Saudi Pharmaceutical Journal (2013) **21**, 85–91

King Saud University

Saudi Pharmaceutical Journal

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ORIGINAL ARTICLE

Paclitaxel loaded carrier based biodegradable polymeric implants: Preparation and *in vitro* characterization

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Received 3 October 2011; accepted 15 December 2011
Available online 5 January 2012

KEYWORDS

Implants;
Paclitaxel (PTX);
Poly(ε-caprolactone);
β-Cyclodextrin

Abstract The objective of this study was to develop paclitaxel (PTX) loaded poly(ε-caprolactone) (PCL) based tiny implants. β-Cyclodextrin (β-CD) and polyethylene glycol (PEG 6000) were used to enhance solubility and release of the drug in the phosphate buffer saline pH 7.4. Implants were evaluated in terms of color, shape, thickness, surface area, weight, drug content. Developed implants were characterized for their surface morphology (SEM analysis), drug physical state by thermal analysis (DSC studies), crystalline nature (XRD studies) and drug excipients compatibility (FT-IR spectroscopy). Macroscopically all the tiny implants were white in color and cylindrical in shape with smooth surfaces. PTX was entrapped within implants in the polymeric amorphous form. *In vitro* drug release studies showed prolonged and controlled release of PTX with zero order and Korsmeyer–Peppas model being exhibited. Excipients and method of preparation did not affect chemical stability of PTX.

1. Introduction

Chemotherapy of cancer involves use of chemotherapeutical agents that are directed to kill or control the growth and proliferation of cancer cells. These agents are often toxic or even life threatening. Cancer chemotherapy was first successfully practiced in the 1950s when nitrogen mustard was found to be effective in inhibiting tumor growth. Due to its extreme toxicity, however, effective chemotherapy with anticancer drugs was not widely applied until the 1960s. Despite aggressive therapy using conventional treatment (surgical resection, radiation and chemotherapy), the median reported survival rate has not changed significantly over the past three decades and remains less than 1 year (Avgeropoulos and Batchelor, 1999).

Paclitaxel is a naturally occurring microtubule-binding agent, which has been shown to have tumoricidal activity against several human neoplasms, including non-small lung cancer, breast cancer, ovarian cancer and brain cancer. Paclitaxel (PTX) has been proven to exhibit significant activities in

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Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

1319-0164
http://dx.doi.org/10.1016/j.jsps.2011.12.002

Table 1 Composition of the formulations.

Ingredients	P1 (mg)	P2 (mg)	P3 (mg)	P4 (mg)
PTX	6	9	6	9
β-CD	6	9	–	–
PEG-6000	–	–	6	9
PCL	18	12	18	12

clinical trials against a wide spectrum of cancers (Rowinsky et al., 1992; Spencer and Faulds, 1994). Since, PTX is insoluble in water; the clinically available PTX injection used an emulsifier reagent called Cremophor EL (Singla et al., 2002). This has been found to cause serious side effects (Weiss et al., 1990; Dorr, 1994). The primary goal of formulation development for PTX was to eliminate the Cremophor EL. Polymeric implant may provide an ideal solution to the problem by eliminating the use of such adjuvant.

Biodegradable polyesters derived from lactic acid, glycolic acid and ε-caprolactone have gained much interest in biomedical research for the delivery of various drugs. Attention was drawn to poly(ε-caprolactone) (PCL) owing to its numerous advantages over other biodegradable polyesters. This led to its application in the preparation of different delivery systems in the form of implants, microspheres and nanoparticles (Ramesh et al., 2002; Sinha et al., 2004).

The production of drug loaded polymeric implant, wafer, microspheres and hydrogels has introduced a new concept in drug administration. Drugs can be delivered to tumor in a sustained, continuous and predictable release fashion using polymers as delivery vehicles. The implantable and intratumoral injectable microspheres drug delivery systems commercially available for the treatment of prostate cancer are Decapeptyl® (d-Trp) LH-RH, Lupron Depot® (Leuprolide), Zoladex® (D-ser(Bu), AzGly-GnRH and local delivery Gliadel® (Carmustine) for brain tumor.

The development of implantable drug delivery systems is perhaps the most widely investigated application of biodegradable polymers. Due to their transient nature, biodegradable polymers do not require surgical removal after their intended application and thus can circumvent some of the problems related to the long-term safety of non-degradable implanted devices. Drug release from a biodegradable matrix type implant device occurs by one or a combination of mechanisms viz., erosion of the matrix, diffusion through the matrix or combination of both diffusion and erosion mechanisms (Horikoshi et al., 1997). The present research work was aimed to prepare PTX loaded biodegradable polymeric implants by melt technology and carry out their *in vitro* characterization.

2. Materials and methods

2.1. Materials

Poly(ε-caprolactone) (Mn 90,000) was purchased from Sigma–Aldrich, Bangalore, India. PTX was obtained as a gift sample from Naprod Life Sciences Pvt. Ltd., Mumbai, India. β-Cyclodextrin, PEG-6000, sodium chloride, sodium dihydrogen orthophosphate, potassium dihydrogen orthophosphate were purchased from SD Fine Chemicals, Mumbai, India. All other reagents and solvents were of an analytical grade.

2.2. Methods

2.2.1. Preparation of the PTX loaded biodegradable polymeric implants

Implants were prepared by melt method. Polymer (PCL) was melted on a hot plate below its glass transition temperature (~60 °C). As the polymer starts melting at its glassy state, previously triturated drug (PTX) and PEG-6000 were mixed homogenously into molten polymer. Next, temperature was reduced slowly to 42 °C; during this time, uniform cylindrical implants were prepared by using two flattened stainless steel rods. Implants with β-CD and blank (without drug) were prepared in the same manner. The composition of the formulations and photographs is shown in Table 1 and Fig. 1, respectively.

2.3. Physicochemical evaluation of implants

Prepared implants were characterized for their physicochemical parameters like weight, color, shape, height and area. The implant diameter (d) and height (h) were measured by using digital vernier calipers and area calculated using the formula $[2\pi r(r + h)]$.

2.3.1. Estimation of drug content

The extraction procedure was employed for the determination of PTX content in implants. Implant was dissolved in 15 ml of dichloromethane (DCM). PBS pH 7.4 and ethanol (1:9 v/v, 10 ml) mixture was introduced to this solution. DCM was evaporated completely and solution was then filtered using 0.22 μm nylon membrane (Millipore, Bangalore, India) and suitably diluted with PBS pH 7.4 and ethanol mixture. The PTX content was determined at 229.60 nm using double beam UV–Visible spectrophotometer against ethanol and PBS 7.4 mixture as a blank solution.

2.3.2. Fourier transform infrared analysis (FT-IR)

The FT-IR spectral measurements of pure PTX, polymer, carrier, physical mixtures and formulations were taken at ambient temperature using a FT-IR spectrophotometer (Perkin Elmer, Japan). About 5 mg of samples were mixed with KBr and vacuum-packed to obtain pellets of the material. The implant samples were cast onto NaCl plates from solution in dichloromethane, which were analyzed. All the spectra acquired scans between 400 and 4000 cm^{-1} at a resolution of 4 cm^{-1}.

2.3.3. Thermal analysis (DSC)

Differential scanning calorimetry analysis (DSC) of pure drug, polymer, carrier, physical mixtures and formulations was conducted using DSC 822e (Mettler Toledo star system). Samples were weighed (2.00–5.00 mg) and placed in sealed aluminum pans. The coolant was liquid nitrogen. The samples were scanned at a rate of 10 °C/min from 10 to 230 °C.

2.3.4. X-ray diffraction analysis (XRD)

X-ray diffraction patterns of the pure PTX, polymer, carrier, physical mixtures and drug loaded PCL implants (by using sample holder grid technique) were determined using a Bruker AXS D8 Advance diffractometer, equipped with a rotating