Degradation Mechanisms of Absorbable Polymers used in Drug Eluting Stents (DES)

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Statement of Purpose: Drug eluting stents (DES) are combination products that currently consist of a composite coating of drug and polymer on a traditional metallic stent used to treat atherosclerosis. In recent years, the trend in the industry is to incorporate polymers that degrade in-vivo. Also on the horizon are stents composed of entirely degradable constituents. Degradable polymers used in DES applications undergo hydrolysis reactions in-vivo that cleaves the initially long polymer chains forming progressively shorter lengths of polymer. The locations and rates of chain cleavage will depend on a myriad of factors, including chain length, chemical structure, and device size, as well as the geometry and chemistry of the implant location. The intermediate chemical entities that arise during the degradation process and the rate at which these individual reactions occur have yet to be established.

Therefore, we conducted a series of experiments to illustrate degradation mechanism of absorbable polymers, poly(lactic-co-glycolic) acid (PLGA), which has been used as polymeric coating for DES. We identified and quantified major intermediate chemical entities and associated hydrolysis rates, which help to evaluate devices containing these materials to ensure that neither the degradation products nor rate give rise to adverse events after stent implantation.

Methods: PLGA 50/50 and PLGA 85/15 (iv 0.55-0.75 dL/g, Durect Co.) were casted on cover glass (18 x18 mm) and dried by vacuuming overnight. Then the PLGA film on each cover glass was immersed in PBS (pH 7.4) at 37 °C to degrade. PBS media was replaced every week to maintain consistent pH environment. The degradation behaviors of PLGA films were analyzed at Day 4, 7, 14, 21, 28, 35, 42, 49, and 56 days At each time point, PLGA films were freeze dried, weighed and evaluated with Gel Permeation Chromatography (GPC). The pH values of the degradation solution were recorded at all the time points. The intermediate degradation products in the collected solution were further identified and quantified with Mass Spectrometry (MS).

Results: We investigated the degradation mechanism of PLGA under physiological conditions. Both PLGA 50/50 and PLGA 85/15 are amorphous random copolymers with the same intrinsic viscosity (0.55-0.75 dL/g) range. However, the degradation behavior of two polymers was found to be significantly different. As shown in Figure 1, the weight loss for PLGA 50/50 started from the third week of degradation, compared to the sixth week for PLGA 85/15. Another interesting observation is the molecular weight of the residual PLGA 85/15 films. The GPC results demonstrated a bi-modal distribution in molecular weight for PLGA 85/15 after degraded for 5 weeks, compared to uni-modal distribution of degradants from PLGA 50/50.

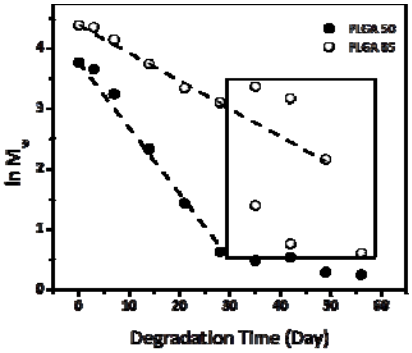

Figure 1. Dependence of lnM_w on degradation time, the slope of each line is calculated to be degradation rate. Note the bi-modal molecular weight points as emphasized by the box for PLGA 85/15.

We also identified and quantified the intermediate products throughout degradation using MS. PLGA 50/50 degrades significantly faster than PLGA 85/15, as large amount of oligomers were presented at the 21st day. The major degradants for PLGA 50/50 are L_4G_2 at initial stage, followed by the long chain oligomers $G_{12\text{-}14}$ and short chain oligomers L_7 at the later term of degradation. On the contrary, the major degradants for PLGA 85/15 are oligomers G_{10} and L_7 at initial stage, followed by $L_{6\text{-}8}$ in the later term.

Conclusions: We investigated the degradation mechanism of absorbable polymer PLGA with two model polymers, PLGA 85/15 and PLGA 50/50. The major intermediate degradants and their abundance for these two polymers are dramatically different, which change with the degradation process. Our study indicated that the degradation of PLGA strongly depends on polymer composition and chain sequences. The degradation behavior of PLGA polymers demonstrates the mechanism of heterogeneous cleavage of ester bonds, whose hydrolysis prefers to start with G-G bonding than L-G bonding.

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