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Double layer paclitaxel delivery systems based on bioresorbable terpolymer with shape memory properties

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ABSTRACT

The growing interest in the bioresorbable polymers contributed to developing a number of commercially available controlled drug delivery systems. Due to a variety of drugs and their physicochemical properties, there is a necessity of choosing an appropriate drug carrier. Terpolymer with shape memory properties was used to obtain double layer matrices composed of drug free matrix and paclitaxel containing layer. The in vitro degradation and drug release study were conducted at 37 °C in PBS (pH 7.4). The investigated materials were characterized by GPC (gel permeation chromatography) and DSC (differential scanning calorimetry). HPLC (high-pressure liquid chromatography) was applied to analyze the amount of released paclitaxel. The main purpose of this work was to determine the usefulness of the studied terpolymer as an anti-restenotic drug vehicle. Based on the obtained results it was established that polymer's degradation proceeded regularly and provided even paclitaxel release profiles. Double layer systems allowed to modify the amount of released drug which may be considered while developing the self-expanding drug-eluting stents tailoring different clinical indications.

1. Introduction

Shape-memory polymers (SMPs) belong to the class of intelligent materials possessing desirable property of recovery from temporary to permanent shape. This phenomenon results from the polymer chains arrangement comprising stimuli-sensitive integrands: switches associating with a temporary form and netpoints determining permanent shape (Behl et al., 2010). Shape-memory effect (SME) may be induced by pH, temperature, light, electric power, etc. (Yakacki and Gall, 2010). For medical purposes, the most suitable SMP are these activated by temperature of the human body. The first phase of memory shape cycle constitutes manufacturing the permanent shape of polymer (e.g. extrusion, injection-molding, cast polymerization). At defined temperature the material is formed by the external stress and fixed in the temporary shape while cooling. Re-exposure to the temperature causes deformation and return to the primary state (free-strain recovery) or the shape limited by surrounding (fixed-strain recovery) (Yakacki et al., 2008).

The most studied SMPs for biomedical application are segmented polyurethanes (PU) synthesized in two-step reaction: obtaining macrodiols of cyclic polyesters or lactones via ring-opening polymerization and then condensation with coupling compound and chain extenders (Lendlein and Langer, 2002). Some of PUs have been commercialized like DiAPLEX or CHEM foams (cold hibernated elastic memory; Mitsubishi Heavy Industry and Jet Propulsion Laboratory) which are studied as materials for e.g. aneurysm embolization (Metcalfe et al., 2003). A different approach to obtain shape-memory polymers is the ring-opening polymerization (ROP) of lactides, glycolides and cyclic carbonates with the use of zirconium (IV) acetylacetonate $Zr(Acac)_4$ as an initiator that is an alternative to the commonly used and relatively toxic stannous compounds (Zini and Scandola, 2007; Gębarowska et al., 2011).

Biocompatibility and biodegradability of aliphatic polyesters and polyester carbonates contributed to development of numerous medical products like sutures (Dexon®, Vicryl®, Maxon®); orthopedic devices e.g. screws – BioScrew®, Bio-Anchor® or pins – SonicPins Rx®, ReUnite® Orthopedic Pin System; scaffolds for tissue engineering (Osteocure®/Polygraft®); drug delivery systems (DDSs) (Nair and Laurencin, 2007). Since the first DDS based on bioresorbable polymer has been commercially available, the era of new dosage forms has begun. Lupron Depot® consisting of poly(L-lactide-co-glycolide) was introduced in 1986 as leuprolide acetate delivery system for the treatment of prostate cancer and is still used also for the management of endometriosis, fibroids and central precocious puberty. The most studied forms of polymer DDSs are nano- and microspheres, nano- and microcapsules,

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polymerosomes, hydrogels and implants. Different dimensions and shapes are designed for particular application including the route of administration, type of drug, time of drug release and polymer bioresorption (Vilar et al., 2012). The majority of polymer DDSs are in the form of microparticles such as Risperdal Consta®, Nutropin Depot® or above mentioned Lupron Depot®. Controlled drug delivery systems (CDDS) offer many advantages when compared to conventional dosage forms. The most important seems to be the decrease of the adverse effects by sustained release lower doses of an active agent and reduction in drug concentration fluctuation. Those systems are designed to release the drug at a predetermined period of time throughout the body or within a desired area. However, they are also employed to transport of poorly soluble drugs as well as improve their pharmacokinetics and protect against inactivation or untimely elimination from the body (Kraljevic and Pavelic, 2005; Yang and Pierstorff, 2012).

In recent years, scientists were focused on polymer-based delivery systems for controlled release of anticancer agents (Huo et al., 2005), antibiotics (Pandey and Khuller, 2007), antifungal drugs (Italia et al., 2009) and hormones (Buntner et al., 1998). Paclitaxel (PTX), one of the antineoplastic agent commonly used in the treatment of several types of cancers (e.g. breast, lung, ovarian, head cancers and AIDS-associated Kaposi's sarcoma), binds to β-subunit of tubulin and stabilizes microtubules by inhibiting depolymerization which results in the G2/M cell cycle arrest. Apart from anticancer properties, PTX suppresses smooth muscle cells (SMSs) proliferation and migration which is desirable to prevent restenosis (Singla et al., 2002; Lao and Venkatraman, 2008; Burt and Hunter, 2006) and was the reason for paclitaxel usefulness in production of drug-eluting stents (DES).

Bioresorbable, shape-memory polymers have a huge potential in medicine and pharmacy. Due to their excellent properties they may combine multiple functions and thus serve as e.g. self-expandable paclitaxel-eluting stents. On the one hand, the application on polymer stents with SME gives the opportunity to eliminate elastic recoil after stent implantation and offer better adjustment inside the vessel. On the other hand, such smart materials can also perform as localized paclitaxel delivery systems. Drug release profile as well as drug release rate are one of the most important factors taken into consideration when designing drug delivery systems. Tailored amount of released drug and time of drug release can be achieved by production of double layer structures. PLLA and PLGA were used to fabricate biodegradable double layer stent prototypes with elastic memory. However the obtained stents did not contain any pharmacological agent (Venkatraman et al., 2006).

In this work, shape-memory polymer based on L-lactide, glycolide and trimethylene carbonate (TMC) was applied to obtain double layer systems for paclitaxel delivery that may help to develop tailor-made self-expanding DES.

2. Materials and methods

2.1. Double layer matrices preparation

Shape-memory terpolymer synthetized from L-lactide, glycolide and oligo-TMC with the zirconium (IV) acetylacetonate $Zr(Acac)_4$ as an initiator of ROP was used to obtain matrices with 3 wt% and 5 wt% of paclitaxel as well as drug free matrices. The 10 mm diameter matrices were prepared by dissolving terpolymer in methylene chloride and casting on a glass plate, then evaporated in ambient temperature and dried under reduced pressure. In case of matrices with drug, solution of polymer was first mixed with solution of paclitaxel (LC Laboratories®) in methylene chloride.

Each type of double layer matrices were fabricated by laminating of two films between heated stainless steel blocks of a hydraulic press at pressure of 150 kg for 1 min. The layers combinations were as follows: 0/0, 0/3, 3/3, 0/5 and 5/5, where 0 constituted a layer without drug, 3 – layer containing 3% of PTX and 5 – 5% of PTX.

2.2. Hydrolytic degradation

The matrices were immersed separately in phosphate buffered saline (PBS, pH 7.4) in screw-capped vials and incubated at 37 °C with constant shaking. PBS was changed once a week and collected for the assessment of drug release. At regular intervals, each type of matrix was excluded from the study, washed with distilled water, wiped and weighted. After drying under reduce pressure, specimens were reweighted and 0/0, 3/3 and 5/5 types of matrices submitted for further analyses.

Water uptake and weight loss were calculated from the following equations:

$$\text{Water uptake } (\%) = \left[\frac{W_{wet} - W_{dry}}{W_{dry}}\right] \times 100 \quad (1)$$

$$\text{Weight loss } (\%) = \left[\frac{W_0 - W_{dry}}{W_0}\right] \times 100 \quad (2)$$

2.3. Measurements

Differential scanning calorimeter (TA DSC 2010, TA Instruments, New Castle, DE) was employed to define thermal properties such as: glass-transition temperature (T_g), melting temperature (T_m), melting enthalpy (ΔH_m), crystallization temperature (T_c) and crystallization enthalpy (ΔH_c). Samples were scanned twice in the range of −50 °C to 200 °C at a heating rate of 20 °C/min and quenched in liquid nitrogen between scans. DSC was calibrated using high purity gallium and indium standards.

Number average molecular weight (M_n) as well as molecular weight dispersity (D) were determined by means of gel permeation chromatograph (Spectra-Physics 8800) with refractive index detector and chloroform as solvent (flow rate of 1 ml/min). GPC was calibrated with low dispersity polystyrene standards.

^{1}H NMR spectra were recorded in $CDCl_3$ as a solvent at 600 MHz with the Avance II Bruker 3 Ultrashield Plus Spectrometer in order to evaluate the comonomer ratio and average length of lactidyl, glycolidyl and carbonate blocks.

High-performance liquid chromatography measurements were performed on a VWR-Hitachi LaChrom Elite® apparatus with the use of LiChrospher® RP-18 column (4 mm × 250 mm, 5 μm) and LiChrospher® RP-18 guard column (4 mm × 4 mm, 5 μm). The mobile phase consisted of acetonitrile and water (60:40) at the flow rate of 1 ml/min. Paclitaxel and the internal standard (docetaxel, LC Laboratories®) were monitored by diode array detector at 227 nm. Release data were analyzed on the basis of zero order and first order mathematical models as well as Higuchi model and Korsmeyer–Peppas model.

All reported data were carried out in triplicate and results were presented as the average with standard deviation.

3. Results

3.1. Characterization of SMP

Double layer matrices were prepared from poly(L-lactide-co-glycolide-co-oligo-trimethylene carbonate) in order to evaluate its usefulness as paclitaxel delivery system. Fig. 1 presents ^{1}H NMR spectrum of bioresorbable terpolymer with SME and Table 1 contains its characteristics. Poly(L-lactide-co-glycolide-co-oligo-TMC)