A non-toxic additive to introduce X-ray contrast into poly(lactic acid). Implications for transient medical implants such as bioresorbable coronary vascular scaffolds

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Statement of Purpose: Biodegradable stents, also called *drug-eluting transient bioresorbable vascular scaffolds,* are built from one or more biodegradable materials with the drug impregnated therein. The scaffolds perform their essential tasks (structural support and drug release), and then degrade and disappear altogether. Poly(lactic acid), is used to build such devices, due to its excellent biodegradability and biocompatibility.[1] The polymer is ideal, except for one aspect: the material is radiolucent (transparent for X-radiation). Therefore, one or more metallic "contrast points" are incorporated in the scaffolds, to enable the interventional cardiologist to monitor the position of the stent prior to its deployment. This is a major difference with metallic stents, which are fluoroscopically visible entirely, and for which deployment can be verified.

Triggered by this, we designed a novel X-ray contrast agent, to impart radiopacity into poly(lactic acid). Two boundary conditions were kept in mind: (i) the molecule should contain covalently bound iodine; (ii) mixing of the contrast agent into poly(lactic acid) should afford a homogeneous blend. This was achieved by the new compound (S)-2-hydroxy-3-(4-iodobenzyloxy) propanoic acid. Two blends with poly(D, L-lactic acid) (5 wt. % and 10 wt. %) were prepared though micro-extrusion/mixing. Two blends containing sodium diatrizoate (5 wt. % and 10 wt. %) were made for comparison.

Methods: The new contrast agent was synthesized successfully. The compound could be blended with a medical-grade poly(D,L-lactic acid): PURASORB DL20. DSC, SEM (in backscatter mode) and XPS were used to physically characterize all blends. Cytotoxicity of the blends *in vitro* was studied by MTT tests and Live-Dead assay. Both mouse 3T3 cells and human microvascular endothelial cell-line (HMEC-1) were used.

Results: Figure 1 shows a SEM micrograph of materials 2 through 6 simultaneously. The processed poly(D, L-lactic acid) (2) and both blends with (S)-2-Hydroxy-3- (4-iodobenzyloxy) propanoic acid (5 (5%), 6 (10%)) appeared as homogeneous surfaces. On a grey scale, they differed as follows: material 2 (darkest) < material 5 < material 6 (lightest). The blends containing sodium diatrizoate (3 (5%), 4 (10%)) were heterogeneous: white dots (contrast agent) were scattered over the surface, thus revealing phase-separation. Figure 2 shows X-ray images of all materials. The intrinsic attenuation coefficients (i.e. the capacity of the materials to absorb X-radiation) increase in the order: poly(D, L-lactic acid) < 3 < 5 < 6 < 4. Results of MTT tests and Live-Dead Cells Assay indicated all the blends were non-toxic.

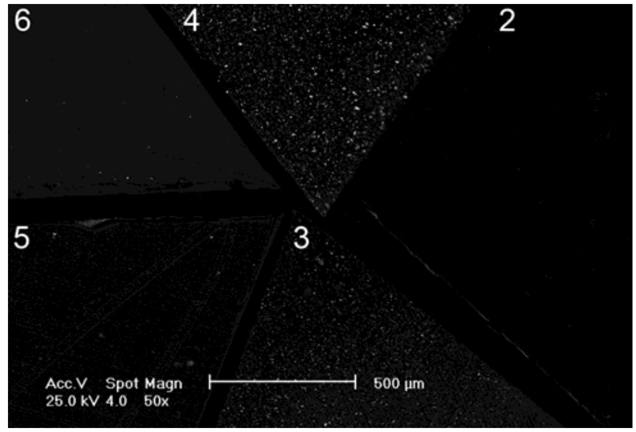

Figure 1. Scanning electron microscopy (backscatter mode) of poly(D, L-lactic acid) (2), and the four blends (3 through 6).

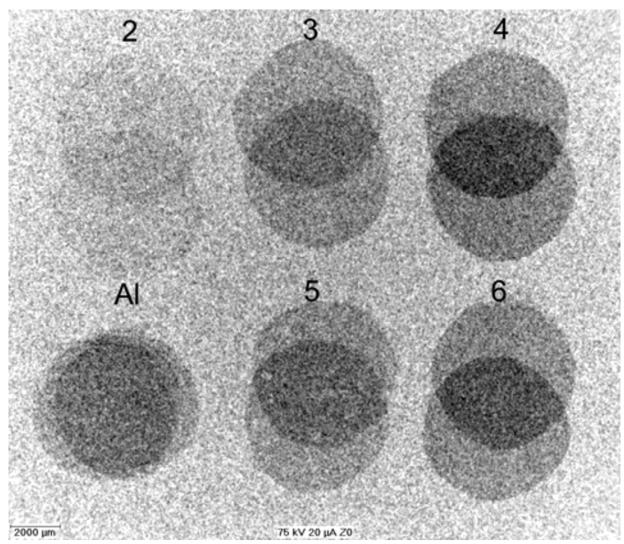

Figure 2. X-ray images of two overlapping specimens of poly(D.L-lactic acid) (2), materials 3 – 6, and aluminum (10 overlapping foil specimens; total thickness 120 µm).

Conclusions: (S)-2-Hydroxy-3-(4-iodobenzyloxy)propanoic acid can be used to introduce radiopacity into poly (lactic acid). The resulting blends are homogeneous, non-cytotoxic and radiopaque. This approach provides a promising route to fully radiopaque bioresorbable vascular scaffolds.

Reference:

1. Brugaletta S, Garcia-Garcia HM, Onuma Y, Serruys PW. Expert Rev Med Devices. 2012;9,327-338.