Processing and Hydrolytic Degradation of Aromatic, *Ortho*-Substituted Polyanhydrides

CHRISTI BEDELL,* MENG DENG,† THEODORE J. ANASTASIOU, KATHRYN E. UHRICH

Department of Chemistry, Rutgers University, Piscataway, New Jersey 08854

Received 30 April 1999; accepted 7 June 2000

ABSTRACT: Polyanhydrides containing 1,3-bis(*p*-carboxyphenoxy)propane, abbreviated poly(*p*-CPP), are currently being used as controlled-release devices for the treatment of brain cancer. These polymers are biodegradable and biocompatible and release pharmaceuticals in a controlled fashion. However, polyanhydrides have an important drawback: The polymers themselves are highly insoluble in both organic solvents and water and have high melting temperatures, rendering them difficult to process into fibers and/or films. Previously, we synthesized polymers that overcame the solubility and, thus, processing problems associated with poly(*p*-CPP). In this report, we describe the mechanical properties and hydrolytic degradation characteristics of these newly developed polyanhydrides. After formation of films by either compression-molding or solvent-casting, the polymer surfaces were examined by SEM. Mechanical studies were also performed on the compression-molded samples. Compression-molded samples were sterilized by γ-irradiation and then examined by GPC for changes in their polymer structure. Lastly, the polymers and the degradation media were evaluated by TGA, DSC, GPC, and HPLC to gain a better understanding of the degradation process. © 2001 John Wiley & Sons, Inc. J Appl Polym Sci 80: 32–38, 2001

Key words: polyanhydrides; degradation; hydrolysis; mechanical analysis

INTRODUCTION

Poly[1,3-bis(*p*-carboxyphenoxy)propane anhydride], abbreviated poly(*p*-CPP), is an aromatic polyanhydride currently used in drug-delivery vehicles for the treatment of brain cancer.[1] Polyanhydrides of aromatic diacids offer several advantages over aliphatic polyanhydrides, including longer release and degradation times[2] as well as higher mechanical strength and stability.[3,4] However, aromatic polyanhydrides are insoluble in organic solvents and melt at high temperatures.[5] These properties limit the uses of purely aromatic polyanhydrides as they cannot be easily fabricated into films or microspheres using solvent or melt techniques. Because of these limitations, polyanhydrides of aromatic monomers must be copolymerized with aliphatic monomers to attain the necessary solubility characteristics. Relative to copolymers based on aliphatic and aromatic monomers, we designed homopolymers that have aliphatic and aromatic moieties combined into one monomer unit. Despite interest and need, only one other report[6] has been published on the synthesis and properties of anhydride homopolymers of aromatic monomers.

Correspondence to: K. E. Uhrich (uhrich@rutchem.rutgers.edu).

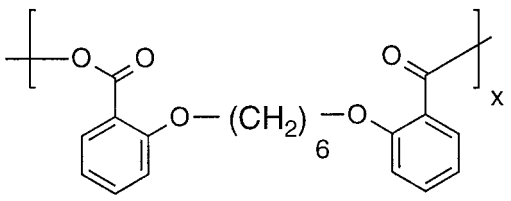
**Present address:* Albermarle Corp., Baton Rouge, LA 70898.

†*Present address:* PolyMed, Pendleton, SC 29670.

Contract grant sponsors: New Jersey Commission on Science and Technology; ConvaTec.

Journal of Applied Polymer Science, Vol. 80, 32–38 (2001)

In an effort to improve upon the solubility characteristics of poly(*p*-CPP), we synthesized a series of structurally related polymers.[7] The design motivation behind these new polyanhydrides was to maintain their ability to hydrolytically degrade while enabling a wider range of processing capabilities. In our previously published work, we identified the characteristics of poly[1,6-bis(*o*-carboxyphenoxy)hexane anhydride] [poly(*o*-CPH)] (structure shown below) such as solubility, water contact angles, glass transition temperatures, and decomposition temperatures:



poly(*o*-CPH)

This report focuses on the most promising polymer system evaluated in previous studies: poly(*o*-CPH). Specifically, we evaluated the polymers after solvent casting, compression molding, and γ-irradiation to monitor possible chemical or thermal degradation of the polymers that may have occurred as a result of processing. Furthermore, we extensively characterized the polymers and their degradation media throughout several weeks of *in vitro* degradation to understand the degradation process.

EXPERIMENTAL

Materials

All chemicals, except phosphate buffer, were purchased from Aldrich (Milwaukee, WI) and used as received. Phosphate buffer was obtained from Sigma (St. Louis, MO) and the solution made by dissolution into 1 L of distilled water. Polyanhydrides were synthesized as previously described.[7] Poly(*o*-CPH) had an MW = 15,000 and PDI = 1.1.

Sample Preparation

For compression-molded samples, polymer powder (170 mg) was compressed at 5000 lbs in circular molds (13-mm diameter) at 50°C for 5–10 min using a Carver laboratory press (Model M). For solvent-cast samples, the polymer (400 mg) was dissolved in a solvent (e.g., $CHCl_3$), cast into Teflon-lined Petri dishes, covered, and allowed to dry overnight at room temperature.

γ-Irradiation

Compression-molded polymer samples (in triplicate) were placed in clear glass vials. As a control, polymer samples were stored at room temperature but not irradiated. The samples were irradiated by Isomedix Operations (Whippany, NJ) with a delivered minimum and maximum dose of 25.6 and 294 kGy, respectively, for a total exposure time of 310 min.

Degradation Studies

Compression-molded polymer discs were placed in vials with 10 mL of a phosphate buffer solution at pH 7 for 5 weeks in triplicate. The vials were then placed in an incubator at 37°C and shaken continuously at 60 rpm throughout the study. Media was replaced every hour for the first day, every day for the following 3 days, every other day for the next 6 days, and every week for the remainder of the study. At designated time points, the samples were removed from the buffer solution, patted dry with KimWipes, then dried overnight under a vacuum before analysis. The solid polymer samples were evaluated using thermal gravimetric analysis (TGA), differential scanning calorimetry (DSC), and gel permeation chromatography (GPC) as described below. The spent solutions were evaluated using high-pressure liquid chromatography (HPLC) analysis to determine the concentration of the degradation products.

Gel Permeation Chromatography (GPC)

Molecular weights were determined on a Perkin–Elmer Series 200 LC system equipped with a PL-Gel column (5 μm, mixed-bed) operated at 30°C, a Series 200 refractive index detector, a Series 200 LC pump, and an ISS 200 autosampler. A DEC Celebris 466 computer was used to automate the analysis via a PE Nelson 900 interface and a PE Nelson 600 Link box. PE Turbochrom 4 software was used for data collection and processing. Tetrahydrofuran (THF) was used as an eluent for analysis at a flow rate of 0.5 mL/min. Samples (~5 mg/mL) were dissolved in the eluent and filtered using a 0.45-μm PTFE syringe filters prior to column injection. Molecular

weights were calibrated relative to narrow molecular weight polystyrene standards (Polysciences, Dorval, Canada).

High-pressure Liquid Chromatography (HPLC)

HPLC was performed on a Perkin–Elmer Series 200 LC system equipped with a PE-CR C18 column operated at 25°C, an Applied Biosystems ultraviolet detector (785 nm), a Series 200 LC pump, and an ISS 200 autosampler. A DEC Celebris 466 computer was used to automate the analysis via a PE Nelson 900 interface and a PE Nelson 600 Link box. PE Turbochrom 4 software was used for data collection and processing. The eluent was methanol:water (40:60) with ~1% phosphoric acid at a flow rate of 0.5 mL/min. Samples (~5 mg/mL) were dissolved into water and filtered using a 0.45-μm PTFE syringe filters prior to column injection.

Thermal Analysis

Thermal analysis was performed on a Perkin–Elmer system consisting of Pyris 1 DSC and TGA7 analyzers with TAC 7/7 instrument controllers. PE Pyris 1 and TGA7 software were used for data collection and processing on a DEC Venturis 5100 computer. For DSC, samples (~5 mg) were heated under dry N_2 gas. Data were collected at heating and cooling rates of 10°C/min for a minimum of two cycles. For TGA, samples (~10 mg) were heated under dry nitrogen gas. Data were collected at a heating rate of 20°C/min. Decomposition temperatures were defined as the onset of decomposition.

Mechanical Measurements

Tensile measurements were made using an Instron tensile tester Model 1122 at room temperature according to ASTM standard D638. Tensile strength, tensile modulus, strain at yield, as well as strain at break were determined under ambient conditions. In all cases, tensile values were calculated from the arithmetic average of a minimum of three measurements. Dynamic mechanical analysis was performed on a Perkin–Elmer DMA 7e dynamic mechanical analyzer with a TAC7/DX instrument controller using a three-point bending apparatus. PE Pyris 1 software was used for data collection and processing on a DEC Venturis 5100 computer. The polymers were subject to a static load of 110 mN and a dynamic load of 100 mN at 1 Hz. Samples were heated from −1.0 to 50.0°C at 5.0°C/min.

Scanning Electron Microscopy (SEM)

An amalgam of AuPd was sputtered onto polymer samples using a Baltec SCD 004 sputter coater. The SEM was a Hitachi S450 (6-nM resolution) using Orion 4.1 on Windows 95 software.

RESULTS AND DISCUSSION

The design motivation behind these new polyanhydrides was to maintain their hydrolytic degradability while enabling a wider range of processing capabilities. In this work, we evaluated the polymer systems after solvent casting, compression molding, and γ-irradiation to monitor possible chemical or thermal changes of the polymers that may occur as a result of processing. Furthermore, we extensively characterized the polymers and their degradation media throughout several weeks of *in vitro* degradation.

Processing

We evaluated the polymer systems after solvent-casting and compression-molding methods created transparent, light brown films. Visually, the surfaces of the raw polymer [Fig. 1(a)] appeared rough. The solvent-cast films [Fig. 1(b)] had predominantly smooth, nonporous surfaces with "billowing" wrinkles. The surfaces of the compression-molded [Fig. 1(c)] films were also wrinkled with a closed pore structure. A cross section of the compression-molded samples [Fig. 1(d)] shows a large number of unconnected pores with sizes ranging from 25 to 250 μm. Solvent casting and compression molding slightly decreased the T_g's of the polymer to 25.8 and 28.7°C, respectively, from the initial value of 34°C. However, neither processing method affected the decomposition temperature, which remained at 420°C.

Mechanical properties were evaluated on compression-molded films under ambient conditions (Instron) and while heating (DMA). Because the mechanical properties are indicative of an elastic material, the values are discussed relative to an aliphatic-based polyanhydride, specifically poly(sebacic acid-*co*-hexanedecanedioic acid) in a 1:1 ratio.[8] The strain at yield (14%) for poly(*o*-CPH) is

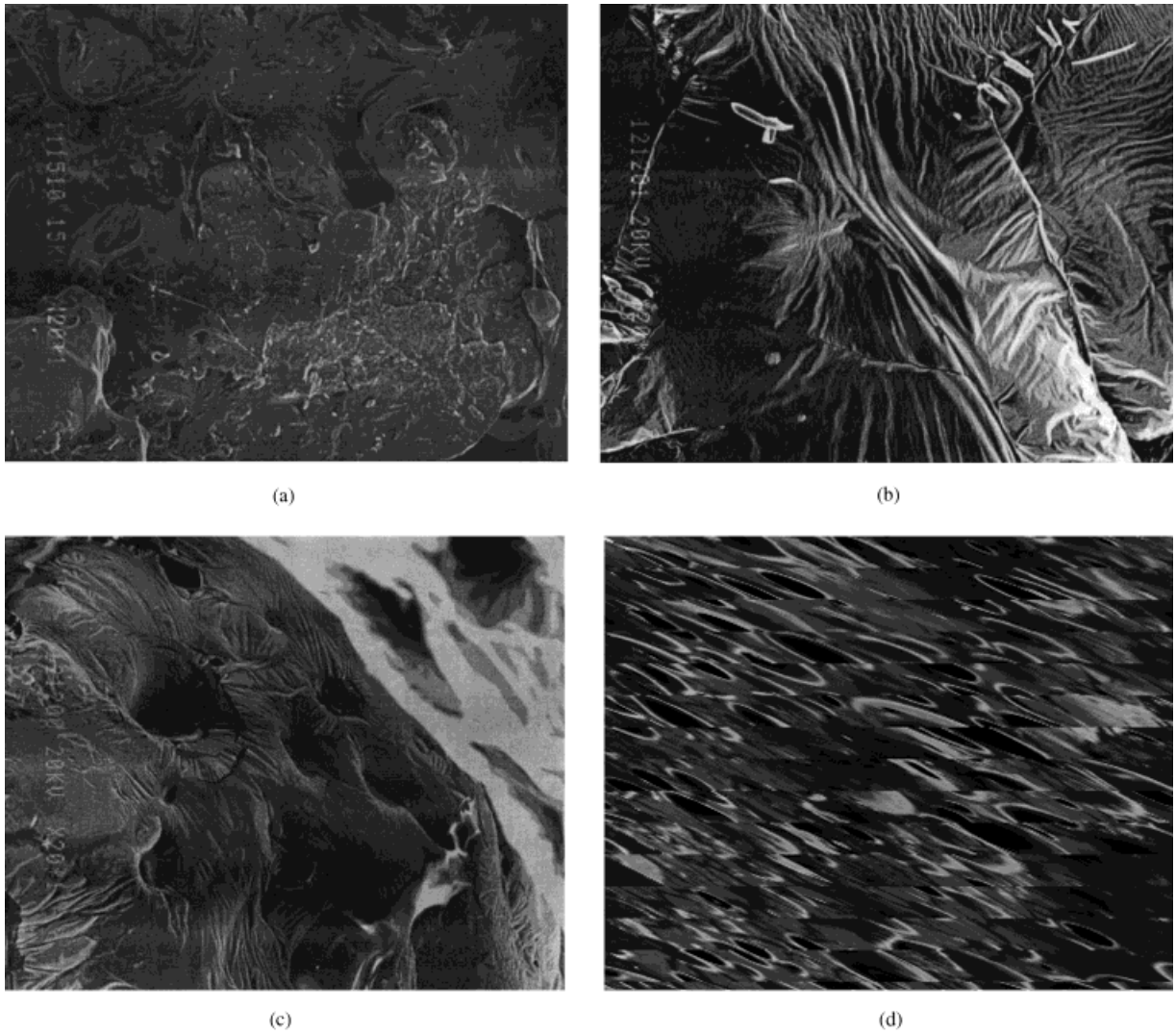


Figure 1 SEM photos of poly(*o*-CPH) of (a) the surface of an unprocessed powder (magnification ×20), (b) the surface of a solvent-cast film (magnification ×20), (c) the surface of a compression-molded film (magnification ×20), and (d) a cross section of a compression-molded film (bar is 140 μm).

identical to that of the aliphatic polyanhydrides, whereas the strain at break (120%) is higher than that of the aliphatic polyanhydrides (85%). Yield stress for poly (*o*-CPH) (1.1 MPa) is lower than that for the aliphatic systems (4 MPa), while the tensile modulus (200 MPa) is 4.5 times higher (45 MPa). These attributes are of particular interest when molecular weight is taken into account—the molecular weight of poly(*o*-CPH) was lower (15,000) than that of the aliphatic polyanhydrides (142,000). The preceding data indicate that even at low molecular weights the presence of aromatic moieties in poly(*o*-CPH) has a profound influence on the mechanical characteristics at room temperature. When the poly(*o*-CPH) is heated to 37°C, the modulus drops dramatically to 3.9 MPa, indicating that this material is more appropriate for use as a tissue sealant, for example, rather than for weight-bearing (i.e., orthopedic) applications.

The stability of the polymers toward typical sterilization procedures was evaluated by monitoring potential changes in molecular weight following γ-irradiation. Samples of compression-molded polymer films were placed in clear glass vials and irradiated for a total exposure time of 310 min. As a control, compression-molded poly-

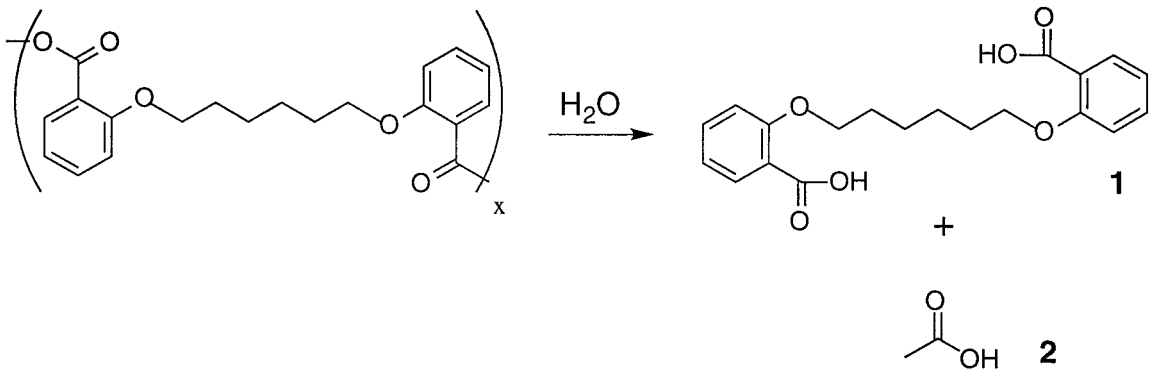
mer samples were stored at room temperature but not sterilized. No change in molecular weight or polydispersity of the irradiated polymers was observed relative to the control (nonirradiated) samples as determined by GPC. Additionally, no change in the color or texture of the polymeric matrices was observed.

In Vitro Degradation

We extensively characterized both the polymers and the degradation media from the *in vitro* studies over a period of several weeks. Compression-molded samples were placed in a phosphate buffer solution at neutral pH over a 3-week period. Two separate sets of experiments were performed to focus on specific aspects of degradation. In one study, the degradation media was analyzed by HPLC. In the second study, compression-molded polymer samples were analyzed for changes in glass transition temperatures (T_g), decomposition temperatures (T_d), molecular weight, and polydispersity.

Degradation Products

Samples of poly(*o*-CPH) polymers hydrolytically degraded into compound **1** and the byproduct, acetic acid (**2**), as outlined in the scheme below:



Using HPLC methods, the degradation media was monitored for the appearance of compound **1**, an aromatic acid, using ultraviolet detection. These data were used to generate the degradation curve shown in Figure 2.

The cumulative release of compound **1** is shown over the 3-week study. Compound **1** is released in a nearly linear fashion over this time period. By 16 days, the release of **1** is complete, indicating the completion of polymer degradation.

In comparison, poly(*p*-CPP) matrices degrade over a much longer time period.[9] Leong et al. extrapolated that compression-molded poly(*p*-CPP) matrices with the same mass as utilized in the current study would completely degrade in over 3 years. In summary, while poly(*o*-CPH) completely degrades within 17 days, poly(*p*-CPP) degrades only minimally (<5%) during this time.

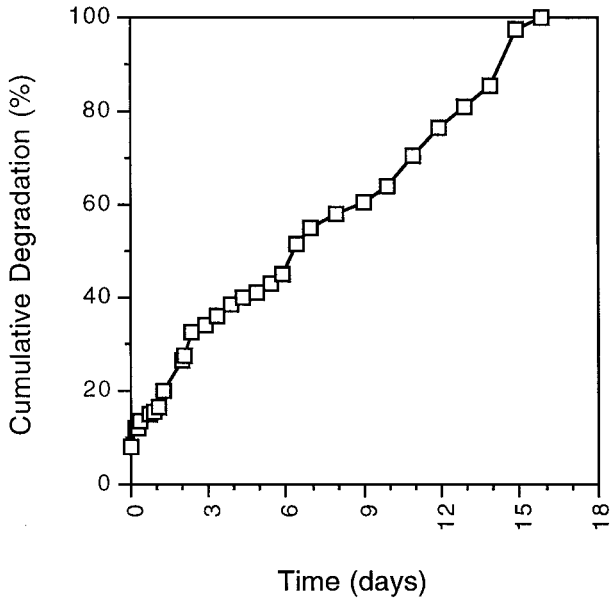


Figure 2 Cumulative percent of degradation product (**1**) released from poly(*o*-CPH) during degradation in buffered media.

Changes in Polymer Characteristics

At the appropriate time points, the polymer matrices were removed from the buffered media, dried, and then analyzed for changes in molecular weight

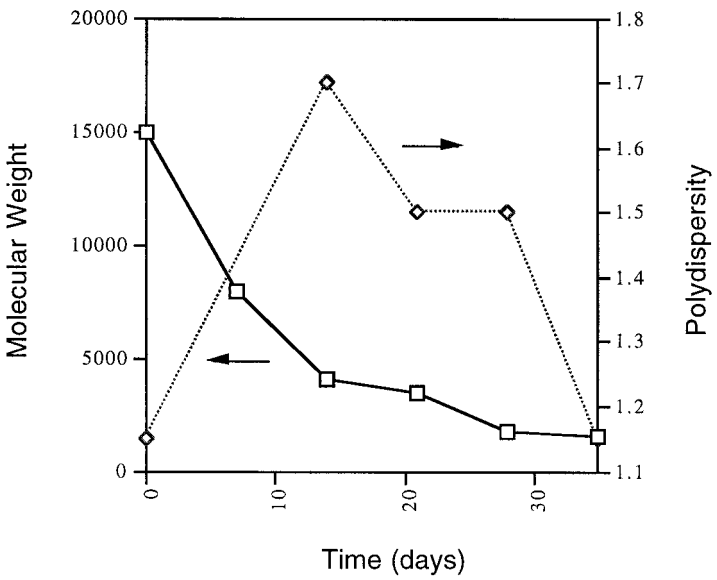


Figure 3 Change in molecular weight and polydispersity of compression-molded polymer samples undergoing *in vitro* degradation.

and thermal properties. After 1 week, the molecular weight was nearly half (55%) of the original value (Fig. 3). The molecular weight continued to decrease throughout the remainder of the study. After 2 weeks, the molecular weight stabilized at approximately 3000, corresponding to oligomers containing ~8 repeat units. Concurrently, the PDI significantly increased through the first 4 weeks. This result is due to the increasing number of variable chain lengths as the polymer degrades. At the end of the study (week 5), we expected that only undissolved monomer remains in the solution, thus yielding low molecular weights and small PDI values.

The thermal properties changed linearly throughout the degradation process (Fig. 4). The T_d decreased linearly over time, initially from 420 to 390°C (week 5). Similarly, the T_g decreased linearly over 5 weeks from an initial value of 34°C to only 8°C.

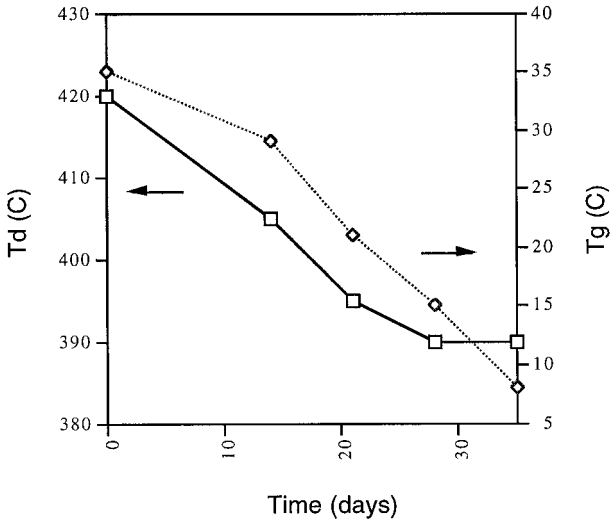


Figure 4 Change in T_g and T_d of compression-molded polymer samples undergoing *in vitro* degradation.

CONCLUSIONS

This aromatic polyanhydride can be readily compression-molded or solvent-cast into transparent films with minimal effect on the glass transition temperatures. Methods describing the fabrication of solid as well as hollow fibers are forthcoming.[10] The polymer can be successfully sterilized with no measurable change in the molecular weight or color. The polymers predictably degrade in a linear fashion. Because of the inherent, elastic nature of these systems, they may be appropriate for soft tissue applications such as for a tissue sealant. In addition, the high solubility of the polymers in organic solutions may be useful for drug-delivery formulations such as microspheres or membranes.

The financial assistance of the New Jersey Commission on Science and Technology and ConvaTec is gratefully

acknowledged by the authors. The authors also thank Dawan Palms and Cheryl Campo for their contributions to this project.

REFERENCES

1. Brem, H.; Piantadosi, S.; Burger, P.; Walker, M.; Selker, R.; Vick, K.; Black, K.; Sisti, M.; Brem, S.; Mohr, G.; Muller, P.; Morawetz, R.; Schold, S. Lancet 1995, 345, 1008.
2. AAOS, Orthopaedic Knowledge Update; Rosemont, Illinois, 1990; Chapter 13.
3. Attawia, M.; Uhrich, K.; Botchwey, E.; Fan, M.; Langer, R.; Laurencin, C. J Biomed Mater Res 1995, 29, 1233.
4. Carter, D.; Gates, E.; Harris, W. J Biomed Mater Res 1982, 16, 647.
5. Attawia, M.; Uhrich, K.; Botchwey, E.; Langer, R.; Laurencin, C. J Ortho Res 1996, 14, 445.
6. Carter, D.; Hayes, W. C. Science 1976, 194, 1174.
7. Campo, C.; Anastasiou, T.; Uhrich, K. Polym Bull 1999, 42, 61.
8. Engelberg, I.; Kohn, J. Biomaterials 1991, 12, 292.
9. Leong, K.; Brott, B.; Langer, R. J Biomed Mater Res 1985, 19, 941.
10. Twardowski, T.; Anastasiou, T.; Erdmann, L.; Uhrich, K., in preparation.