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Preparation and characterization of a novel conformed bipolymer paclitaxel-nanoparticle using tea polysaccharides and zein

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ABSTRACT

To improve the aqueous solubility of the anticancer agent paclitaxel (PTX), a newly conformed bipolymer paclitaxel-nanoparticle using tea polysaccharide (TPS) and zein was prepared and characterized. Tea polysaccharide was used as a biopolymer shell and zein was as the core and the optimal formula was subjected to the characteristic study by TEM, DSC, FTIR and *in vitro* release study. Results showed that the optimal particle was acquired with particle yield at 40.01%, drug loading at 0.12% and diameters around 165 nm when the concentration of tea polysaccharide was set at 0.2%, and the amount of PTX:zein = 1:10. The particle was a nanoparticle with spherical surface and the encapsulated PTX was in an amorphous form rather than cystalline form. PTX was interacted with zein and polysaccharide through O— H and C═O groups and it had a sustained release. The results suggested that the novel bipolymer might be a promising agent for PTX delivery and tea polysaccharide was demonstrated its function in drug delivery system.

1. Introduction

Paclitaxel (PTX) was a highly effective anticancer drug that acts by stabilizing microtubules, blocking cancer cells at the G_2/M phase, and inducing apoptosis, and the ability of PTX had already been proved against a wide variety of cancers including lung, ovarian, bladder, breast, and head- and- neck cancers (Ruttala & Ko, 2015). Despite of the potential health benefits, PTX was found to have the poor aqueous solubility, so the clinical application of PTX was extremely limited (Xin et al., 2010). To increase the aqueous solubility of PTX, various approaches had been used. The most common PTX formulation used in the clinic was Taxol® (Bristol-Myers Squibb, Princeton, NJ), however, along with the increase of solubility, it also induced various serious side effects (Fang, Yang, Wang, & Qian, 2015). Many attempts have been made to develop new drug delivery systems, such as liposomes, polymer-drug conjugates, lipid-based nanoparticles and copolymeric micells, which could improve the drug accumulation at the tumor site in a passive manner, known as the Enhanced Permeability and Retention effect (Ha Phuong et al., 2015). Polymeric micelles, self-assembling nano-constructs of amphiphilic copolymers, are widely considered as convenient nano-carriers for a variety of applications, such as diagnostic imaging, and drug and gene delivery. They have been demonstrated a variety of favorable properties including biocompatibility, longevity, high stability *in vitro* and *in vivo*, capacity to effectively solubilize a variety of poorly soluble drugs, and changing the release profile of the incorporated pharmaceutical agents (Movassaghian, Merkel, & Torchilin, 2015). The amphiphilic chitosan derivatives were used to synthesize Meloxicam-loaded polymeric micelles (Woraphatphadung et al., 2016). And polyhydroxyalkanoates (PHAs) (natural), poly-lactide-*co*-glycolide (PLGA) (synthetic) and cyclodextrins (CDs) (synthetic) were employed to form nanoparticles which encapsuled with Ellipticine, Cisplatin, Thymoquinone (Masood, 2016). In this case, the need of non-toxic, biodegradable and environmental friendly formulation for copolymers- constructed PTX-loaded nanoparticle is still urgent.

Tea polysaccharide (TPS) was the carbohydrate component in the water extract from green tea which is a protein bounded acidic polysaccharides with average molecular weight about 120 kDa. The monosaccharides was composed of L-arabinose, D-ribose, D-xylose, D-glucose and D-galactose with a molar ratio of 4.9: 2.2: 3.1: 1.8: 1.0 with both α and β configurations and high-branched chains (Chen, Wang, Lu, & Xie, 2008). TPS is one of the main components in the tea with various bioactivities such as antitumor, hypoglycemia, antioxidant and immuno-enhancing activities (Cao, 2013). In the previous

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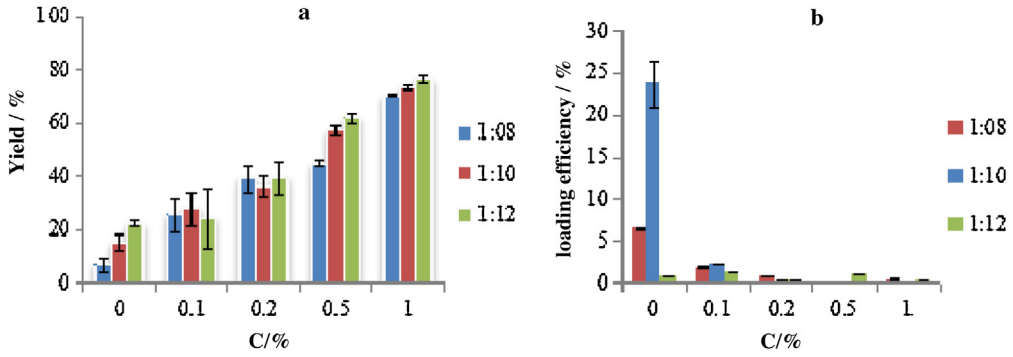

Fig. 1. Particle yields and loading efficiencies of PTX nanoparticles of different groups. (a) Particle yields of PTX nanoparticles; (b) the loading efficiencies of PTX nanoparticles.

studies on TPS, the attentions were mainly paid on its pharmacological actions rather than technology of pharmaceutics. Previous reports showed that some polysaccharides such as chitosan (Liu et al., 2012), high-methoxyl pectin (Perez, Sponton, Andermatten, Rubiolo, & Santiago, 2015), fucoidan (Chang & McClements, 2015) were used as the shell of nanoparticles, which indicated that the acid polysaccharide TPS might be a potential agent in the drug fabrication.

Zeins, natural storage proteins derived from foods, are ideal materials for delivery of nutrients and drugs (Song et al., 2015). Zein was soluble in ethanol in concentrations over 70%. Hydrophobicity makes zein capable of self association in the presence of polar solvents such as water (da Rosa et al., 2015). Due to its inherent biodegradability and biocompatibility, zein nanoparticles were successfully applied as a carrier for the controlled release of drugs and dietary supplements (Liu, Lv, He, Pei, & Wang, 2015). And zein-biopolymer nanoparticles had already been used to encapsulate a variety of lipophilic bioactivites, including α- tocopherol, vitamin D_3, and thymol (Hu et al., 2015). However, there is no information on the zein- biopolymer nanoparticles with tea polysaccharides.

The objective of this study was to fabricate a biodegradable, nontoxic and environmental- friendly PTX loaded nanoparticle using zein as the core and TPS as the shell. The optimum proportion of TPS with PTX was determined. The optimal formula was then subjected to the characteristic studies by TEM, DSC, FTIR and the *in vitro* release study. It was the first time that TPS was employed to the drug delivery system to fabricated a new form of nanoparticle, which would broaden the application of TPS and give a new thought to the clinical application of poor aqueous solubility drugs.

2. Materials and methods

2.1. TPS preparation

Green tea was purchased from Huangshan (AnHui Province, China). The preparation of TPS was following the previous method developed in our laboratory (Zhang et al., 2013). Briefly, green tea (50 g) was mixed with 500 mL of 80% (v/v) ethanol and shaken at 30 °C for 24 h to remove most of the polyphenols and monosaccharide. After the mixture was filtered, the residues were dried in air and then extracted with hot water (80 °C) three times (1:20, w/v). The tea extract was concentrated in a rotary evaporator under reduced pressure, precipitated by 95% (v/v) ethanol at 4 °C for 24 h, and then centrifuged (3000*g*, 10 min). The precipitate was decolored with ethanol and vacuum freeze-dried, and the TPS was obtained.

2.2. Nanoparticle preparation

The preparation method of nanoparticle was according to Hu et al. with minor modifications (Hu et al., 2015). Briefly, zein (1.7 g) was added to 100.0 mL of 85% (v/v) aqueous ethanol solution with magnetic stirring at 500 rpm for 1 h, then different amount of PTX powder was added to obtain PTX: zein = 1:8, 1:10 and 1:12 (w/w) mixture and stirred continuously for another hour. In the meanwhile, different TPS powders were dispersed in double distilled water at a concentrations of 0%, 0.1%, 0.2%, 0.5%, 1% (w/v), and stirred for 1 h, then centrifuged at (3000*g*, 10 min) to remove any insoluble components. Then 6.00 mL of each PTX- zein ethanol solution was rapidly dropped into 25.00 mL of water (pH 4.0) using a

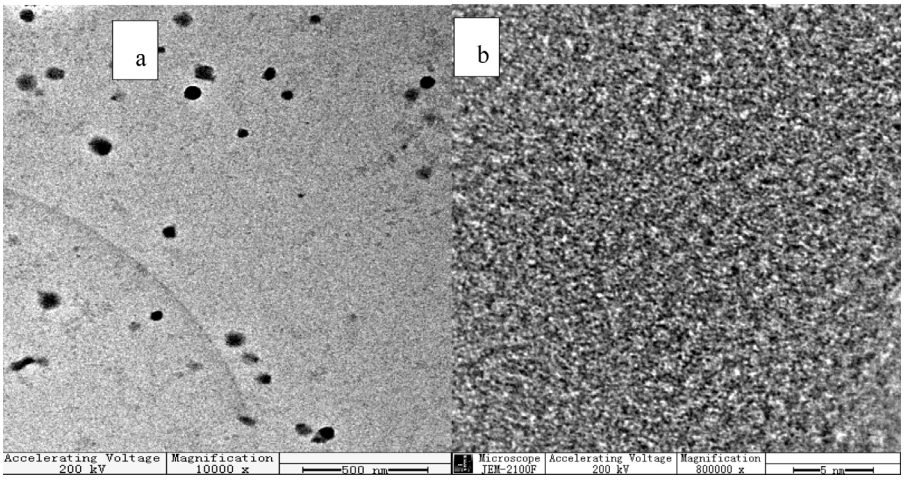

Fig. 2. TEM image of PTX nanoparticles. (a) TEM image of nanoparticles (×10000). (b) TEM image of nanoparticles (×800000).