New Oxidative Mechanism for the Biodegradation of Poly(carbonate urethanes)

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Introduction
Polyurethane elastomers have been utilized extensively in medical applications due to their favorable mechanical properties and biocompatibility. However, these elastomers have been shown to undergo biodegradation after long-term implantation. Poly(ester urethanes) were shown to be susceptible to rapid hydrolysis and were replaced by more hydrolytically stable poly(ether urethanes). Poly(ether urethanes), although more stable than poly(ester urethanes), were found to be susceptible to oxidation by free radicals released by adherent macrophages and foreign body giant cells (FBGC). Poly(carbonate urethanes) are a new class of polyurethanes that have been shown to be more hydrolytically stable than poly(ester urethanes) and less susceptible to oxidation than poly(ether urethanes).

Several studies have outlined the increase in biostability of poly(carbonate urethane) (PCU) over poly(ether urethanes) (PEU). However, significant evidence of in vivo biodegradation of poly(carbonate urethane) and a correlating mechanism is lacking. Previous cell culture and in vitro studies have hypothesized that these polyurethanes undergo hydrolysis of the polycarbonate soft segment due to hydrolytic enzymes released by adherent cells. In the present study, chemical changes observed in poly(carbonate urethane) after long-term implantation have been correlated with oxidation of the soft segment and hard segment degradation. Corollary in vitro studies were used to validate the new oxidative mechanism of biodegradation.

Materials and Methods
Materials: Elastane™ 80A and Bionate 80A were provided by The Polymer Technology Group Inc., Berkeley, CA. Elastane™ 80A has a methylene bis(4-phenyl isocyanate) hard segment chain extended with 1,4-butanediol and a poly(2,6-cyclohexylene glycol) soft segment. Bionate™ 80A has a methylene bis(4-phenyl isocyanate) hard segment chain extended with 1,4-butanediol and a poly(1,4 hexyl, 2-ethyl carbonate) diol (PHECD) soft segment.

Sample Preparation: Medtronic, Inc., Minneapolis, MN fabricated tubes with a 2.5mm inner diameter from pellets using a Microextruder with an annular die. The tubes were then stretched over rectangular glass mandrels (2cm x 2mm x 2mm) to a 400% grip to grip displacement in an Instron mechanical testing device. Polyurethane films were extruded using a Nordmeister Model RC 0620 extruder and a chilled roll take-off.

In Vivo Biodegradation Experiment: Strained samples were implanted using our standard cage implant protocol. Briefly, strained specimens were placed in stainless-steel wire mesh cages (3.5cm x 1cm). Cages were then sterilized with ethylene oxide and implanted subcutaneously in the backs of 6 week old, female Sprague-Dawley rats. Samples were explanted at 1, 3, 5, 10, 20, and 30 weeks to study biodegradation. Explanted samples were washed with 1% aqueous Triton X-100 to remove adherent cells. Specimens were rinsed and vacuum dried prior to examination of degradation by ATR-FTIR and SEM analysis.

Chemical degradation of the soft segment was quantified by measuring percent carbonate ether loss using peak height analysis of the 1253 cm⁻¹ carbonate ether linkage normalized to the 1591 cm⁻¹ aromatic reference peak of the hard segment. Hard segment degradation was quantified by measuring percent amide bond loss using peak height analysis of the 1530 cm⁻¹ C-N amide bond normalized to the 1591 cm⁻¹ aromatic reference peak. Specimens were then examined for physical degradation with SEM. Scanning electron micrographs were collected with a JEOL 640-A scanning electron microscope. All specimens were vacuum dried at room temperature and coated with 100Å of gold prior to imaging.

In Vivo Accelerated Degradation Experiment: A solution of 20% hydrogen peroxide and 0.1 M cobalt chloride was used to mimic the oxidative in vivo environment. Unstrained films were placed in solution and treated at 37ºC for 24 days. The solution was changed every three days to maintain relatively constant levels of oxygen radicals. The samples were removed, rinsed and vacuum dried prior to examination of degradation by ATR-FTIR and SEM analysis as described above.

Results and Discussion
Physical degradation was observed in the form of surface pitting on explanted Bionate 80A after 15 months in vivo. Similarly, pitting of Bionate 80A after 24 days in vitro was observed (Figure 1A-B). Pitting on Elastane 80A was more extensive than Bionate 80A after 24 days in vitro (Figure 1B-C). These results suggest that although the PEU, Bionate 80A, is more stable than the PCU, Elastane 80A, the FCU is still susceptible to degradation in vitro.

Figure 1: SEM of physical degradation

Figure 2: ATR-FTIR of chemical degradation

Bionate 80A after 15 months in vivo

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<tr>
<th>Peak Height Ratio</th>
<th>Percent Remaining</th>
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<tr>
<td>1253 cm⁻¹/1591 cm⁻¹</td>
<td>73 ± 9%</td>
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<tr>
<td>1530 cm⁻¹/1591 cm⁻¹</td>
<td>81 ± 6%</td>
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The chemical changes in the ATR-FTIR spectra observed on Bionate 80A after implantation were reproduced using our oxidative in vitro experiment, 20% H₂O₂/0.1M CoCl₂. The same peak height loss and appearance of new peaks were observed using this oxidative system (Figure 2). This suggests that the biodegradation observed in vivo is due to oxidation by adherent macrophages and foreign body giant cells. Currently, blends of the poly(carbonate urethane) and antioxidant additives are being tested both in vitro and in vivo to confirm that the mechanism of biodegradation is oxidative.

This study has demonstrated that the chemical and physical biodegradation of poly(carbonate urethanes) can be reproduced and accelerated with an oxidative in vitro system.

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