Novel Biodegradable Amino Acid Containing Anhydride Oligomers for Orthopedic Applications

Dong Xie,[1] Ildoo Chung,[1] Aaron D. Puckett,[2] Jimmy W. Mays[3]

[1]*Department of Biomedical Engineering, Purdue School of Engineering and Technology, Indiana University–Purdue University at Indianapolis, Indianapolis, Indiana 46202*
[2]*Department of Biomaterials, School of Dentistry, University of Mississippi Medical Center, Jackson, Mississippi 39216*
[3]*Department of Chemistry, University of Tennessee, Knoxville, Tennessee 37996*

Received 12 October 2004; accepted 19 November 2004
DOI 10.1002/app.21654
Published online in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Novel synthetic biodegradable methacrylated anhydride oligomers (MAOs) based on methacrylated alaninyl maleamic acid (MAMA) and methacrylated aminocaproyl maleamic acid (MACMA) were synthesized and characterized. Injectable and *in situ* crosslinkable polymer networks were formulated by the copolymerization of MAOs with triethylene glycol dimethacrylate (TEGDMA). Furthermore, composites composed of MAOs, TEGDMA, and β-tricalcium phosphate were prepared. The networks and composites were initiated by photopolymerization and redox polymerization, respectively. The initial compressive strength (CS) and diametral tensile strength (DTS) of these materials were determined and used to evaluate the effects of the MAO/TEGDMA ratios on the degradation behavior of the materials. The MAMA-based composites had initial DTS values of 5.7–17.1 MPa and CS values of 30.7–114.2 MPa. The MACMA-based composites had initial DTS values of 2.8–20.8 MPa and CS values of 19.1–119.5 MPa. During the course of degradation, the neat polymer resins lost 97 and 87% of their initial CS values after 6 months with 50/50 MAMA/TEGDMA and MACMA/TEGDMA ratios, respectively. The composite with a 25/75 MACMA/TEGDMA ratio showed a significant increase in CS after an initial decrease for 7 days and then lost 57% of its initial CS value after 3 months. The composite composed of 100% methacrylated anhydride oligomer (MAOs) showed complete degradation after 21 days. The degrees of conversion of the neat resins were 60–77%. Both the neat resins and the composites had low polymerization shrinkage ranging from 3.8 to 5.6%.
 J Appl Polym Sci 96: 1979–1984, 2005

Key words: biodegradable; degradation; oligomers; strength

INTRODUCTION

Hydrolytically degradable synthetic polymers have found diverse applications in medicine ranging from resorbable vascular grafts to tissue-engineering scaffolds.[1] For example, a biodegradable bone cement, providing immediate structural support and subsequently allowing normal bone healing and remodeling processes to occur, would have great potential in orthopedic applications in younger patients.[2–4] β-Tricalcium phosphate (β-TCP) and hydroxyapatite have been used as alternatives to bone grafts in the filling of skeletal defects.[5] Poly(methyl methacrylate) (PMMA), the current standard for bone cement, has enabled the successful rehabilitation of many elderly patients with a relatively short life expectancy, but it has several inherent problems, such as interference with bone formation at the cement–bone interface, relatively low mechanical strength, and high polymerization shrinkage, which cause ultimate loosening of prostheses.[6] The nondegradable materials presently used may cause deterioration of surrounding bone and thus lead to repeated surgeries and a long-term inflammatory response due to fragmentation and particulate formation. Several research efforts have been focused on the development of biodegradable polymers and bone cements;[7–10] however, most of these medical devices are made of biodegradable polyesters and polyanhydrides, which are semicrystalline thermoplastics. These polymers have limited applications in such areas as *in situ* orthopedic bone filling and fixation and soft-tissue repairs because they cannot be processed into the desired shapes and forms during surgery.

Biomaterial applications in orthopedics require materials that possess a liquid- or putty-like consistency that can be easily polymerized and molded to any shape under physiological conditions. The system developed by Mikos and coworkers[11–13] is composed of a matrix phase of a polypropylene fumarate prepolymer crosslinked with either methyl methacrylate or *N*-vinylpyrrolidone that can be polymerized *in situ* with benzoyl peroxide (BPO) as an initiator, similarly to PMMA bone cement. Unfortunately, the mechanical strengths of these materials are rather low; the com-

Correspondence to: D. Xie (dxie@iupui.edu).
Contract grant sponsor: National Science Foundation; contract grant number: EPS-0083128.

pressive strength (CS) ranges from 7 to 30 MPa. Therefore, there is a strong need to create such types of biodegradable materials with high strength and easy handling.

The objective of this study was to synthesize and characterize biodegradable liquid anhydride oligomers, use them to formulate resins and composites with biodegradable β-TCP as a filler, and evaluate their properties, including the mechanical strengths, degradation, degree of conversion (DC), and polymerization shrinkage.

EXPERIMENTAL

Materials

Methacrylic anhydride (MAAn), BPO, *N,N′*-dimethyl-*p*-toluidine (DMT), and triethylene glycol dimethacrylate (TEGDMA) were used as received from Aldrich Chemical Co. (Milwaukee, WI). β-Alanine, 6-aminocaproic acid, maleic anhydride, DL-camphoroquinone (CQ), 2-(dimethylamino)ethyl methacrylate (DMAEM), dichloromethane, petroleum ether, and diethyl ether were used as received from Fisher Scientific/Acros, Inc. (Pittsburgh, PE). β-TCP was granted by Stryker/Howmedica/Osteonics Corp. (Rutherford, NJ). All other chemicals were reagent-grade and were used without further purification.

Syntheses and characterization of methacrylated anhydride oligomers (maos)

The biodegradable MAOs, methacrylated alaninyl maleamic acid (MAMA), and methacrylated aminocaproyl maleamic acid (MACMA) were synthesized with a two-step reaction, as illustrated in Figure 1.

Amino maleamic acids were prepared from maleic anhydride and amino acids according to the methods described by Rich et al.[14] with a minor modification. Briefly, a solution of maleic anhydride in acetic acid was added to a solution of amino acid in acetic acid, and the mixture was stirred at room temperature for 3 h. After the reaction was completed, the white precipitate was filtered, washed with cold H_2O, and freeze-dried. The yields were 90% for alaninyl maleamic acid (AMA) and 92% for aminocaproyl maleamic acid (ACMA). Crystallization from water or methanol afforded analytically pure amino maleamic acids. The amino maleamic acids were further reacted with MAAn at 90°C for 3–5 h under a nitrogen blanket. An equal volume of methylene chloride was added to the reaction mixture; this was followed by the filtration of unreacted diacid, and the filtrate was precipitated in petroleum ether. The crude product was collected and redissolved in diethyl ether to remove unreacted acid and impurities. A clear, viscous liquid was obtained after the solution was dried with anhydrous magnesium sulfate, and the solvent was removed. The yields were 65% for MAMA and 58% for MACMA.

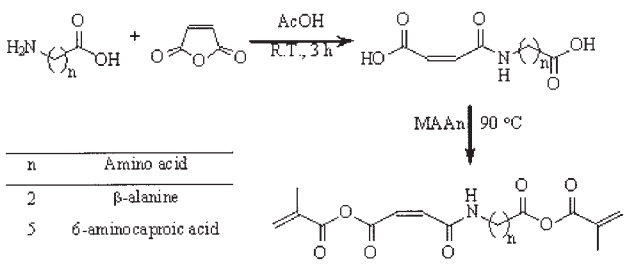

Figure 1 Scheme for the synthesis of MAOs.

TABLE I
Initial CS, DC, and Viscosity Values of the Neat Polymer Resins

Formulation	CS (MPa)[a]	Viscosity (cP)	DC (%)
MAMA/TEGDMA			
100/0	2.8 (0.9)	1602	77
50/50	220.2 (18.4)	68	69
MACMA/TEGDMA			
100/0	8.7 (2.1)	807	75
75/25	117.9 (4.0)	198	73
50/50	218.0 (21.5)	55	60
25/75	284.2 (17.6)	19	60
TEGDMA			63

[a] Mean values with standard deviations in parentheses.

The products were identified with Fourier transform infrared (FTIR) spectroscopy (Research Series FT/IR 1000 spectrophotometer, Mattson, Madison, WI) and nuclear magnetic resonance (NMR; ARX-300 300-MHz FT spectrophotometer, Bruker, Ettlingen, Germany; with deuterated methyl sulfoxide as the solvent).

Preparation of the polymer networks and the composites

The formulations prepared for the initial mechanical strengths are described in Tables I and II.

The specimens for the neat resins, in which the sample sizes were $n = 6$, were fabricated by the thorough mixing of MAMA or MACMA, TEGDMA, CQ (0.7 wt %; a photoinitiator) and DMAEM (1.4 wt %; an activator); the mixture was placed in glass tubing (4 mm in diameter and 8 mm long) and immediately exposed to blue light (EXAKT 5020 Blue Light Polymerization Unit, 9W/71, GmbH, Germany) for 10 min at room temperature. The cured specimens were then removed from the mold and conditioned before testing.[15] The composites were fabricated by the mixing of two equal parts of pastes A and B with the same compositions, that is, an oligomer (MAMA or MACMA), a diluent (TEGDMA), and a

TABLE II
Initial Strengths of the Composites

Formulation	Matrix	P/L[a] ratio	DTS (MPa)[b]	CS (MPa)[b]
MAMA/TEGDMA				
100/0	β-TCP	2.5	5.7 (0.4)	30.7 (1.8)
75/25	β-TCP	2.5	13.1 (0.8)	68.8 (4.6)
50/50	β-TCP	2.5	14.3 (1.5)	85.7 (5.8)
25/75	β-TCP	2.5	17.1 (1.7)	114.2 (6.0)
MACMA/TEGDMA				
100/0	β-TCP	2.5	2.8 (0.2)	19.1 (1.0)
75/25	β-TCP	2.5	10.7 (0.2)	52.9 (2.2)
50/50	β-TCP	2.5	15.9 (1.4)	78.2 (5.7)
25/75	β-TCP	2.5	20.8 (1.1)	119.5 (8.3)

[a] P/L ratio = filler powder/resin liquid ratio.
[b] Mean values with standard deviations in parentheses.

filler [β-TCP pretreated with 3-(trimethoxysilyl)propyl methacrylate], except that paste A contained 1 wt % BPO as an initiator and paste B contained 1 wt % DMT as an activator. The filler powder/resin liquid (P/L) ratio was 2.5/1 (w/w). The liquid compositions used in this study ranged from 100/0 to 25/75 (w/w) oligomer/TEGDMA. The specimens for the composites, in which the sample sizes were $n = 6$, were fabricated by the mixing of equal amounts of pastes A and B at room temperature and were immediately placed in glass tubing (4 mm in diameter and 8 mm long for compression testing and 4 mm in diameter and 2 mm thick for diametral compression testing). The specimens were removed from the glass tubing after 30 min and were conditioned before testing.

Strength measurements

The mechanical testing of the specimens[15] was performed on a screw-driven mechanical testing machine (model 858 Mini Bionix, MTS Systems Corp., Eden Prairie, MN) at a crosshead speed of 1 mm/min for all tests. CS at fracture was defined as the maximum stress carried by a specimen during the test and was calculated as follows: $CS = P/\pi r^2$, where P is the load at fracture and r is the radius of the sample cylinder. The diametral tensile strength (DTS) was determined from the following relationship: $DTS = 2P/\pi dt$, where d is the diameter and t is the thickness, respectively, of the cylinder.

Measurement of the viscosity and dc

The viscosities of the formulated oligomers were measured at 23°C with a programmable cone/plate viscometer (RVDV-II + CP, Brookfield Engineering Laboratories, Inc., Middleboro, MA). DC for the resins was measured with FTIR and was calculated with a method described by Wang et al.[16]

Shrinkage measurement

The polymerization shrinkage was determined with the following equation: shrinkage (%) = $(1 - d_{uncured}/d_{cured}) \times 100$, where d_{cured} is the density of the cured resin and $d_{uncured}$ is the density of the uncured resin.[17] d_{cured} and $d_{uncured}$ were determined by the weighing of the cement paste injected from a calibrated syringe and the cured cylindrical specimens, whose volumes were measured in a calibrated buret, respectively. The volumes of the resins were measured in hexane. The mean values were averaged from three readings.

Biodegradation studies

The degradation study of the synthesized polymer networks was conducted at 37 ± 2°C in phosphate buffered saline (PBS) with pH 7.4. PBS was changed every 8 h for the first week and then every 3 days to keep the pH constant for all the samples. The specimens were collected at 0.25 (6 h), 1, 3, 7, 21, 90 (3 months), and 180 (6 months) days for the polymer neat resins and at 1/24 (1 h), 0.5 (12 h), 1, 3, 7, 21, 30 (1 month), and 90 (3 months) days for the composites. The initial CS and DTS values of the materials are illustrated later in Figure 4 and are listed in Tables I and II. The polymer degradation was characterized by an evaluation of the change in the CS values.

RESULTS AND DISCUSSION

Characterization of maos

The structure of the synthesized MAOs was identified with FTIR and ^{1}H-NMR spectroscopy, as shown in Figures 2 and 3. The typical chemical shifts of ^{1}H-NMR and the peaks in FTIR are shown as follows.

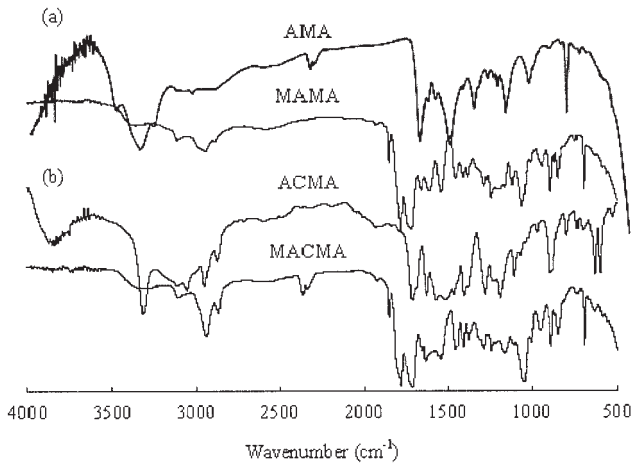

Figure 2 FTIR spectra of (a) AMA and MAMA and (b) ACMA and MACMA.

MAMA

^{1}H-NMR (DMSO-d_6, δ, ppm): 7.9 (t, 1H, N*H*), 6.3 (d, 2H, C*H*═C*H*), 5.8 and 5.4 (d, 4H, CH_2═C), 3.2 (m, 2H, —NH—CH_2—), 2.4 (m, 2H, —CH_2—CO—), 2.1 and 1.8 (d, 6H, —C—CH_3). IR (neat, cm^{-1}): 1850 and 1780 (anhydride linkage), 1715 (C═O stretch), 1655 and 1608 (vinyl absorption).

MACMA

^{1}H-NMR (DMSO-d_6, δ, ppm): 7.9 (t, 1H, N*H*), 6.2 (d, 2H, C*H*═C*H*), 6.0 (s, 1H, CH_2—C), 5.8 (s, 1H, CH_2═C), 5.6 (m, 1H, CH_2═C), 5.3 (m, 1H, CH_2═C), 3.1 (m, 2H, —NH—CH_2—), 2.2 (t, 2H, —CH_2—CO—), 1.8 (d, 6H, —C—CH_3), 1.5 (m, 4H, —CH$_2$CH_2-CH$_2$CH_2CH$_2$—), 1.3 (m, 2H, —NH—CH$_2$CH$_2$CH_2—). IR (neat, cm^{-1}): 1849 and 1780 (anhydride linkage), 1711 (C═O stretch), 1654 and 1633 (vinyl absorption).

Strength evaluation

The initial DTS and CS values of the synthesized polymers and composites are shown in Figure 4 and Tables I and II. Increasing TEGDMA in the formulation led to an increase in both DTS and CS. For the MAMA-based materials, the mean values ranged from 5.7 to 17.1 MPa for DTS and from 30.7 to 114.2 MPa for CS for the composites. For the MACMA-based materials, the mean values ranged from 8.7 to 284.2 MPa for CS for the polymer neat resins and from 2.8 to 20.8 MPa for DTS and from 19.1 to 119.5 MPa for CS for the composites.

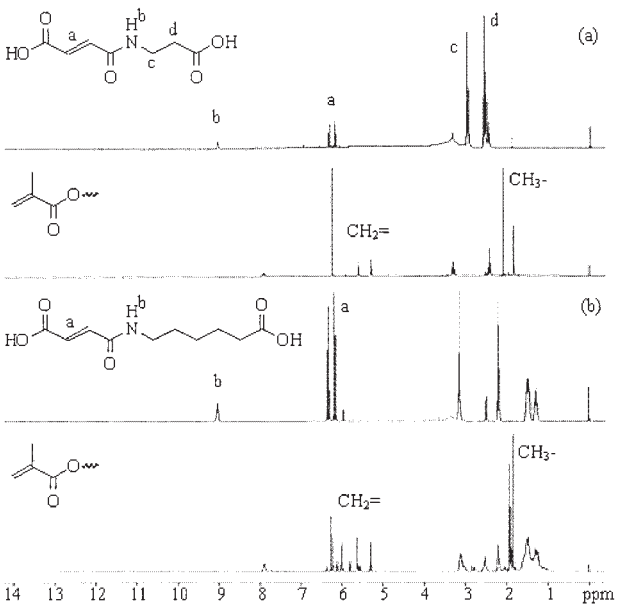

Figure 3 ^{1}H-NMR spectra of (a) AMA and MAMA and (b) ACMA and MACMA (DMSO-d_6).

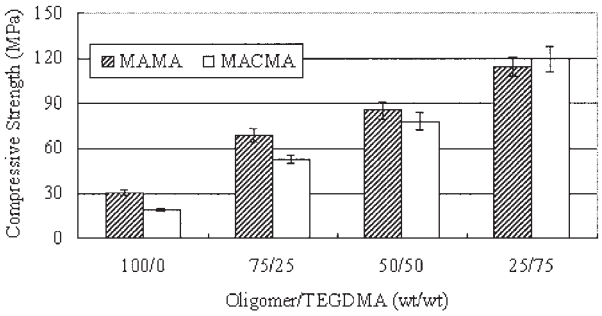

Figure 4 Initial CS values of β-TCP-containing composites (P/L = 2.5).

TEGDMA was added to the system as a crosslinker to strengthen the polymer network because the mechanical strength of the 100% MAO composed polymer itself was not strong enough initially. Although this type of polymer network may have some problems because of the formation of undegraded TEGDMA fragments, the addition of TEGDMA demonstrated that the component could significantly improve the mechanical strengths of both the neat resins and composites. The property enhancements may be attributed to the nature of TEGDMA, the ethylene oxide contributing flexibility and toughness.[18] Tables I and II show that the neat resins exhibited higher CS values than the corresponding composites, except for the resin containing only MAMA or MACMA. This result may be explained by the extent of homogeneity of the systems.[17,19] In general, the conversion for the neat resins was higher than that for the composites because the former were more homogeneous than the latter. Photoinitiation was not used in the composite formulations because the β-TCP filler was opaque and, therefore, prevented the penetration of sufficient light to allow complete polymerization. Redox initiation was used instead. Redox initiation systems are commonly used in orthopedic bone cements because the depth of light penetration in translucent composites is very limited (only 2–3 mm).[20]

Viscosity, DC, and shrinkage evaluation

The viscosity and DC values of the synthesized polymers are shown in Table I. Increasing TEGDMA in the formulation led to a decrease in both the viscosity and DC. In addition to strengthening the resins and composites, adding TEGDMA to the system reduced the viscosity.[20] In comparison with 100% MAMA (1602 cP) or MACMA (807 cP), TEGDMA significantly reduced the viscosity of the system, and this could be beneficial for orthopedic applications for which professionals require materials with a workable viscosity to obtain desired properties. DC ranged from 60 to 77%. With an increase in TEGDMA, DC decreased.

TABLE III
Polymerization Shrinkage of the Neat Polymer Resins and Composites

Formulation	Matrix	P/L ratio	Shrinkage (%)
MAMA/TEGDMA			
50/50	—	0	−5.6
50/50	β-TCP	2.5	−4.1
MACMA/TEGDMA			
50/50	—	0	−4.9
50/50	β-TCP	2.5	−3.8
TEGDMA	—	0	−11.6
PMMA	—	0	−10.2

Pure MAMA and MACMA showed DC values of 77 and 75%, whereas pure TEGDMA showed a value of only 63%. The reason for the reduced DC value of TEGDMA is not clear. The polymerization shrinkage values of the neat resins, ranging from 4.9 to 5.6%, were higher than those of their corresponding composites (3.8–4.1%), as shown in Table III. It can be concluded that the composites contained fewer polymerizable carbon–carbon double bonds. Furthermore, the shrinkage values of the neat resins and composites were significantly lower than those of a commercial PMMA bone cement (10.2%) and poly(triethylene glycol dimethacrylate) homopolymer (11.6%). These results suggest that these novel biodegradable oligomers, consisting of neat resins and composites, may find potential applications in biomedical areas after careful formulations of MAOs, TEGDMA, and β-TCP.

Biodegradation studies

Figure 5 shows the *in vitro* biodegradation curves for 50/50 MAMA/TEGDMA and MACMA/TEGDMA neat resins. The two curves show similar degradation patterns, that is, burst degradation within the first 6 h and then more steady degradation to the end in about 6 months. There was some degradation difference between the MAMA- and MACMA-containing neat resins. As we expected, the MACMA-containing neat resin had a slower degradation rate than MAMA, and this could be attributed to a longer hydrophobic carbon–carbon chain in MACMA than in MAMA. The results suggest that these resins are capable of breaking down to the point at which no compressive properties can be measured, although the networks contain nonbiodegradable TEGDMA. On the other hand, the results also indicate that MAOs and TEGDMA polymerize randomly, forming a polymer containing degradable MAO moieties. It is well known that polyanhydrides belong to very surface-eroding biodegradable polymers, and this means that they usually maintain their mechanical properties while undergoing degradation.[21] Therefore, it may be possible to formulate neat polymer networks with different amounts of MAOs and TEGDMA to achieve a spectrum of desired properties, including degradation rates and mechanical strengths.

The degradation behaviors for the composite materials (Figures 6 and 7) were a little different from those shown for the neat resins. First, the burst effect for the composites was not as evident as that for the nest resins; second, there was nearly no change in degra-

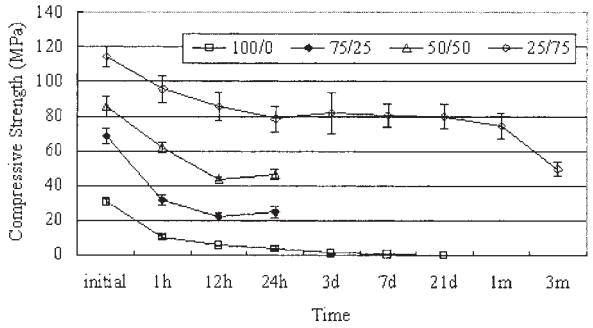

Figure 6 CS values of the MAMA-based composites with β-TCP as a function of the degradation time (P/L = 2.5/1; MAMA/TEGDMA = 100/0, 75/25, 50/50, or 25/75).

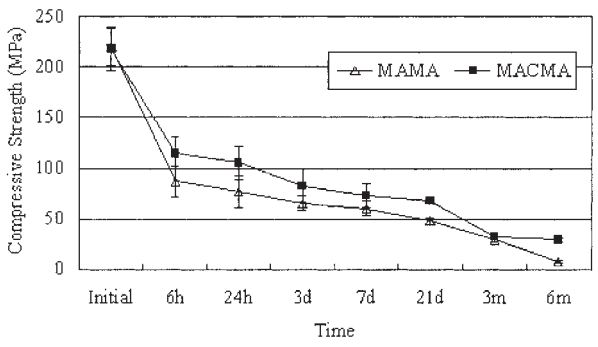

Figure 5 CS values of neat polymer resins as a function of the degradation time (50/50 MAMA/TEGDMA or MACMA/TEGDMA).

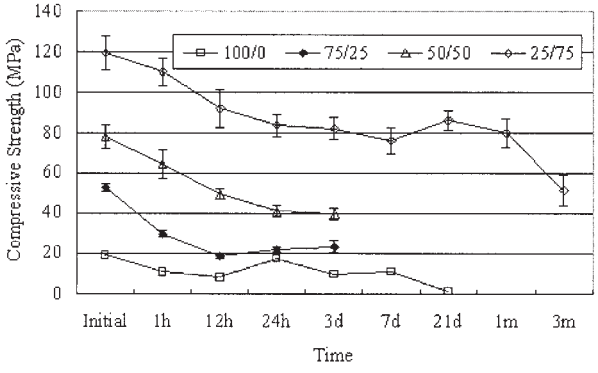

Figure 7 CS values of the MACMA-based composites with β-TCP as a function of the degradation time (P/L = 2.5/1; MAMA/TEGDMA = 100/0, 75/25, 50/50, or 25/75).

dation between 24 h and 1 month for most of the composites; and third, unlike the neat resins, the composites with different oligomer/TEGDMA ratios had significant strength differences. However, the MAMA/TEGDMA and MACMA/TEGDMA composites showed similar degradation patterns or degradation rates.

Almost all the degradation curves followed the same pattern: decreasing initially, increasing during the course of degradation, and finally decreasing. This is particularly evident in Figure 7. We believe that this can be attributed to salt-bridge formation during the course of degradation. At the very beginning, the polymer network degraded with anhydride bone breakage with the formation of dicarboxylic acid, and this led to a significantly reduced strength. With increasing carboxylic acid formation, the salt bridges started to form between the carboxyl groups on polymer fragments and calcium cations from β-TCP, and this resulted in an ionomer. The ionic crosslinks, combined with partially degraded polymer networks (still having a relatively high molecular weight), resulted in an increase in CS. With continuous degradation, however, the molecular weight of the polymer fragments became smaller and smaller, and this led to a further decrease in CS. Our results were consistent with the typical behaviors exhibited by conventional glass-ionomer cements.[22] Furthermore, different formulations exhibited the CS increase at different times, and this may be attributed to the role of TEGDMA. The nondegradable component TEGDMA actually slowed down the degradation process by maintaining the molecular weight of the polymer fragments and thus facilitating the salt-bridge formation. This phenomenon can be of clinical interest because it may allow structures to be designed that maintain their strength for an extended period of time. These types of materials may also allow medical devices to be designed that lose their mass and strength at the same rate, in contrast to the majority of biodegradable materials, which may still be present months or years after they have lost their mechanical strength.

CONCLUSIONS

Novel difunctional oligomers, MAMA and MACMA, were synthesized from β-alanine or 6-aminocaproic acid, maleic anhydride, and MAAn. The oligomers were used to formulate neat polymer networks with TEGDMA and composites with both TEGDMA and β-TCP. The neat polymer structures had initial CS values ranging from 2.8 to 284.2 MPa, and the composites had initial DTS values ranging from 2.8 to 20.8 MPa and CS values ranging from 19.1 to 119.5 MPa. For both the neat resins and composites, reducing the MAO/TEGDMA ratio increased the initial CS and DTS values. The polymer neat resins with a 25/75 MAMA/TEGDMA ratio completely degraded after 6 months. For the composites containing β-TCP, the CS values increased after the composites aged for various times. The CS increase was attributed to salt-bridge formation, with the characteristic time for the increase depending on the MAO/TEGDMA ratio. The composite composed of 100% MAOs showed complete degradation after 21 days. The DC values of the neat resins were 60–77%. Both the neat resins and composites had low polymerization shrinkage ranging from 3.8 to 5.6%. This research describes novel network structures that may have potential applications in orthopedic surgery. Future studies will focus on the synthesis of oligomers with different backbones (hydrophilic and hydrophobic) to improve the ability to control degradation and allow the design of new biomedical materials and devices for disease and improved quality of life.

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