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Preparation of Paclitaxel-loaded Alginate-chitosan Complex Microcapsules

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Abstract

Paclitaxel-loaded alginate-chitosan complex microcapsules were successfully prepared by the high-voltage electrostatic technique. The effect of paclitaxel concentration and drug-loading methods on drug loading of alginate-chitosan microcapsules, and the effect of methanol concentration, chitosan concentration and chitosan molecular weight on encapsulation efficiency were investigated. Experimental results showed that calcium alginate beads had a good degree of sphericity and a uniform size of 299.8±3.6 μm. After encapsulation with chitosan membrane followed by freeze drying, microcapsules shrunk and collapsed with a mean particle size of about 60.0 μm. Drug loading results showed that as paclitaxel concentration increased from 2 mg/mL to 8 mg/mL, drug loading of microcapsules was increased from 1.95% to 11.16%. Microcapsules with dynamical paclitaxel-loading at 30 °C had the highest drug loading, followed by those with statical paclitaxel-loading at 4 °C and 37 °C. Encapsulation efficiency results showed that microcapsules washed with 0.5% (v/v) methanol had the highest encapsulation efficiency of 2.85%. The encapsulation efficiency was decreased with the increase of chitosan concentration, while it firstly decreased and then increased with the increase of molecular weight of chitosan. These results provide primary information about drug loading and encapsulation efficiency properties of paclitaxel-loaded alginate-chitosan microcapsules as a novel drug carrier.

Keywords: Paclitaxel; Alginate; Chitosan; Microcapsules; High-voltage Electrostatic Technique

1 Introduction

Paclitaxel (PTX) as an effective anticancer therapeutic agent has been widely applied in the treatment of a variety of cancers, including the breast, ovary, lung, head and neck, esophagus, and hematological malignancies [1, 2]. However, the poor water solubility of PTX significantly hampers its clinical application [3, 4]. To solve this problem, the current commercial product of PTX is dissolved in cremophor EL and ethanol mixture (1:1, v/v), which usually cause serious toxic side effects such as hypersensitivity, nephrotoxicity and neurotoxicity [5-7]. Therefore, the development of novel formulation converting PTX into water-soluble drug as well as reducing

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adverse reactions has attracted great interest recently [8-11]. The application of drug carriers such as nanoparticles [12], microspheres [13, 14] and microcapsules [15] to entrap pharmaceutical agents into biodegradable polymers has been utilized as a preferred method for delivering PTX. These strategies can combine the conversion of PTX into a water-soluble drug with the release of drugs to specific tissues at a therapeutically optimal rate. The utilized polymers should possess good biodegradability, low toxicity and ideal bonding ability with bioactive molecules [16]. The most frequently studied polymers are chitosan [17], poly (lactic acid) (PLA) [18], poly (lactic-co-glycolic acid) (PLGA) [19, 20]. Chitosan as a natural biodegradable polymer, is abundant in source and inexpensive for price. It is a polycation polymer with excellent biocompatibility and widely used in drug delivery systems, accelerating drug absorption and inhibiting tumor cell [21-24]. Chitosan can be combined with the polyanion polymer such as alginate through ionic cross-link to form microcapsules with non-toxicity, excellent biocompatibility and pharmacological efficacy.

Several methods have been used for preparation of microcapsules, such as spray drying [25], emulsion solvent-extraction/evaporation [26-28], layer-by-layer assembly [29] and supercritical CO_2 [30]. However, these methods have drawbacks of organic solvent removal in a subsequent procedure and tedious operation process. The high-voltage electrostatic technique, which can produce uniform size of calcium alginate beads in superior degree of sphericity without the usage of organic solvent, has aroused most interest [31-33]. Herein, in the present study, calcium alginate beads were produced by a high-voltage electrostatic droplet generator and then coated with chitosan as membrane materials through polyelectrolytical complex reaction between alginate and chitosan to prepare water-solvable drug carriers. The PTX loading and encapsulation efficiency of alginate-chitosan complex microcapsules were also investigated.

2 Materials and Methods

2.1 Materials

Sodium alginate (Alg), calcium chloride, sodium hydroxide and sodium bicarbonate were all purchased from National Pharmaceutical Group Chemical Reagent Co., Ltd. (China), and its aqueous solution was filtrated through 0.8 μm, 0.45 μm and 0.22 μm membranes in sequence. Chitosan (CS) was purchased from Zhejiang Golden-shell Biochemistry Co., Ltd. (China). Paclitaxel (PTX, purity $\geq$ 99.9%) was purchased from Beijing Yi-he Bioengineering Co., Ltd. (China). Other reagents were all of analytical reagent grade. All the chemicals were used as received without further purification.

2.2 Preparation of Calcium Alginate Beads

4 mL of sodium alginate solution (2.0%, w/v) was extruded into 100 mL calcium chloride solution (1.5%, w/v) by a syringe pump at a speed ratio of 50 mm/h under the high-voltage generator with a voltage of 6.3 kV. The distance between the flat pinhead (7#) and the surface of the calcium chloride solution was set at 20 mm. The prepared calcium alginate beads were collected and washed with distilled water twice to remove redundant calcium ion.