [3], universally classified into three types: single-walled and dual-walled and multi-walled carbon nanotubes [4]. The properties of CNTs including high aspect ratio and surface area, high mechanical strength, as also as easiness of drug loading via $\pi-\pi$ stacking interactions have attracted and inspired scientists of all over the world to develop them to be the candidate for targeted drug delivery [5,6]. Except being drug carriers in chemical and biological field, many examples about the possible use of CNTs can be found in literature, such as cancer therapy, catalysis and biosensor [7–9]. However, pristine CNTs possessed poor biocompatibility and high biological toxicity owing to their highly hydrophobic surface, low functionality and the large particle size, coupled with vander Waals force and strong $\pi-\pi$ interactions between the individual tubes. Thus, several non-covalent or covalent modification strategies have been attempted to increase the hydrosolubility of CNTs [10–12]. Surface modification on CNTs through macrocyclic host molecules can overcome the poor aqueous solubility of CNTs and decrease the medical risk.

Cyclodextrin (CD), one of the member of macromolecules, is known as drug carrier with the nature of innocuity, cheapness and easy accessibility [13]. To introduce hydroxypropyl into β-cyclodextrin can break the intramolecular hydrogen bond, thereby overcome the disadvantages of poor water solubility of CD while keeping the cavity of cyclodextrin, as the result of hydroxypropyl-beta-cyclodextrin (HP-β-CD) being widely used. There is sufficient evidence that the enhancing dispersibility of CNTs can be obtained through the combination of CNTs and HP-β-CD, allowing more promising applications of CNTs in medical and chemical field [14,15].

Numbers of synthetic approaches for CD-CNTs have been proposed [16,17], and our research focused on the combination of SWCNTs-COOH and HP-β-CD to fabricate HP-β-CD surface modified SWCNTs-COOH (CD-SWCNTs) as drug carrier system, which could improve the treatment efficiency of loaded drug and reduce adverse side effects.

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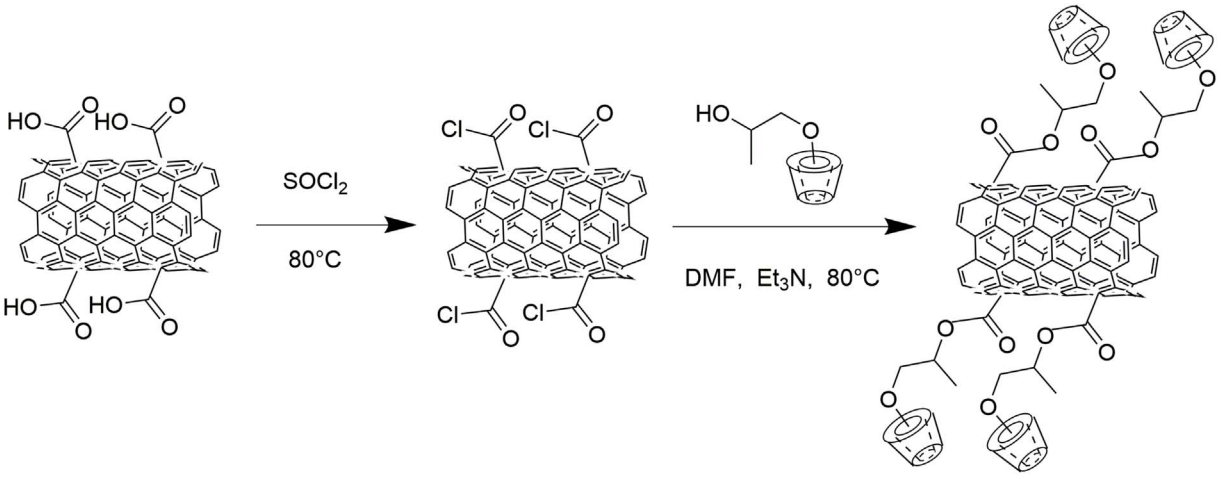

Fig. 1. The procedures for the preparation of CD-SWCNTs.

2. Materials and methods

2.1. Materials

FMN (high-performance liquid chromatography grade) was supplied by Chengdu Ruifensi Biological Technology Co. Ltd (Chengdu, China). Carboxylic group functionalized single-walled carbon nanotubes (purity > 95%, diameter 1–2 nm, length 1–3 μm) were produced by Chengdu Organic Chemicals Co. Ltd, Chinese Academy of Sciences (Chengdu, People's Republic of China). 2-Hydroxypropyl-beta cyclodextrin (HP-β-CD, Mw 1460 g/mol), Dulbecco's modified Eagle's medium (DMEM) and Fetal bovine serum (FBS) were purchased from Sigma-Aldrich (St. Louis, MO). Water soluble Tetrazolium (WST-1) was purchased from Shanghai Beyotime Institute of Biotechnology (Shanghai, China).

2.2. HPLC analysis

2.2.1. High performance liquid chromatography (HPLC) condition

The chromatography separation was performed using a Diamonsil C_{18} column (5 μm, 4.6 × 250 mm, Dikama Technologies, Beijing, China) with a column temperature of 30 °C. The mobile phase consisted of methanol and 0.1% phosphoric acid solution (70:30, v/v), and the flow rate was 1.0 ml/min. The injection volume was 20 μL, the solution was detected at 249 nm for determining the content of FMN.

2.2.2. Standard curve

The primary stock solution of FMN was prepared in methanol at the concentration of 30 μg/ml. The standard curve was plotted by serial dilution of stock solutions with methanol with the concentration of 0.75, 1.50, 3.00, 6.00, 12.00, and 24.00 μg/ml. The peak area of FMN (*Y*) and the concentrations of FMN (*X*) were used to plot the calibration curves.

2.2.3. Precision test

To evaluate the intra- and inter-day precision of the method. 0.5, 2.0 and 4.0 ml stock solutions were put in 10 ml volumetric flask and diluted to the mark with methanol. According to the chromatographic conditions above, high, middle and low concentration of the solution was determined respectively. Precision was assessed by determining the replicate samples at six times per day for three consecutive days.

2.2.4. Recovery test

Proper amounts of CD-SWCNTs were mixed precisely with 0.5, 2.0 and 4.0 ml of stock solution. 100 ml methanol and 100 mg NaOH were added to the mixtures, sonicated for 30 min and stirred at room temperature for 48 h. After filtering through a 0.45 μm sterile membrane, the filtrate was collected for determination. Recovery was evaluated by comparing the average concentration obtained from the tested solutions according to the above chromatographic conditions.

2.2.5. HPLC determination

The tested solution was prepared in accordance with a reported method in the literature [18]. 5.0 mg of CD-SWCNTs-FMN were dissolved in solution containing 100 ml methanol and 100 mg NaOH, sonicated for 30 min and stirred at room temperature for 48 h. The supernatant (4 000 r, 20 min) was stored for further measurement. The calculation equations are as follows:

$$\%\ \text{Entrapment efficiency} = \frac{\text{Weight of entrapped FMN in conjugate}}{\text{Weight of original FMN}} \times 100\%$$

$$\%\ \text{Loading capacity} = \frac{\text{Weight of entrapped FMN in conjugate}}{\text{Weight of conjugate}} \times 100\%$$

2.3. Preparation of CD-SWCNTs

The CD-SWCNTs were prepared according to a previously reported procedure [19,20]. Briefly, 100.0 mg SWCNTs-COOH were dispersed into 20 ml thionyl chloride and 3 drops of anhydrous N, *N*-Dimethylformamide in 100 ml round bottom flask protected by drying tube. After ultrasonic dispersion for 30 min, the reflux was carried out for 24 h at 80 °C. The excess of unreacted thionyl chloride was removed by rotary distillation. Then, 1.0 g HP-β-CD, 3 drops of anhydrous triethylamine and 20 ml anhydrous N, *N*-Dimethylformamide were added into the reaction mixture, sonicating for 30 min with ensuing reflux for 24 h at 80 °C. The solution was then cooled down to room temperature and filtered, and the obtained solid residue was washed repeatedly using distilled water for several times. The desired products were dried under vacuum for 24 h at 80 °C to obtain CD-SWCNTs. The preparation procedure was shown in Fig. 1.

2.4. Preparation of CD-SWCNTs-FMN

FMN was dissolved in methanol and mixed with CD-SWCNTs. The mixture was sonicated for 10 min with 3 s intervals using an ultrasonic probe sonicator (Scientz-IID ultrasonic cell disruptor, Ningbo Scientz Biotechnology Co., Ltd, Ningbo, China), followed by magnetic stirring overnight at room temperature. Then the nanosuspension was filtered with a 0.45 μm sterile membrane, the collected black solid was washed by methanol to remove the unconjugated FMN, and dried at 50 °C in an

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