Michael Teske*, Katharina Wulf, Daniela Arbeiter, Thomas Eickner, Klaus-Peter Schmitz and Niels Grabow

Influence of bulk incorporation of FDAc and PTX on polymer properties

Abstract: In the last decades PLLA-based copolymers have been among the most attractive polymeric candidates used to fabricate devices for drug delivery and stent applications in the cardiovascular system. PLLA is biocompatible and biodegradable, exhibits a wide range of erosion times and has tunable mechanical properties. Therefore, the influence of drug incorporation on the physicochemical properties of biodegradable PLLA copolymers were examined in this study using Fluorescein diacetate (FDAc) and Paclitaxel (PTX). A percental amount of these drugs (17.5 %) were incorporated into poly(L-lactide-co-glycolide) (P(LLA-co-GA)) and poly(L-lactide-co-ε-caprolactone) (P(LLA-co-CL)) made via spray coating. The polymer surface properties, such as surface morphology and hydrophilicity were also examined and remained rather unchanged for both polymers after drug loadings. Furthermore, also the contact angle changed rather marginally. However, both polymers have already different thermal properties without the drug embedded, especially the glass transition temperature (T_G) is for P(LLA-co-CL) under 37 °C and for P(LLA-co-GA) considerable above with around 66 °C. An rather high increase in T_G achieved by addition of FDAc or PTX, crucial influences the drug release profiles for P(LLA-co-CL) in contrast to P(LLA-co-GA). Besides these results preliminarily experiments of additional coupling of other drugs on the polymer surface were performed and we obtained an influence of FDAc or PTX. The drug incorporation and physicochemical characterization data obtained in this study is relevant in optimizing the incorporation or coupling of further drugs on the polymer surface and delivery properties of these potential multi drug delivery coatings.

Keywords: Fluorescein diacetate, Paclitaxel, PLLA-co-GA, PLLA-co-CL, physicochemical, morphology, hydrophilicity, glass transition temperature

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1 Introduction

Drug-eluting stents (DES) were a breakthrough in the treatment of stenosed arterial blood vessels. DES with cytostatic drugs such as Paclitaxel (PTX) reduce in-stent restenosis by neointimal hyperplasia [1] but in contrast they have a higher late in-stent thrombosis risk due to arresting also endothelial cells [2]. To overcome this drawback biodegradable polyesters such as poly(L-lactide-co-ε-caprolactone) (P(LLA-co-CL)) and poly(D,L-lactide-co-glycolide) (P(DLLA-co-GA) were used instead of permanent polymers for drug immobilisation. Furthermore, surface modifications are a promising approach to accelerate the re-endothelialization process [3].

Due to our promising surface modification studies [4] we aim to create a dual drug delivery method combining polymer surface drug immobilisation with bulk drug immobilisation. Therefore, we developed a spray coating procedure with a high bulk drug incorporation and with minor surface changes for possible further surface modifications. As model drug we used FDAc beside PTX because of the similar diffusion and distribution coefficients like PTX [5]. Furthermore the coatings were investigated with respect to changes in glass transition (T_G) because of the potent impact on drug release.

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2 Material and methods

2.1 Polymers and drugs

Poly(L-lactide-co-glycolide) (P(LLA-co-GA)) was received from Evonik Industries AG (Darmstadt, Germany) and poly(L-lactide-co-ε-caprolactone) (P(LLA-co-CL)) was purchased from Corbion (Amsterdam, The Netherlands). Fluorescein diacetate (FDAc) and Paclitaxel (PTX) were purchased from Fisher Scientific GmbH (Schwerte, Germany) and Cfm Oskar Tropitzsch GmbH (Marktredwitz, Germany).

2.2 Coating procedure

0.2 g or 0.075 g of P(LLA-co-CL) or P(LLA-co-GA) were solved in 100 mL chloroform as spray coating solution. Polymer/drug ratio was adjusted to 82.5/17.5%. As substrate for spray coating glass slides were used. Coated slides were dried at 80 °C under vacuum. The requested amount of 250 µg polymer/drug coating per glass side was checked via weighing.

2.3 Contact angle measurements

The Contact Angle System (OCA 20, Dataphysics Instruments GmbH, Filderstadt, Germany) was used to determine the influence of drug incorporation on the surface hydrophilicity via sessile drop method with ultra-pure water [6]. Presented mean values and standard deviations were calculated from n = 5 samples.

2.4 Differential scanning calorimetry

Differential scanning calorimetry (DSC) measurements were carried out under a nitrogen purge with a DSC1 (Mettler Toledo GmbH, Greifensee, Switzerland). Calibration of the heat of fusion (ΔH) was performed with indium standard. Preliminary scans were analysed with respect to glass transition (TG) and performed at a heating rate of 20 C/min (n = 1).

2.4.1 Morphology analysis

Specimens' morphologies were examined in Environmental Scanning Electron Microscope (ESEM) mode with a Philips XL 30 ESEM (Philips ElectronOptics, Eindhoven, The Netherlands).

3 Results

3.1 Surface characterisation

3.1.1 Contact angle

Results of contact angle measurements are presented in **Table 1**.

The contact angles for P(LLA-co-CL) and P(LLA-co-GA) show only minor changes after FDAc or PTX incorporation.

Table 1: Average water contact angle ΘW ± standard deviation (SD) on pure P(LLA-co-CL) and P(LLA-co-GA) surfaces for sessile drop method (n = 5).

Modification	ΘW ± SD [°] (P(LLA-co-CL))	ΘW ± SD [°] (P(LLA-co-GA))
unmodified	75.1 ± 2.4	76.5 ± 0.4
FDAc incorporation	78.7 ± 0.3	76.1 ± 1.9
PTX incorporation	76.1 ± 0.6	75.8 ± 0.8

3.1.2 Morphology

Morphology analyses were performed via electron microscopy in ESEM mode. Representive results for P(LLA-co-CL) pure polymer and incorporated drug (FDAc or PTX) are presented in **Figure 1**.

For P(LLA-co-GA) no morphology changes were observed after drug incorporation. P(LLA-co-CL) revealed many cavities up to 35 µm diameter after FDAc incorporation. After PTX incorporation we determined also cavities, but less than for FDAc, up to 20 µm in diameter.

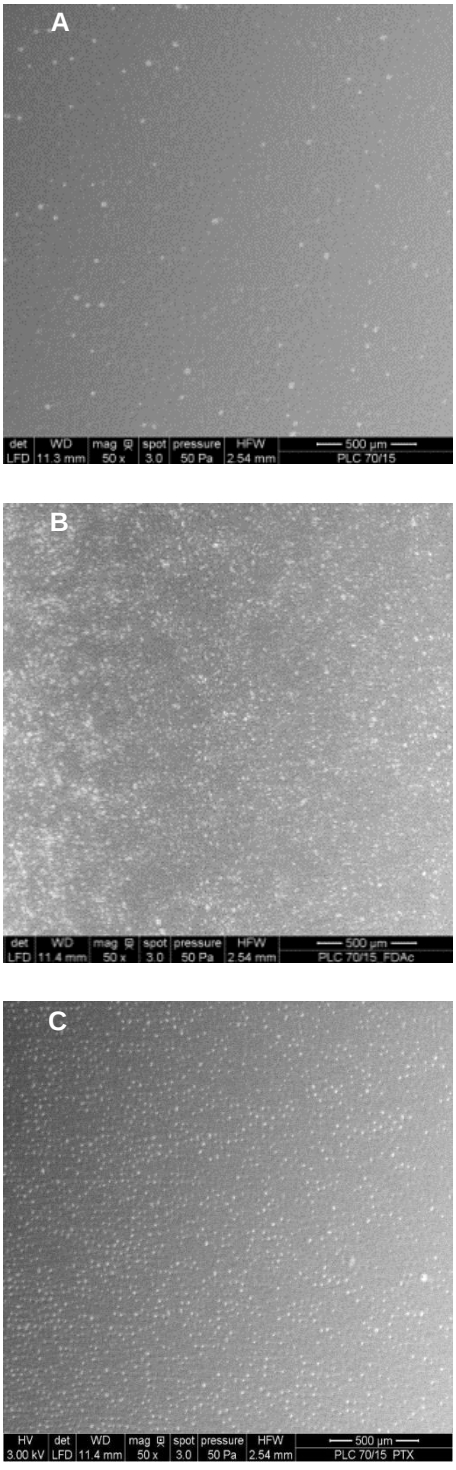

Figure 1: ESEM pictures of P(LLA-co-CL) films at 50x magnification. Pure P(LLA-co-CL) after spray coating (A), P(LLA-co-CL) with FDAc (82.5/17.5%) after spray coating with cavities up to 35 µm diameter (B) and P(LLA-co-CL) with PTX (82.5/17.5%) after spray coating with cavities up to 20 µm diameter (C). (HV = high voltage; det = detector; LFD = large field detector; WD = working distance, HFE = horizontal field width, mag = magnification).

3.2 Thermal behavior

DSC measurements were performed to investigate the thermal properties of the pure P(LLA-co-GA) and P(LLA-co-CL) polymers in comparison to the drug loaded polymers (17.5% (w) FDAc or PTX). T_G analyses are presented in **Table 2**.

Table 2: Glass transition temperature (T_G in °C) of unmodified and drug loaded P(LLA-co-CL) and P(LLA-co-GA) (n = 1).

Modification	T_G [°C] (P(LLA-co-CL))	T_G [°C] (P(LLA-co-GA))
pure	17.1	67.5
FDAc incorporation	29.1	67.4
PTX incorporation	37.1	70.6

TG of P(LLA-co-CL) show a clear increase after drug incorporation. Surprisingly the drug seems to enhance the stiffness of the polymers and did not work as plasticizer as it could be estimate. In contrast the T_G of P(LLA-co-GA) seems to be only marginally influenced by addition of FDAc or PTX.

4 Conclusion

Morphology studies reveal only minor surface changes after drug incorporation. This is also revealed by contact angle measurements. In contrast drug incorporation has a strong impact on T_G. Here we observed a high increase for P(LLA-co-CL) meanwhile only minor changes for P(LLA-co-GA) were observed. This has also influence on the drug diffusion and their release profiles.

In summary, the presented coating procedure enables dual drug delivery coatings based on the biodegradable polylactide-co-polymers P(LLA-co-CL) and P(LLA-co-GA) using polymer surface modifications as a further drug source. The combination of a re-endothelialization process promoting biomolecule and PTX seems to be a promising approach to overcome late in-stent thrombosis.

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