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Featured Letter

The influence of drug-polymer interactions on release of antirestenotic agent from bioresorbable scaffolds

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ABSTRACT

Localized drug delivery from vascular scaffolds can effectively prevent restenosis after stenting procedures. However, one of the current challenge remains to provide controlled release of antirestenotic drug and identify drug eluting mechanisms. The aim of study was to analyze the influence of polymer forming eluting layer, drug and intermolecular interactions on the release process. In vitro release of sirolimus or paclitaxel from coating of scaffolds obtained from poly(L,L-lactide)-co-trimethylene carbonate and poly(D,L-lactide)-co-trimethylene carbonate was studied. Differences between paclitaxel and sirolimus elution from crystalline copolymer were observed due to intermolecular interactions. Interaction of drug with amorphous polymer did not affect release process.

1. Introduction

Novel bioabsorbable vascular scaffolds are alternative to permanent metal stents to treat arterial restenosis and overcome the long-term complications [1–3]. They also serve as a localized drug delivery systems, which control or reduce, smooth muscle cell growth and migration and prevent inflammatory response - the predominant causes of in-stent restenosis [1,4].

Drug release profile is an important aspect in the performance of drug eluting device since too high dose increase toxicity, whereas too low may have no therapeutic effect [5]. Therefore, the ability to control delivery of drugs is critical for further development of the new generation vascular devices [6]. For achieving this goal, it is imperative to understand the drug delivery mechanisms [4,6]. Therefore, the aim of the study was to analyze the influence of type of polymer forming eluting layer, drug and drug-polymer interactions on the release process. Sirolimus and paclitaxel were selected for the study as representatives of two major classes of anti-proliferative drugs commonly used in drug-eluting vascular devices (mTOR (mammalian target of rapamycin) inhibitors and taxanes) [4].

2. Materials and methods

2.1. Materials

All reagents and organic solvents of analytic grade were purchased from Sigma-Aldrich. Sirolimus (rapamycin) and paclitaxel were purchased from LC Laboratories (Woburn, MA).

2.2. Coating of scaffolds

Poly(L-lactide) (PLA) scaffolds (length 30 mm; Ø 4 mm) were coated with drug eluting layer composed of poly(L,L-lactide)-co-trimethylene carbonate (PLLA/TMC) or poly(D,L-lactide)-co-trimethylene carbonate (PDLA/TMC). The copolymers were synthesized according to the previous report [7]. The scaffolds were coated with solution of drug-polymer mixture in methylene chloride 1% (w/w) by dip-coating method (1 layer; 1 s of immersion time). The polymer to drug ratio was 4:1 (w/w).

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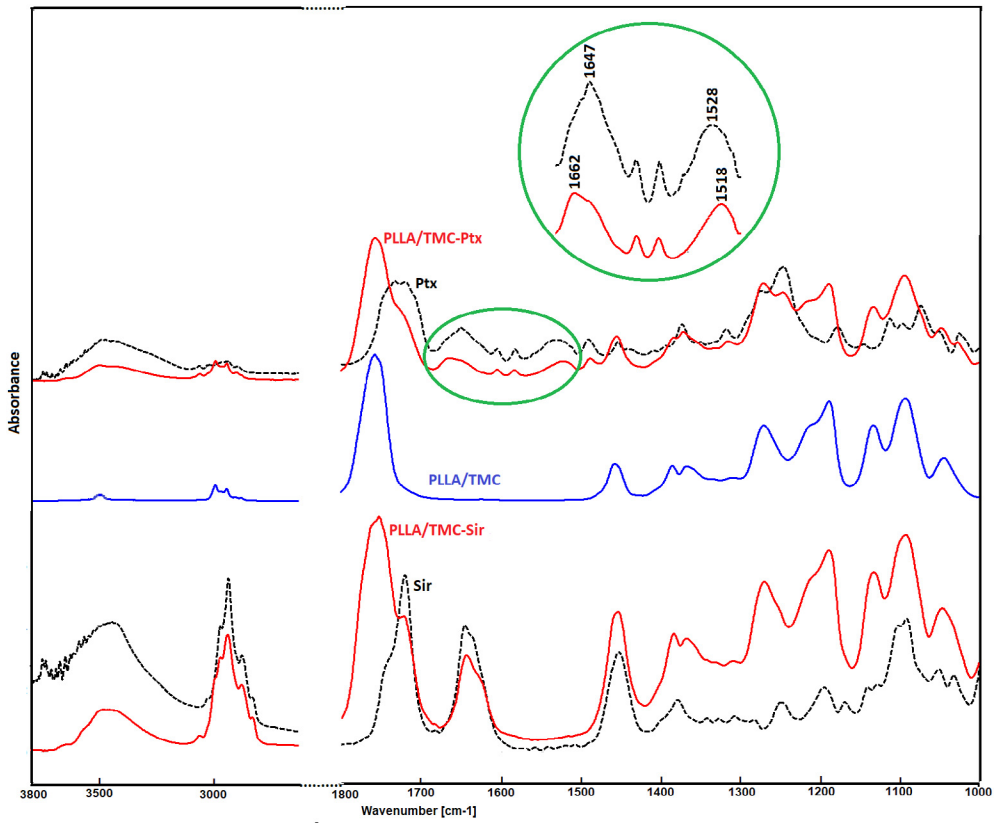

Fig. 1. FTIR spectra of PLLA/TMC, paclitaxel (Ptx), sirolimus (Sir), PLLA/TMC–Ptx, PLLA/TMC–Sir.

2.3. In vitro drug release

In vitro drug release was realized in triplicate at 37 °C in 5 ml of physiological saline at pH 7.4 under agitation (120 rpm). The medium was exchanged once a week. The released drug was assessed by extraction method [8]. Quantitative assessment was conducted by means of HPLC (C18 column; flow rate of 1 ml/min). Sirolimus was analyzed at 287 nm with methanol and 0.1% formic acid (85:15 v/v) as the mobile phase and paclitaxel at 227 nm with 55:45 (v/v) water–acetonitrile as the mobile phase.

The data were analyzed using the student *t*-test. P value of <0.05 was considered statistically significant.

2.4. Analysis of drug-polymer interactions

FTIR spectra were acquired on FT/IR-6000 Jasco instrument with 2 cm^{-1} resolution and 64 scans. Samples in a form of films were obtained after evaporating solvents from their solutions in CH_2Cl_2 onto potassium bromide (KBr) windows (copolymers and copolymer – drug systems) or as pellets in KBr (drugs).

3. Results and discussion

3.1. FTIR analysis

The most characteristic bands of PLLA/TMC appeared at 1755 cm^{-1} with a shoulder at 1748 and 1269, 1187, 1132 and 1091, 1044 cm^{-1} (stretching vibrations of C=O and C—O ester groups), 2995, 2945, 2907, 2881 and 1455, 1383 1363 cm^{-1} (stretching and deformation vibrations of aliphatic groups).

In spectrum of sirolimus the bands at 3445 cm^{-1} (stretching vibrations of bonded OH groups), 1720 cm^{-1} with a shoulder at 1742 cm^{-1} and 1644 cm^{-1} with a shoulder at 1635 cm^{-1} (stretching vibrations of C=O groups), 1101, 1091 cm^{-1} (stretching vibrations of C—O groups), 2965, 2932 and 1452, 1377 cm^{-1} (stretching and deformation vibrations of aliphatic groups) were observed. Relatively broad band at 3445 cm^{-1}, shoulders at 1742 and 1635 cm^{-1} indicate the presence of hydrogen bond between OH and C=O groups.

For paclitaxel, the band at 3485, 3423 cm^{-1} (stretching vibrations of bonded OH and NH groups), 1730, 1715 cm^{-1} (stretching vibrations of C=O groups) 1647 cm^{-1} (the amide I band; mainly stretching vibrations of bonded C=O amide groups) with a shoulder at 1638 cm^{-1} (stretching vibrations of C=O group), 1528 cm^{-1} (the amide II band; mainly deformation vibrations of bonded NH groups), 1271, 1245, 1176, 1096, 1051 cm^{-1} (stretching vibrations of C-O and deformations of NH groups), 3063, 3029, 3013 (stretching vibrations of CH groups in aromatic ring) 1602, 1580, 1488 cm^{-1} (stretching vibrations of aromatic rings), 2985, 2970, 2940, 2896 and 1451, 1371 cm^{-1} (stretching and deformation vibrations of aliphatic groups) were detected. Broad bands assigned to OH, NH and C=O groups in ester and amide groups proves that OH and NH groups form hydrogen bonds with C=O groups of ester and amide groups.

Some changes were observed in PLLA/TMC–paclitaxel spectrum compared to particular components (Fig. 1), mainly concerning the bands of amide I and II and bands attributed to stretching vibrations of NH and OH groups. In paclitaxel spectrum, the maximum of the amide I band was detected at 1647 cm^{-1} and a shoulder at 1662 cm^{-1} due to bonded and free C=O amide groups, respectively. In spectrum of PLLA/TMC–paclitaxel the relations between these two bands changed and the maximum was detected at 1662 cm^{-1} and a shoulder at 1647 cm^{-1}, which means increase of free amide C=O groups relative to paclitaxel. Simultaneously, shape of the 3700–3100 cm^{-1} band did not change, which indi-