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ORIGINAL ARTICLE

Synthesis, characterization and in vitro drug release of cisplatin loaded Cassava starch acetate–PEG/gelatin nanocomposites

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Abstract The aim of the present study is to examine the feasibility of Cassava starch acetate (CSA)–polyethylene glycol (PEG)–gelatin (G) nanocomposites as controlled drug delivery systems. It is one of the novel drug vehicles which can be used for the controlled release of an anticancer drug. Simple nano precipitation method was used to prepare the carriers CSA–PEG–G nanocomposites and they were used for entrapping cisplatin (CDDP). Through FT-IR spectroscopy, the linking among various components of the system was proved and with the help of scanning electron microscope and transmission electron microscopy (TEM), the surface morphology was investigated. The particle sizes of the CSA–CDDP, CSA–CDDP–PEG and CSA–CDDP–PEG–G polymer composites were between 140 and 350 nm, as determined by a Zetasizer. Drug encapsulation efficiency, drug loading capacity and in vitro release of CDDP were evaluated respectively. The findings revealed that the cross linked CSA–PEG–G nanocomposites can be a potential polymeric carrier for controlled delivery of CDDP.

1. Introduction

Starch, a biodegradable polymer is a promising carrier for drug delivery. It has been used in various fields like biomedical, agriculture and food etc. However, native starch cannot fit into some parental controlled drug delivery systems, as many drugs are released quickly from such unmodified starch-based systems (Michailova et al., 2001); due to considerable swelling and quick enzymatic degradation of native starch in biological systems.

One of the efficacious methods, applied in this study to improve the properties of starch, is the chemical modification of starch which includes esterification. Over the past two decades extensive studies have been conducted on starch ester called as acetylated starch (Wang and Wang, 2002). Chemically transformed starch acetates are less hydrophilic than most of the other modified starches, due to the hydrophobic nature of the acetoxy substituent ($OCOCH_3$). In the drug delivery applications, starch acetate has been extensively used (Korhonen et al., 2004; Nutan et al., 2005, 2007; Pajander et al., 2008; Pohja et al., 2004; Pu et al., 2011; Tuovinen et al., 2004a,b; van Veen et al., 2005; Xu et al., 2009) and tissue engineered scaffold has also been investigated (Guan and Hanna, 2004; Reddy and Yang, 2009).

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In cancer chemotherapy, platinum compounds play an important role. One of the most common anticancer agents is Cisplatin (CDDP), the first generation of platinum based chemotherapy drug. It is used in the treatment of solid tumors including gastrointestinal, head and neck, genitourinary and lung tumors (Kelland, 2007; Boulikas and Vougiouka, 2003).

The clinical application of cisplatin for cancer chemotherapy is still in limited use because of its nonspecific biodistribution and severe side effects. In an attempt to overcome this shortcoming, various studies have been conducted by many groups. They are magnetically mediated controlled delivery systems (Likhitkar and Bajpai, 2012), click chemistry (Huynh et al., 2011), SiO_2/polymer for the controlled release of cisplatin (Czarnobaj and Lukasiak, 2007), platinum-tethered gold nanoparticle (Brown et al., 2010). Chemotherapy with cisplatin is connected with some serious side effects, such as: vomiting, nephrotoxicity, ototoxicity, neuropathy, anemia and nausea (Uchino et al., 2005). Owing to these side effects other methods of administering cisplatin are required. In the present study, CSA/PEG/G has been chosen as the raw material to prepare the drug carrier.

The key objective of the current study is to encapsulate the anticancer drug cisplatin (CDDP) into Cassava starch acetate/polyethylene glycol/gelatin (CSA/PEG/G) nanocomposites through the interaction between cisplatin (CDDP) and CSA/PEG/G nanocomposites. Gelatin is a naturally occurring biodegradable macromolecule with well-documented biocompatible properties over other synthetic polymers that make it an appropriate material to be used as a nanoparticulate carrier (Lai et al., 2006). To develop the microspheres, nanoparticles and polymers, Polyethylene glycol (PEG), a suitable graft-forming polymer, has been extensively employed in pharmaceutical and biomedical fields (Jeong et al., 2008). The viability of CDDP-loaded polymeric nanocomposites as a drug delivery system was verified by evaluating its in vitro studies and instrumental characteristics.

2. Materials and methods

2.1. Materials

Native Cassava starch powder was obtained from Sago Serve Industries (Salem, India). Acetic acid ($\geqslant$99%) and acetic anhydride ($\geqslant$98%) were of analytical grade procured from Sigma–Aldrich (St. Louis, USA). PEG 10000, gelatin Type-B, phosphate-buffered saline (PBS) were prepared in deionized water using NaCl (0.14 M), KCl (2.68×10^{-3} M), Na_2HPO_4 (0.01 M), KH_2PO_4 (1.76×10^{-3} M). Sodium hydroxide (NaOH) and absolute ethanol were purchased from Merck (Mumbai, India Ltd). Cisplatin was obtained from Dabur Pharma Ltd. (New Delhi, India). All chemicals were used without additional purification.

2.2. Preparation of cassava starch acetate

Native cassava starch was permitted to react with acetic anhydride (1:4 ratio) with pyridine as a catalyst as previously described (Singh and Nath, 2012) with few modifications. Before acetylation, cassava starch was dried in an oven for 20 h at 45–60 °C. Dried starch (25 g) was mixed with acetic anhydride (100 g) through the medium of pyridine (200 g). The reaction was carried out at 120 °C for a period of 3 h. The final product was precipitated with ethanol, filtered and dried in vacuum oven. Lastly, the modified starch was milled and sifted in a sieve (#50 mesh) to obtain a homogeneous particle size and stored in desiccators until further study.

2.3. Preparation of CSA–CDDP nanorods

The CSA nanorods were prepared by a simple nanoprecipitation technique as reported by Chin et al., 2011 with slight modification. CSA (10 mg) was dissolved in 8:10 wt% of NaOH/urea (NU) solution mixtures; this solution mixture was used as a solvent system for the dissolution of acetylated cassava starch. Cisplatin was dissolved in CSA solution and prepared at various concentrations i.e., 10%, 20%, 30%, 40% and 50%, using 4, 8, 12, 16 and 20 mg of drug, respectively. An aliquot of CSA solution (10 mg/mL) containing the various concentrations of the drugs was added drop-wise into a 10 ml of absolute ethanol solution, which was constantly stirred using a magnetic stirrer at a constant stirring rate (1500 rpm). The CSA nanorods were made immediately. This dispersion of nanorods was vacuum evaporated to remove the organic solvent fully. Finally the resultant mixture was centrifuged at 13,000 rpm and the supernatant was removed to obtain the CSA-cisplatin nanorods and freeze-dried at −40 °C for 20 h.

2.4. Preparation of the CSA–CDDP–PEG and CSA–CDDP–PEG–G nanocomposites

The various percentage of encapsulated CSA–CDDP in the PEG and G solution were prepared by a method described in our previous report (Rajan et al., 2013) as follows. First, 10% of PEG solution was prepared in water. Then, the solution was gradually added to a correct portion of the CSA–CDDP nanorods under constant magnetic stirring at room temperature for 1 h. The resulting encapsulated nanocomposites (CSA–CDDP–PEG) were collected by centrifugation at 1500 rpm and freeze-dried at −30 °C for 20 h. Later gelatin (20 mg) was dissolved in water in a similar manner and gradually added to CSA–CDDP–PEG nanocomposites under constant magnetic stirring at room temperature for 1 h. Finally the resulting encapsulated nanocomposites (CSA–CDDP–PEG–G) were collected by centrifugation at 1500 rpm and freeze-dried at −30 °C for 20 h.

2.5. Particle size analysis

Drug loaded polymeric nanocomposites were characterized for the particle size, size distribution and zeta potential using Zetasizer (Malvern Instruments, UK).

2.6. Scanning electron microscopy (SEM) and Fourier transform infrared spectroscopy (FT-IR) analysis

Morphological characteristics of the freshly prepared (CSA–CDDP, CSA–CDDP–PEG, and CSA–CDDP–PEG–G) nanocomposites were viewed using scanning electron microscopy (SEM-Hitachi-S-2700), FT-IR spectrum was taken to study the interaction between polymers and drug using Perkin Elmer spectrum RXI. KBr pellets were concisely prepared by

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