Oxidative and hydrolytic stability of a novel acrylic terpolymer for biomedical applications

Anka N. Veleva,[1] Saad A. Khan,[1] Stuart L. Cooper[2]
[1]*Department of Chemical and Biomolecular Engineering, North Carolina State University, Raleigh, North Carolina 27695*
[2]*Department of Chemical and Biomolecular Engineering, Ohio State University, Columbus, Ohio 43210*

Received 24 November 2004; accepted 27 January 2005
Published online 27 May 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jbm.a.30349

Abstract: Oxidative and hydrolytic biostability assessment was carried out on a novel acrylic material made of hexamethyl methacrylate (HMA), methyl methacrylate (MMA), and methacrylic acid (MAA). To simulate the *in vivo* microenvironment, solutions of $H_2O_2/CoCl_2$ and buffered solutions of cholesterol esterase (CE) and phospholipase A2 (PLA) were used. As controls, film specimens were incubated in deionized water. Samples were incubated in these solutions at 37°C for 10 weeks before physical and mechanical properties were evaluated by size exclusion chromatography (SEC), ^{1}H- nuclear magnetic resonance (^{1}H-NMR), acid-base titration, and Instron tensile testing. The results from this study indicate excellent biostability of HMA-MMA-MAA terpolymers and thus their potential for use in biomedical devices for long-term implantation. © 2005 Wiley Periodicals, Inc. J Biomed Mater Res 74A: 117–123, 2005

Key words: acrylic terpolymers; *in vitro* biostability; oxidative stress; hydrolytic stress; small-diameter vascular grafts

INTRODUCTION

Placement of a biomaterial in the *in vivo* environment initiates tissue and cellular responses to injury.[1] The degree to which the homeostatic mechanisms are perturbed and the extent of pathophysiologic responses are measures of the host reactions to the biomaterial. Although injury causes the inflammatory response, released chemicals from plasma cells and injured tissue mediate the response. Chemical mediators of inflammation can have a major effect on an implanted material's stability. Activation of monocytes and macrophages, due to implantation of medical devices, results in a respiratory burst and degradation that releases oxidative and hydrolytic agents, some of which are considered to be of significance for the biostability of an implanted material.[2] Degradation of polymers *in vivo* can induce significant changes in physical properties of the polymer, which may ultimately lead to malfunction and possibly failure of the implant. Chemical changes involve covalent bond cleavage, crosslinking, or ionic bond formation. Physical changes include swelling, plasticization, crystallization or loss of crystallization, fatigue fracture, creep, degradation, and kinking. This study investigates *in vitro* biostability of a novel compliant acrylic terpolymer to oxidative and hydrolytic stress and evaluates its potential to be used in biomedical applications, more specifically for small-diameter vascular grafts.

Vascular grafts are implanted in the body in order to replace damaged vessels or bypass blocked arteries and veins.[3] Although synthetic vascular grafts such as expanded polytetrafluoroethylene (e-PTFE) and polyethylene terephthalate (PET, Dacron) have been successfully used in treating pathology of large arteries, currently there is no clinically acceptable synthetic small-diameter vascular graft, i.e., one less than 6 mm internal diameter. The compliance of the material is believed to be a critical factor for the success of the material for small-diameter vessels. The compliance is the strain or elongation response to an applied stress, and is the reciprocal of Young's modulus. Ideally, a material for small-diameter vascular prosthesis should match the viscoelastic nature of the vessel wall as closely as possible. Natural arteries show an increase in diameter of about 10% when pressurized to 150 mm Hg (normal arterial pressure). In comparison, e-PTFE and PET grafts distend by about 1% under these conditions. New materials have been developed to meet

Correspondence to: A. N. Veleva; e-mail: anveleva@unity.ncsu.edu
Contract grant sponsor: National Institutes of Health; Contract grant number: HL57917

these mechanical requirements. Fussell and Cooper designed an elastic acrylic terpolymer[4,5] as a possible replacement for e-PTFE and PET in small-diameter vascular graft applications. By selecting appropriate monomers with different lengths and chemical nature of the pendant groups, it is possible to vary the mechanical properties of the terpolymer through the ability to manipulate the glass transition temperature, Tg, and thus allow for tuning the compliance of the vascular graft as needed. These materials are designed to be biostable, in contrast to other approaches of tissue engineering where biodegradable scaffolds are employed. Biostable small-diameter vascular grafts should avoid the problems of diameter growth and aneurysm formation over long implant periods.

Here we report findings on the *in vitro* biostability of these novel elastomeric materials. To simulate the oxidative and hydrolytic environments encountered *in vivo*, solutions of $H_2O_2/CoCl_2$ and buffered solutions of cholesterol esterase (CE) and phospholipase A2 (PLA) were used. Size exclusion chromatography (SEC), proton nuclear magnetic resonance (^{1}H-NMR), acid-base titration, and Instron tensile testing were performed to assess oxidative and hydrolytic degradation.

MATERIALS AND METHODS

Terpolymer synthesis

Acrylic terpolymers for this research were prepared by a free radical polymerization reaction as described by Fussell and Cooper.[4] The monomers used in the reaction were n-hexyl methacrylate (HMA) (Alfa Aesar, Ward Hill, MA), methyl methacrylate (MMA) (ACROS Organics, Pittsburgh, PA), and methacrylic acid (MAA) (ACROS Organics, Pittsburgh, PA). The polymerization reaction was performed in dimethyl formamide (DMF) (Sigma-Aldrich, Milwaukee, WI) using 2, 2-azobisisobutyronitrile (AIBN) (Aldrich Chemical, Milwakee, WI) as the initiator. The molar ratios of the monomers in the feed were 90 mol% HMA, 8 mol% MMA, and 2 mol% MAA. The amount of the initiator comprised 0.01 mol% of the total monomer content. Some of the monomers contained small amounts of hydroquinone as an initiator, which was not removed prior to the polymerization. The reaction was carried out overnight at 55–60°C. Figure 1 shows the chemical structure of the HMA-MMA-MAA terpolymer.

To remove unreacted monomers and oligomers, the polymer was soaked for 24 h in 50/50 v/v methanol/water mixture. The purified terpolymer was dried in a vacuum oven at 55°C for 48 h and then kept in a desiccator. Films of the terpolymer were prepared by casting from 2% (wt/v) tetrahydrofuran (THF) solutions on clean Teflon Petri dishes at room temperature. After air drying the film samples, residual solvent was removed under vacuum at 55°C for at least 48 h.

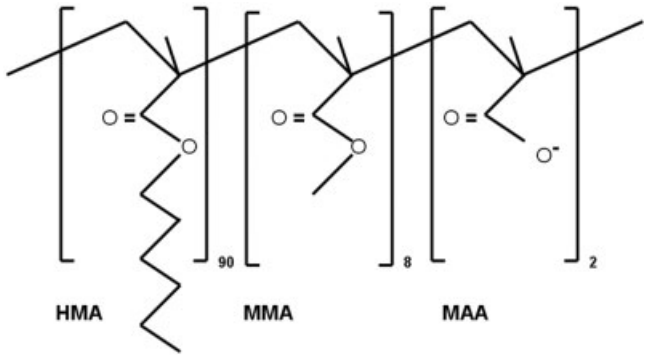

Figure 1. Chemical structure of the HMA-MMA-MAA terpolymer. The molar ratios of the monomers in the feed were 90 mol% HMA, 8 mol% MMA, and 2 mol% MAA.

In vitro stability evaluation of acrylic terpolymers

The polymer susceptibility to degradation was assessed by incubating film specimens in chemical/biological solutions at 37°C for a total of 10 weeks. Samples incubated in deionized water under the same conditions were used as controls. After treatment, each sample was rinsed in deionized water and vacuum dried at 55°C for at least 48 h.

Chemical oxidation

To study the possibility of oxidative degradation, the HMA-MMA-MAA test materials were exposed to an oxidative solution that mimicked the microenvironment at the implant/tissue interface. Several studies have shown the utility of the *in vitro* $H_2O_2/CoCl_2$ system for reproducing *in vivo* oxidation of biomaterials and for predicting long-term biostability.[6–9] Stabilizer free H_2O_2 (Sigma-Aldrich, Milwakee, WI) and $CoCl_2$. $6H_2O$ (Sigma-Aldrich) were mixed in the following ratio: 1.63M H_2O_2 and 0.10M $CoCl_2$ to generate hydroxyl and superoxide radicals together with singlet oxygen.

Hydrolysis with lysosomal enzymes

Cholesterol esterase (CE) was selected as a hydrolytic enzyme since it exemplifies one of the several enzymes synthesized by macrophages at the site of inflammation.[10] The CE used in this study originated from bovine pancreas. While the chosen enzyme does not originate from human macrophages, it has a similar activity to that of macrophage-derived CE.[11] Solutions of cholesterol esterase were prepared by the dissolution of CE powder (Sigma-Aldrich) in 0.05M phosphate buffered solution at pH 7.4 in a concentration of 1 U/mL. One unit of CE was defined as that which produces a change of the absorbance of 0.01 optical density (OD) per minute at 410 nm using *para*-nitrophenyl acetate (*p*-NPA) as a substrate at pH = 7.0 and 25°C.[12] This definition of activity was selected in order to allow comparisons to be made with degradation studies with other biomaterials that use similar units.[13] The solution was sterile filtered with a 22-μm filter.

To test enzymatic challenge other than esterase, a phospholipase was introduced into the study. Phospholipases are not only abundant and widely distributed *in vivo* but have critical roles in homeostasis. Santerre and co-workers found that phospholipase A2 participates in the process of hydrolytic degradation of polyurethanes.[14] Solutions of phospholipase A2 (PLA; porcine pancreatic PLA, Sigma-Aldrich) were prepared in buffer (50 mM Tris, pH 8.0, containing 6.8 mM $CaCl_2$) at a concentration of 0.18 U/mL. One unit of PLA catalyzes the hydrolysis of 1 μM phosphatidylcholine per minute at pH 8.0 at 37°C.[14] Enzyme solutions were changed every 7 days.

Physicochemical characterization

Size exclusion chromatography

The molecular weights of the materials used in this work were determined using size exclusion chromatography (SEC). A pumping system consisting of Waters 2690 Alliance HPLC equipped with vacuum degasser and column heater were used to perform SEC measurements. Data were collected with a modular double detector setup consisting of a Wyatt DSP Multi-Angle Light Scattering detector (MALLS) followed by a Wyatt OPTILAB refractive index detector (RI). All data were collected at 25°C using HPLC grade toluene running at a flow rate of 1.0 mL/min. Samples were prepared as solutions of 1.0 mg/mL in toluene. Number average molecular weight (M_n), weight average molecular weight (M_w), and polydispersity index (PDI) were calculated for each sample from the output of RI- and MALLS-detectors.

Nuclear magnetic resonance

^{1}H nuclear magnetic resonance (^{1}H-NMR) was used to determine the composition of the terpolymers. NMR experiments were performed using a Bruker AVANCE 500 MHz Spectrometer with an Oxford Narrow Bore Magnet, SGI INDY host workstation, and XWINNMR software version 2.5. The instrument was equipped with three frequency channels with a wave form memory and amplitude shaping unit, a three-channel ground control unit (GRASP III), a variable temperature unit, a precooling and temperature stabilization unit, and a 5-mm ID 1H/BB (109Ag-31P) Triple-Axis Gradient Probe (ID500-5EB, Nalorac Cryogenic Corporation).

A peak at ~3.9 ppm represents the two protons on the methylene carbon immediately adjacent to the ester group of HMA.[4,5] A peak at ~3.6 ppm represents the three protons on the methyl group attached to the ester group in the methyl methacrylate.[4,5] The ratio of the peak area at 3.9 ppm divided by two, for the two protons it represents, and the peak area at 3.6 ppm divided by three, for the three protons it represents, provides the molar ratio of HMA to MMA found in the polymer. The amount of MAA in the terpolymer was determined using acid-base titration. The terpolymer composition was then calculated using the ratio of HMA to MMA, and the moles of MAA.

Acid-base titration

Acid-base titration was used to determine the amounts of MAA in the terpolymer. NaOH solutions were used as the titrant, with phenolphthalein as the indicator. Three flasks of each polymer in solution were titrated. The number of acid groups in each polymer sample was calculated based on the moles of NaOH required to neutralize the polymer solution. Dividing by the mass of polymer in solution allowed calculation of the amount of MAA in the sample.

Mechanical testing

A table model Instron Series IX tensile testing machine was used to perform the uniaxial tensile property analysis. The polymer samples were cut for testing using an ASTM D1708 die. The dimensions of the cut sample were 4.74 mm in width and 22.3 mm in length. The thickness varied for the different materials, in the range of approximately 0.4–1.1 mm. The tests were performed at room temperature with a constant strain rate of 10 mm/min. A minimum of three samples was tested for each polymer.

Statistical analysis

All data were averaged and standard deviations were determined. The effect of oxidative and hydrolytic conditions was compared statistically with the Student *t* test. If the probability values for a set of data were calculated to be less than 0.05 ($p < 0.05$), differences observed in the data were considered statistically significant.

RESULTS AND DISCUSSION

Terpolymer synthesis and characterization

Random terpolymers comprising HMA, MMA, and MAA units were synthesized using free radical polymerization. The monomer compositions in the feed were 90 mol% HMA, 8 mol% MMA, and 2 mol% MAA. This polymer composition was chosen because it was desired to produce a T_g below 0°C, which would result in a flexible material. Several methods, SEC, ^{1}H-NMR, acid base titration, and tensile testing were used to characterize this material. A summary of the physical and mechanical properties is given in Table I.

Figure 2 shows the ^{1}H-NMR spectrum of the HMA-MMA-MAA terpolymer. The NMR peak at 3.9 ppm was used to determine the HMA content and the peak at 3.6 ppm was used to determine the MMA content.

TABLE I
Physical and Mechanical Properties of the HMA-MMA-MAA Terpolymer

Physical/Mechanical Property	Method	Value
Number average molecular weight (Mn)	SEC	116,000 ± 3500
Weight average molecular weight (Mw)	SEC	150,800 ± 2700
Polydispersity index (PDI)	SEC	1.3 ± 0.1
Molar percent monomers in the feed		90 HMA 8 MMA 2 MAA
Actual composition (mol%)	1H-NMR and acid-base titration	96 HMA 2 MMA 2 MAA
Young's modulus (MPa)	Instron	2.36 ± 0.34
Maximum strength (MPa)	Instron	1.45 ± 0.30
Elongation at break (%)	Instron	657 ± 143

From the data in Table I, it can be seen that the actual percent of HMA is higher than that fed to the reactor while the amount of MMA is less than expected based on the input compositions. This indicates that the HMA monomer reacted more readily than the MMA monomer. The higher reactivity of the HMA could be due to stabilization of the radical by the larger side groups.[15]

Mechanical properties were calculated from the stress-strain curves of the terpolymer. Young's modulus, maximum stress, and elongation at break are reported in Table I. These values are similar to data from the literature for the mechanical strength of natural blood vessels.[16] Young's modulus, tensile strength, and elongation at break are sensitive to the degradation of elastomeric materials.

Materials for long-term implants must have physical properties that are stable for the service life of the device. Exceptions for this statement apply to deliberately biodegradable materials designed for use in controlled drug release and some polymer scaffold applications. This study involves a potential biostable scaffold material so it was important to verify the material's resistance to biodegradation. In order to investigate the biostability of this acrylic terpolymer, it was appropriate to first determine whether the mechanical properties deteriorate after exposure to *in vitro* biodegradation conditions.

Biostability evaluation after exposure to degrading solutions

The attractiveness of acrylic materials is due to the fact that their mechanical and chemical properties can easily be modified by changing the length and chemical nature of the backbone and pendant groups, thus creating flexible materials with tunable mechanical properties. This study reports on the chemical and mechanical stability of a novel flexible acrylic material with a low glass transition temperature and elastic properties similar to that of natural blood vessels. Since change of the molecular structure of a polymer

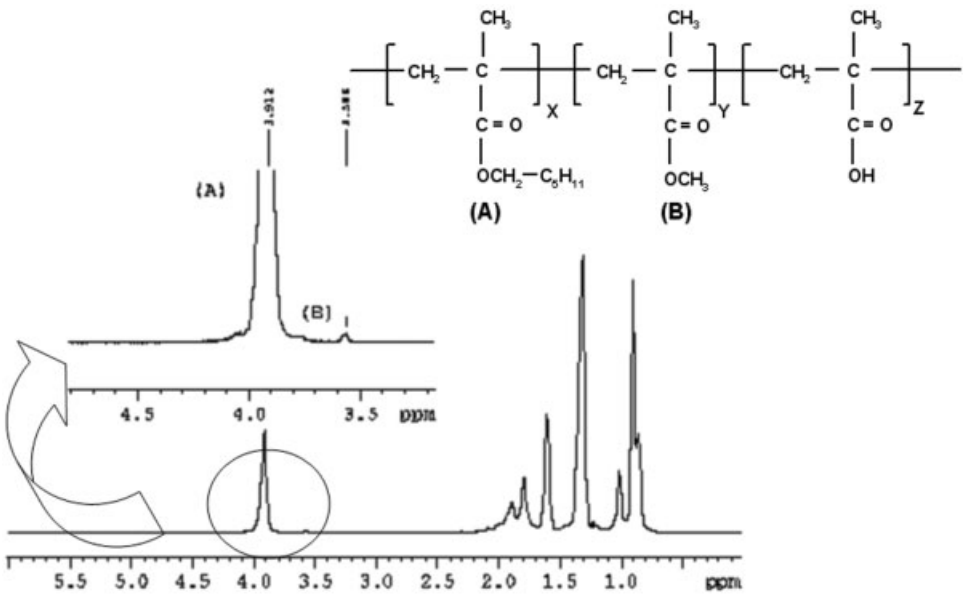

Figure 2. [1]H-NMR spectrum of the HMA-MMA-MAA terpolymer. The inset indicated by the arrow is an enlarged view of the circled area of the spectrum at 3.9 ppm.

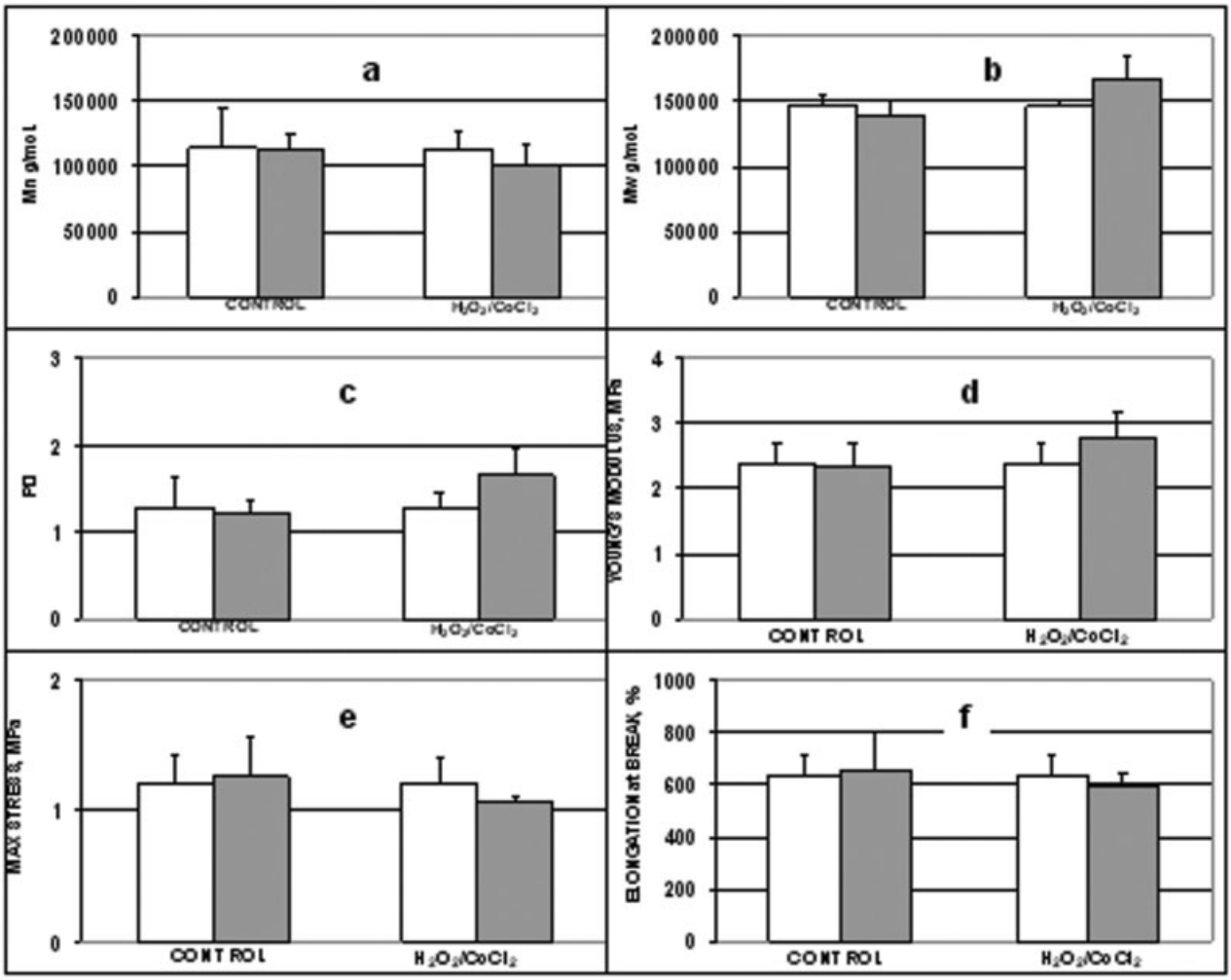

Figure 3. Results from physical and mechanical characterization of HMA-MMA-MAA terpolymer before (white bars) and after (gray bars) exposure to $H_2O_2/CoCl_2$ solution for 10 weeks at 37°C: (a) number average molecular weight, M_n; (b) weight average molecular weight, M_w; (c) polydispersity index, PDI; (d) Young's modulus; (e) maximum stress; (f) elongation at break. Data for HMA-MMA-MAA samples incubated in deionized water are included as a control. The data are the mean of 3 or 4 measurements ± the standard deviation.

usually leads to mechanical property change, it is appropriate to characterize the relationship between the observed chemical changes and mechanical properties.

Biostability of HMA-MMA-MAA terpolymer upon exposure to oxidative solutions

The oxidation of aliphatic polymer chains usually involves three stages: initiation by hydrogen abstraction, formation of hydroxyperoxide by molecular oxygen, and further reaction leading to either crosslinking or chain scission. The rate of degradation, however, can vary dramatically as a function of the polymer's structure and the presence of catalysts. Inflammation and the foreign body response result in release of oxidants, including H_2O_2, O_2^{*-} and *OH.[1,2] These can interact with themselves and/or the polymer in various ways. Thus, oxygen-free radicals propagate oxidation from the outside of the material inward. More stable oxidants, such as H_2O_2, may migrate into the biomaterial to decompose within the polymer. The presence of H_2O_2 and metal ions can produce a synergistic acceleration of oxidation. Based on 37°C H_2O_2 *in vitro* tests and real time (2 years) *in vivo* studies, it has been shown that the most likely catalyst for metal induced oxidation is a cobalt species.[17] In this study, we simulate the *in vivo* oxidative environment by using $H_2O_2/CoCl_2$ solutions. These solutions are capable of generating several oxidizing free-radical species, including hydroxyl, superoxide, and singlet oxygen species.

Figure 3 shows the results from the physical and mechanical characterization of HMA-MMA-MAA terpolymer before and after exposure to $H_2O_2/CoCl_2$ solution at 37°C for 10 weeks. Samples of HMA-

TABLE II
Physical and Mechanical Properties of HMA-MMA-MAA Terpolymer After Exposure to Cholesterol Esterase (CE) Solution for 10 Weeks at 37°C[a]

Physical/Mechanical Property	Value
Number average molecular weight (Mn)	117,000 ± 15,300
Weight average molecular weight (Mw)	137,000 ± 5500
Polydispersity index (PDI)	1.16 ± 0.15
Molar percent MAA	1.94 ± 0.07
Young's modulus (MPa)	2.35 ± 0.11
Maximum strength (MPa)	1.10 ± 0.09
Elongation at break (%)	680 ± 44

[a]The data are the mean of 3 or 4 measurements ± the standard deviation.

TABLE III
Physical and Mechanical Properties of HMA-MMA-MAA Terpolymer After Exposure to Phospholipase A2 (PLA) Solution for 10 Weeks at 37°C[a]

Physical/Mechanical Property	Value
Number average molecular weight (Mn)	116,600 ± 5800
Weight average molecular weight (Mw)	154,000 ± 4600
Polydispersity index (PDI)	1.32 ± 0.08
Molar percent MAA	1.94 ± 0.02
Young's modulus (MPa)	2.04 ± 0.71
Maximum strength (MPa)	0.99 ± 0.40
Elongation at break (%)	626 ± 68

[a]The data are the mean of 3 or 4 measurements ± the standard deviation.

MMA-MAA films incubated in deionized water under the same conditions are included as controls. Weight average molecular weight and polydispersity index, as determined by size exclusion chromatography, reveal a slight increase. This might indicate some crosslinking of the polymer. It is noted, however, that the treated polymer remains soluble in an appropriate solvent such as toluene. The results from acid-base titration show a minor increase of methacrylic acid content from 1.64 ± 0.04 to 2.25 ± 0.05. The changes in molecular weight, polydispersity index, and methacrylic acid content do not result in statistically significant change of maximum stress and elongation at break. Only Young's modulus increases slightly. This may be due to a slight neutralization of the MAA units of the terpolymer by the cobalt cation. It has been observed by us[4] and by others[18] that incubation of acid groups with metal ions could produce an ionic crosslinking effect, potentially increasing the modulus of the material.

Biostability of HMA-MMA-MAA terpolymer upon exposure to hydrolytic solutions

Enzymes are able to catalyze the degradation of synthetic polymers such as polyamides, polyurethanes, and polyesters. When implanted, biomaterials initiate a response to injury.[1] Inflammation, wound healing, and foreign body responses are generally considered as part of the tissue or cellular host responses to injury. Implant/tissue interactions may lead to cellular activation and enhanced enzyme exocytosis by inflammatory cells. The interface between the biomaterial surface, and the layer or layers of foreign body giant cells and/or macrophages contains a high concentration of lysosomal enzymes, some of which are considered to be significant for the stability of the implanted material. Work carried out by Santerre and co-workers has implicated CE[10] and PLA[14] in this process of hydrolytic degradation. Thus, CE- and PLA-mediated hydrolysis of HMA-MMA-MAA terpolymer was investigated in this study.

Tables II and III physical and mechanical characterization of HMA-MMA-MAA terpolymer after exposure for 10 weeks at 37°C to CE and PLA solutions, respectively. Comparison of the data in Table I for the untreated material and data presented in Tables II and III reveals that the effect of lysosomal treatment on the molecular weight and polydispersity is negligible. MAA content remains unaltered: 2.00 ± 0.05 mol% for the untreated sample and 1.94 ± 0.07 mol% for CE-incubated material and 1.94 ± 0.02 mol% for terpolymer challenged with PLA. There is a slight decrease of the maximum strength from 1.45 ± 0.30 MPa to 1.10 ± 0.09 MPa after CE-treatment and 0.99 ± 0.40 MPa after PLA-treatment. Otherwise, the shape of the stress-strain curve and the modulus are unaffected. It was concluded that HMA-MMA-MAA terpolymers are resistant to enzymatic hydrolysis. This finding is consistent with the reported stability of poly(methyl methacrylate) and poly(hexamethyl methacrylate) homopolymers.[19] It is suggested from the current results that ester linkages present in the side chains of HMA-MMA-MAA are inherently resistant to hydrolytic enzymes by nature of the steric hindrance of the proximal carbon in the polymeric chain.

Our study demonstrates that oxidation and hydrolytic stability of the HMA-MMA-MAA terpolymer depends directly on the relationship of the molecular structure and the macroscopic characteristics of the material, thus eliminating the need to formulate systems with additives such as antioxidants and fillers. Our findings that HMA-MMA-MAA is biostable suggests future work be undertaken to assess biocompatibility of this system.

CONCLUSIONS

This study involves a biostable scaffold material and evaluates its suitability for use in chronically im-

planted biomedical devices. Thus, it was important to verify material's resistance to biodegradation by investigating whether mechanical properties deteriorate after *in vitro* biodegradation. The experimental results obtained in this investigation indicate no statistically significant changes in molecular weight, polydispersity index, MAA content, Young's modulus, maximum stress, and elongation at break of the HMA-MMA-MAA terpolymer after exposure for 10 weeks in oxidative and hydrolytic solutions. It is concluded that the HMA-MMA-MAA terpolymer demonstrates excellent *in vitro* biostability in an oxidative and hydrolytic environment and, thus, is a candidate for use in long-term implantable devices.

References

1. Anderson JM. Biological responses to materials. Annu Rev Mater Res 2001;31:81–110.
2. Anderson JM. Inflammation, wound healing and foreign body response. In: Ratner BD et al, editors. Biomaterials science: an introduction to materials in medicine. San Diego: Academic Press, 1996.
3. Lamba NMK, Baumgartner JA, Cooper SL. Cell-synthetic surface interactions. In: Patrick CW, Mikos AG, McIntire LV, editors. Frontiers in tissue engineering. New York: Elsevier Science, Inc.; 1998. p 121–137.
4. Fussell GW, Cooper SL. Synthesis and characterization of acrylic terpolymers with RGD peptides for biomedical applications. Biomaterials 2004;25:2971–2978.
5. Fussell GW, Cooper SL. Endothelial cell adhesion on RGD containing methacrylate terpolymers. J Biomed Mat Res 2004; 70A:265–273.
6. Schubert MA, Wiggins MJ, Schaefer MP, Hiltner A, Anderson JM. Oxidative biodegradation mechanisms of biaxially strained poly(ether urethane urea) elastomers. J Biomed Mater Res 1995;29:337–347.
7. Salacinski HJ, Odlyha M, Hamilton G, Seifalian AM. Thermomechanical analysis of a compliant poly(carbonate-urea)urethane after exposure to hydrolytic, oxidative, peroxidative and biological solutions. Biomaterials 2002;23:3321–40.
8. Heiner J, Stenberg B, Persson M. Crosslinking of siloxane elastomers. Polym Test 2003;22:253–257.
9. Christenson EM, Anderson JM, Hiltner A. Oxidative mechanisms of poly(carbonate urethane) and poly(ether urethane) biodegradation: In vivo and in vitro correlations, J Biomed Mater Res 2004;70A:245–255.
10. Matteson LA, Santerre JP, Labow RS. Changes in macrophage function and morphology due to biomedical polyurethane surfaces undergoing degradation. J Cell Phys 2004;199:8–19.
11. Li F, Hui DY. Modified low density lipoprotein enhances the secretion of bile-salt stimulated cholesterol esterase by human monocyte-macrophages. J Biol Chem 1977;272:28666–28671.
12. Finer Y, Santerre JP. Biodegradation of a dental composite by esterases: dependence on enzyme concentration and specificity. J Biomat Sci Polymer Edn 2003;14:837–849.
13. Salacinski HJ, Tai NR, Carson RJ, Edwards A, Hamilton G, Seifalian AM. In vitro stability of a novel compliant poly(carbonate-urea)urethane to oxidative and hydrolytic stress. J Biomed Mater Res 2002;59:207–218.
14. Labow RS, Santerre JP, Waghray G. The effect of phospholipids on the biodegradation of polyurethanes by lysosomal enzymes. J Biomater Sci Polym Ed 1997;8:779–795.
15. Rawe A. Principles of polymer chemistry. New York: Plenum Press; 1995. p 496.
16. Roeder R, Wolfe J, Lianakis N, Hinson T, Geddes LA, Obermiller J. Compliance, elastic modulus, and burst pressure of small-intestine submucosa (SIS), small-diameter vascular grafts. J Biomed Mater Res 1999;47:65–70.
17. Stokes K, Urbanski P, Upton J. The in-vivo auto-oxidation of polyether polyurethane by metal ions. J Biomat Sci Polym Ed 1990;1:207–230.
18. Coleman MM, Lee JY, Painter PC. Acid salts and the structure of ionomers. Macromolecules 1990;23:2339–2345.
19. Yourtee DM, Smith RE, Russo KA, Burmaster S, Cannon JM, Eick JD, Kostoryz EL, The stability of methacrylate biomaterials when enzyme challenged: kinetic and systematic evaluations. J Biomed Mater Res 2001;57:522–531.