Synthesis and Evaluation of Novel Injectable and Biodegradable Polyglycolide-Based Composites

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ABSTRACT: Novel 3-arm methacrylate-endcapped biodegradable polyglycolide prepolymer was synthesized and characterized. Injectable and *in situ* curable composites formulated with the liquid prepolymer and bioabsorbable β-tricalcium phosphate were prepared. The pastelike composites were cured at room temperature using a redox-initiation system. The initial compressive strengths (CSs), curing time, exotherm, and degree of conversion of the cured composites were determined. The composites showed initial yield CS ranging from 20.1 to 92.3 MPa, modulus from 0.73 to 5.65 GPa, ultimate strength from 119.9 to 310.5 MPa, and toughness from 630 to 3930 N mm. Increasing filler content increased yield strength and modulus but decreased ultimate strength and toughness. Diametral tensile strength test showed the same trend as did CS test. Increasing filler content also increased curing time but decreased exotherm and degree of conversion. During the course of degradation, all the materials showed a significant burst degradation behavior within 24 h, followed by a significant increase in strength between Day 1 and Day 3, and then continuous degradation until no strength was detected. The composites with higher filler content retained their strengths longer but those with lower filler contents lost their strengths in 45 or 60 days. The degradation rate is filler-content dependent. J Appl Polym Sci 103: 2977–2984, 2007

Key words: biodegradable; polyglycolide; degradation; *in situ* curable; compressive strengths

INTRODUCTION

Synthetic biodegradable polymers with ester linkages have been widely used in biomedical and pharmaceutical applications for decades. These polymers include polyesters, polylactones, polyanhydrides, polycarbonates, poly(pseudoamino acid)s, poly(orthoester)s, polyphosphazenes, polyphosphonates, etc.[1] Among them, poly(α-hydroxyacid) polyesters, particularly poly(glycolic acid) (PGA), poly(lactic acid) (PLA), and their copolymers are among the few biodegradable polymers with Food and Drug Administration approval for human clinical use.[1–4] Because of their biocompatibility and controlled degradability, these polyesters have been successfully used as suture materials for wound closure[2]; implant devices for dental and orthopedic restorations[3]; carriers for drug,[2,4] protein[4] and cell delivery[5]; and tissue scaffolds for tissue engineering.[6] The degradation products of these polymers can be either absorbed as metabolites by the body or eliminated through the urine.[2,7]

Currently many applications in tissue engineering, especially in orthopedics and dentistry, require that biomaterials be shaped *in situ* to fit cavities/defects with complicated geometries in tissues. Over the last 20 years, however, only a few research groups have really focused on the development of injectable synthetic biodegradable polymer compositions and thus few reports have been published.[8] So far only two injectable synthetic biodegradable polymer-based compositions have been reported in the literature.[8] One was poly(propylene fumarate)-based system, developed by Mikos and colleagues[9–11]; and the other was polyanhydride-constructed system, developed by Anseth and colleagues.[12–14] The PPF system was composed of a matrix phase of a poly(propylene fumarate) prepolymer crosslinked with a nonbiodegradable diluent, methacrylate or *N*-vinylpyrrolidone, combined with a β-tricalcium phosphate (β-TCP) particulate phase, with an initial compressive strength (CS) of 7.7–30 MPa and compressive modulus of 191–300 MPa.[11] *In vitro* and *in vivo* degradation studies showed different degrees of degradation, based on loss of CS and modulus.[11,15] The weakness of this system was its low mechanical strength[11,15] and high viscosity.[9–14] The polyanhydride system was developed by utilizing polyanhydride as a backbone and endcapping with polymerizable dimethacrylates.[12–14] The system was *in situ* photocured by either UV or visible light[12–14] with potential for dental and orthopedic tissue engineering applications. Yet the high acidity produced by degradation products—diacids—may reduce the biocompatibility of the materials.[16] Xie et al.[17] also developed an anhydride-amino acid-based oligomer

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system, which was purposely designed for orthopedic applications. Although both neat resins and composites made from these oligomers showed a higher mechanical strength and considerable degradation, similar to the poly(propylene fumarate)-based system,[11] these materials had to be mixed with a nonbiodegradable diluent—triethylene glycol dimethacrylate—to form a workable liquid solution because of the high viscosities of the synthesized biodegradable oligomers.[17,18] Apparently, strength, viscosity, and polymer backbone are three key factors for developing attractive injectable, biodegradable, and *in situ* curable biomaterials. In this study, we propose to develop a novel liquid 3-arm biodegradable PGA-based prepolymer system with workable viscosity and high mechanical strength for orthopedic and tissue engineering applications.

This article reports the synthesis and characterization of *in situ* polymerizable and biodegradable liquid PGA prepolymer, the use of it to formulate the composites with bioabsorbable β-TCP filler, and the evaluation of the mechanical strengths, other properties, and *in vitro* degradation behavior.

EXPERIMENTAL

Materials

Methacryloyl chloride, glycolic acid (GA), trimethylolpropane, DL-camphoroquinone, 2-(dimethylamino) ethyl methacrylate, benzoyl peroxide, and *N*,*N*′-dimethyl-*p*-toluidine, triethylamine, 3-(trimethoxysilyl)-propyl methacrylate, ethyl acetate, and anhydrous magnesium sulfate were used as received from Fisher Scientific/Acros (Pittsburgh, PA). β-Tricalcium phosphate (β-TCP) was used as received from Aldrich Chemical Company (Milwaukee, WI). All other chemicals were of reagent-grade and used without further purification.

Synthesis of *in situ* polymerizable 3-arm biodegradable *PGA* prepolymer

Synthesis of hydroxyl-terminated 3-arm PGA polyester prepolymer

The hydroxyl-terminated 3-arm PGA polyester was synthesized using a condensation polymerization technique, according to the method descried by Ajioka et al.,[19] with a sight modification. Briefly, a mixture of trimethylolpropane (3-arm initiator) and GA were added to a reaction vessel equipped with a Dean Stark trap. The molar ratio of trimethylolpropane/GA = 1 : 5. The condensation polymerization reaction was kept at 200°C for 10 h. After the reaction was completed, the reactor was cooled down and the polyester was collected for further modifications. The yield was 98%. A reaction scheme for preparation of the hydroxyl-terminated 3-arm PGA is shown in Figure 1.

Synthesis of methacrylate-terminated 3-arm PGA polyester

The methacrylate-terminated 3-arm PGA polyester was prepared as described here. Briefly, to a three-neck flask containing the hydroxyl-terminated 3-arm PGA, triethylamine, and dry ethyl acetate, a solution of methacryloyl chloride in dry ethyl acetate was added dropwise with stirring at 0°C, followed by a

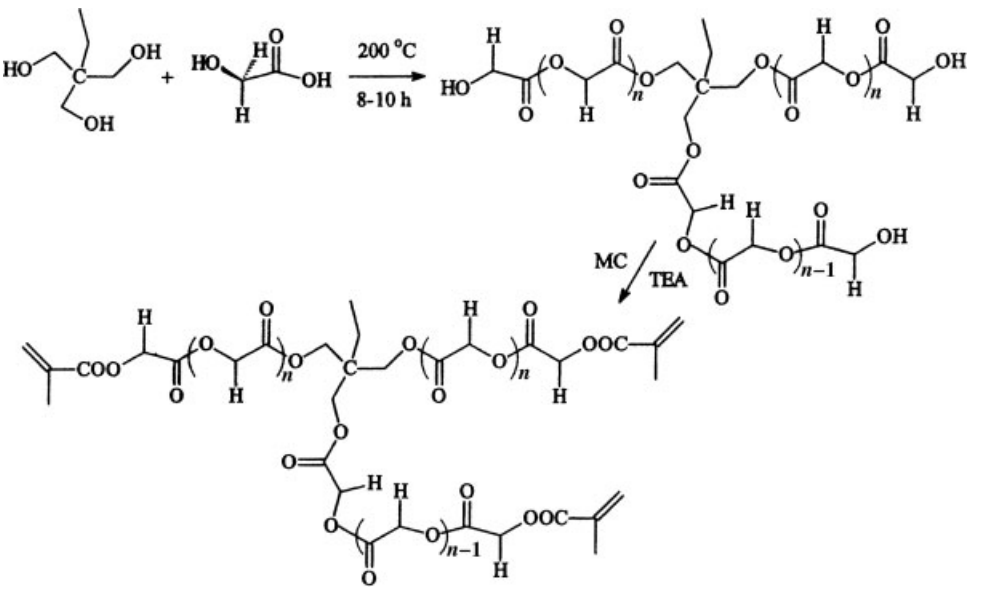

Figure 1 Scheme for synthesis of 3-arm PGA methacrylates.

continuation of reaction for another 10 h. After the reaction was completed, the product-containing solution was purified by filtering out the triethylamine·HCl salts and repeatedly washing with 3% aqueous NaOH and brine. The final oily product was obtained by drying the purified organic layer with anhydrous magnesium sulfate, followed by removing ethyl acetate with a rotary evaporator. The yield was 55–65%. The synthesis scheme for the methacrylate-terminated 3-arm PGA polyester is shown in Figure 1 as well.

Characterization

The products were identified using Fourier transform infrared spectroscopy (FTIR; Mattson Research Series FT/IR 1000 spectrophotometer) and nuclear magnetic resonance (NMR; FT-300 MHz Bruker ARX-300 spectrophotometer, deuterated methyl sulfoxide as solvent). Molecular weight (MW) of the 3-arm PGA polyester triols was determined using a vapor pressure osmometer (K-7000, ICON Scientific, North Potomac, MD). The viscosity of the 3-arm PGA methacrylates was measured at 23°C using a programmable cone/plate viscometer (RVDV-II + CP, Brookfield Eng. Lab., MA, USA).

Preparation of polymer network and its composite

The specimens for neat resin ($n = 6$) were fabricated by thoroughly mixing the synthesized 3-arm PGA prepolymers, DL-camphoroquinone (1.0 wt %, a photo-initiator), and 2-(dimethylamino)ethyl methacrylate (2.0 wt %, an activator),[17,18,20] placing them into the glass-tubing with dimensions of 4 mm in diameter by 8 mm in length for compressive strength (CS) tests and 4 mm in diameter by 2 mm in thickness for diametral tensile strength (DTS) tests, and immediately exposing them to blue light using an EXAKT 520 blue light polymerization unit (9W/71, GmbH, Germany) for 2 min at room temperature. The cured specimens were then removed from the mold and conditioned prior to testing.[17,18] The composite was formulated with two equal parts of pastes (A and B) with the same compositions, i.e., liquid prepolymer and β-TCP filler, except that paste A contained 1 wt % benzoyl peroxide as an initiator and paste B contained 1 wt % *N*,*N*′-dimethyl-*p*-toluidine as an activator. The filler was pretreated with 3-(trimethoxysilyl)propyl methacrylate for a better interfacial bond between the filler and resin, before mixing with the PGA prepolymer.[20] The filler contents studied were 20, 33, 43, 50, 60, 67, and 75% (by weight). The specimens for composites ($n = 6$) were fabricated by mixing equal amounts of pastes A and B at room temperature and immediately placing into a glass tubing mold with the same dimensions as those for the above-mentioned neat resin. The specimens were removed from the mold after 30 min and conditioned before testing. The proposed polymer network and its composite are shown in Figure 2.

Strength measurements

Mechanical testing of specimens[17,18] was performed on a screw-driven mechanical tester (QTest QT/10, MTS Systems Corp., Eden Prairie, MN) with a crosshead speed of 1 mm/min for both CS and DTS. The CS at fracture was defined as the maximum stress carried by the specimen during test and calculated from the equation

$$\mathrm{CS} = P/\pi r^2$$

where P is the load at fracture and r the radius of the sample cylinder. Yield strength (YS), modulus (M), ultimate strength (CS), and toughness (T) from the CS test were determined from stress–strain curves.

DTS was determined from the relationship

$$\mathrm{DTS} = 2P/\pi dt$$

where P is the load at fracture, d the diameter of the cylinder, and t the thickness of the cylinder.

Curing time, exotherm, and degree of conversion measurements

A metal rod was used to evaluate the curing time.[21] Briefly, the rod was inserted into the center of mixture of the composite; immediately after, the two-component paste was mixed and packed into a two-end opened glass tubing with a diameter of 4 mm. Curing time was taken as the period from which the mixing process was initiated to the moment at which the metal rod could not be moved by hand. The average was obtained every three readings.

The heat generated from the setting reaction of the composite was determined with a slightly modified ASTM F 451 procedure.[21] Briefly, the well-mixed composite paste was placed in a cylindrical Teflon mold with dimensions of 30 mm diameter by 6 mm height and covered with a Teflon plunger having holes for allowing the excessive cement to escape. A digital thermocouple (Fisher Scientific, Springfield, NJ) was inserted in the center of the composite and used to record the temperature change. The peak temperature was defined as the exotherm. The average was obtained every three readings.

The degree of conversion for the resin and composites were measured with KBr using FTIR and calculated based on the method described by Wang et al.[22]

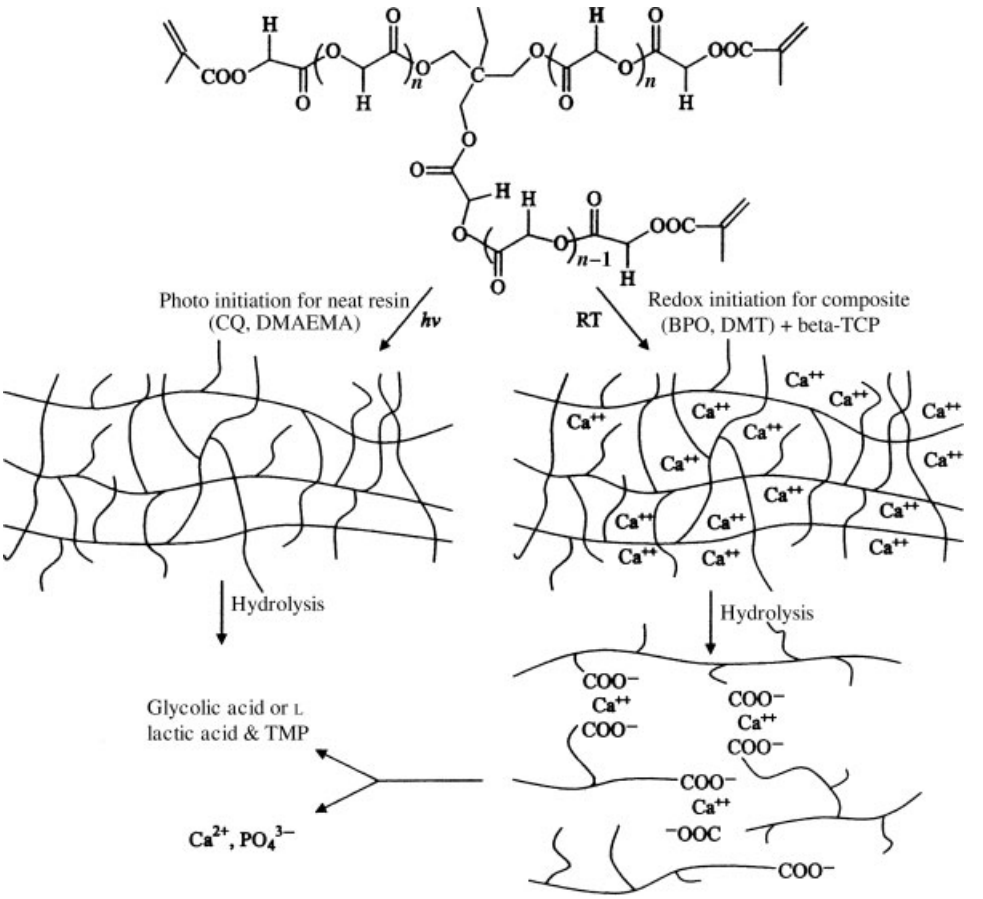

Figure 2 Scheme for resin and composite formations and suggested degradation mechanisms.

In vitro degradation study

The degradation study of the crosslinked polymer neat resin and composites was conducted at (37 ± 2)°C in phosphate-buffered saline (PBS) with a pH of 7.4.[17,18] The pH of the buffer was checked frequently. The buffer was changed when the pH was below 7.0 to keep the pH at 7.4 for all the samples. The cylindrical specimens were collected at 1, 3, 7, 14, 21, 30, 45, 60, 75, and 90 days. The degradation behaviors of the tested materials were characterized by evaluating the change in ultimate CS values.

RESULTS AND DISCUSSION

Characterization of 3-arm PGA triols and trimethacrylate prepolymer

The structures of the synthesized 3-arm PGA polyester triols and trimethacrylates were identified with FTIR and ^{1}H-NMR spectroscopy, as shown in Figures 3 and 4. For FTIR (Fig. 3), the characteristic peaks for the 3-arm PGA polyester triols are shown as follows (cm^{-1}): 3690–3050 (—OH, broad and strong); 2966 (—CH_2— and —CH_3, medium); 1752 (—C=O, strong and sharp); 1426 and 1398 (—CH_2— and —CH_3, medium); 1185 and 1100 (—O—C—O—, strong); and 933 (—CH_3, small). The peaks for the 3-arm PGA trimethacrylate prepolymer are listed as follows: 2963 (C—H, medium); 1759 and 1728 (C=O, strong); 1636 (C=C, sharp and medium); 1454, 1423, and 1395 (—CH_3, —CH_2—, -CH_3); 1147 (—O—C—O—, strong); 1075 (—O—C—O—, small); 948 (—CH_3,

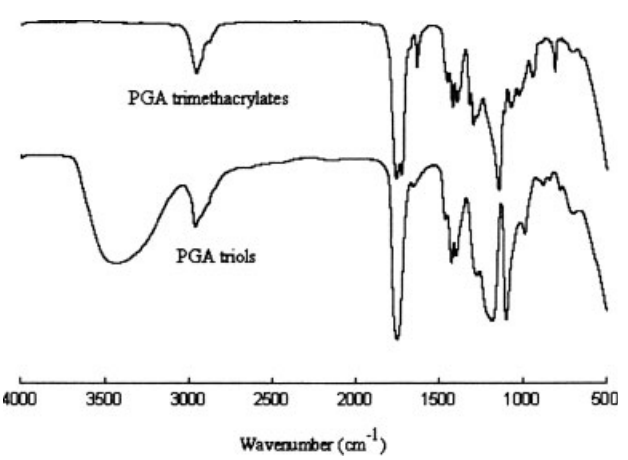

Figure 3 FTIR spectra of 3-arm PGA triols and PGA trimethacrylates.

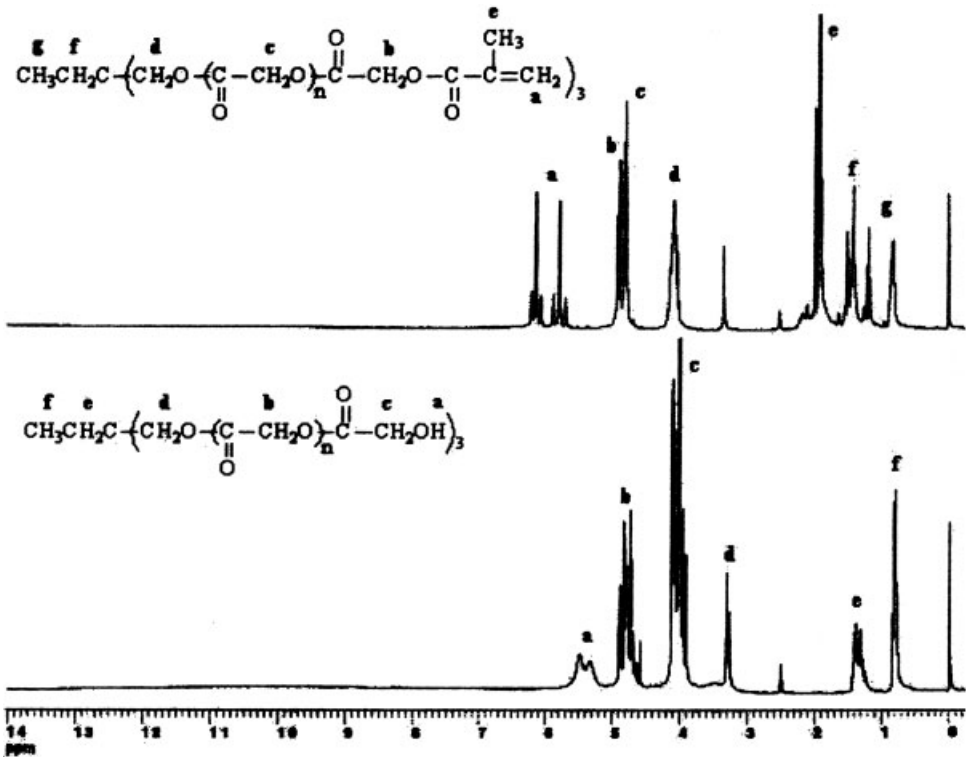

Figure 4 ^{1}H-NMR spectra of (a) PGA triols and (b) PGA trimethacrylates.

small); and 813 (C=C, medium). Disappearance of the hydroxyl group at 3690–3050 and formation of C=C at 1636 confirmed the formation of the 3-arm PGA trimethacrylate prepolymer.

For ^{1}H-NMR (Fig. 4), the chemical shifts of the 3-arm PGA polyester triols were found as follows (ppm): a, 5.5 (OH); b, 4.8 (CH_2); c, 4.1 (CH_2); d, 3.4 (CH_2); e, 1.4 (CH_2); and f, 0.9 (CH_3). The chemical shifts of the 3-arm PGA trimethacrylate prepolymer are listed as follows (ppm): a, 5.8 and 6.2 (CH_2=); b, 4.8 (CH_2); c, 4.95 (CH_2); d, 4.2 (CH_2); e, 1.9 (CH_3); f, 1.4 (CH_2); and g, 1.2 (CH_3). The two typical chemical shifts at 5.8 and 6.2 clearly identified the carbon–carbon double bond formed on the 3-arm PGA trimethacrylate prepolymer.

MW was determined using a VPO and the measured number–average MW (M_n) of 3-arm PGA polyester triols = 395.7 Da. The measured viscosity of the 3-arm PGA trimethacrylates = 105.5 cp (centipoise). Both low MW and viscosity values characterize the nature of this prepolymer, which makes it unique in biomedical and orthopedic applications for which the liquid or paste formulations are often required.[23]

Mechanical property evaluations

It is known that orthopedic restoration often requires the restoratives with injectable and *in situ* polymerizable capability before being solidified. The system we have developed is a paste system even with the filler (β-TCP) content up to 75%, due to the low viscosity and spherical nature of the synthesized prepolymer. Table I shows the initial CS, including CS at yield (YS), modulus (M), ultimate CS (CS), and toughness (T) of the cured materials at different levels of β-TCP content. Apparently, increasing filler content increased YS and M but decreased CS and T. These properties can be attributed to the nature of filler-containing composites.[24] It is known that adding fillers into the polymer increases the brittleness of the system.[24,25] As a result, higher YS, higher modulus, and lower break strength are anticipated. Toughness is a measure of energy absorption of a material when it undergoes a load and

TABLE I
Initial Compressive Properties of the Cured Composites

Filler (%)	YS[a] (MPa)	Modulus (GPa)	CS[b] (MPa)	Toughness (kN mm)
0	20.1 (1.6)[c]	0.73 (0.04)	310.5 (19)	3.93 (0.72)
20	38.7 (2.8)	1.52 (0.08)	261.9 (16)	3.84 (0.22)
33	43.2 (4.2)	1.82 (0.11)	216.1 (8.8)	3.16 (0.21)
43	51.1 (1.5)	1.97 (0.22)	182.7 (4.9)	2.46 (0.14)
50	56.4 (3.3)	2.46 (0.09)	158.9 (2.8)	1.97 (0.05)
60	63.5 (2.3)	2.87 (0.31)	130.8 (6.2)	1.32 (0.07)
67	86.4 (6.9)	4.87 (0.31)	125.1 (13)	0.98 (0.22)
75	92.3 (3.9)	5.65 (0.27)	119.9 (5.6)	0.63 (0.05)

[a] YS, CS at yield.
[b] CS, ultimate CS.
[c] Entries are mean values with standard deviations in parentheses.

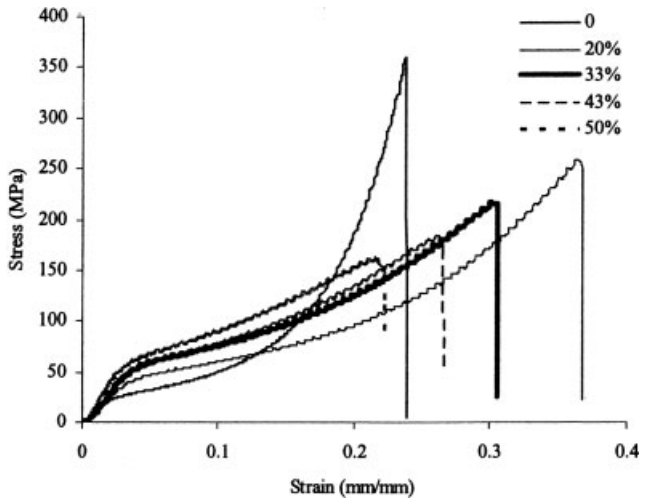

Figure 5 Stress–strain curves for the cured neat resin and composites.

is expressed as the area under a stress–strain curve.[24] The neat resin showed the highest toughness (3.93 kN mm), followed by the composite with 20% filler (3.84). Figure 5 shows several typical stress–strain curves of the neat resin and the selected composites for easy visualization. As we can see, the shape of stress–strain curve with the neat resin was very different from those exhibited by the composites. The curve for the neat resin was high in ultimate strength (the highest) and low in both YS and strain. In contrast, almost all the curves for the composites were high in YS, strain, and modulus.

Figure 6 shows the CS and DTS values of the materials with different filler contents. It is clear that the neat resin showed the highest CS (310.5 MPa) and DTS (89.0 MPa). Increasing filler contents decreased both CS and DTS. However, when the filler content reached 60%, no further significant decreases in both CS and DTS were observed. The composites with 60, 67, and 75% fillers almost shared the same CS and DTS values.

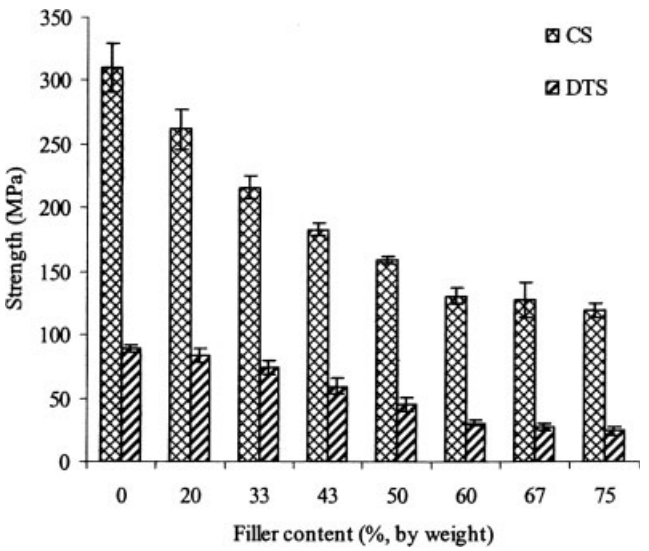

Figure 6 Compressive (CS) and diametral tensile strengths (DTS) of the cured resin and composites with different filler contents. Bar = standard deviation.

In addition to compressive and tensile properties, we also evaluated curing time, exotherm, and degree of conversion. As shown in Table II, increasing filler content increased curing time. This may be attributed to the reason that introduction of fillers reduces a local concentration of the prepolymer and thus slows down the curing. For the exotherm, all the resin and composites exhibited very small temperature increases, with the values ranging from 2.1 to 6.6°C (Table II). It is known that commercial poly(methyl methacrylate) bone cement exhibits a substantially high exotherm up to 86.8°C or a temperature increase of 55–61°C.[21] The low exotherm exhibited by the experimental system is clinically beneficial. Such low exotherm can be attributed to both filler and prepolymer. Ceramics or glass fillers are usually considered as heat insulators.[24] When compared with methyl methacrylate monomer (MW = 100) in the poly(methyl methacrylate) cement, the new experimental 3-arm PGA prepolymer has a relatively higher molecular weight (395.7) and lesser C=C double bonds per mole. Considering the degree of conversion, it is apparent that increasing filler content decreased the degree of conversion. Except for the neat resin, the composite with 20% filler showed the highest degree of conversion (88.1%) and the composite with 75% filler showed the lowest degree of conversion (69.8%). This may be attributed to the interference of filler particles with the polymerization of the resin, because a composite is considered a heterogeneous system when compared with a pure resin.

In vitro degradation study

Degradation study was conducted in PBS solution (pH = 7.4) to mimic the *in vivo* environment.

TABLE II
Curing Time, Exotherm, and DC of the Neat Resin and Composites

Filler (%)	Curing time (min)	Exotherm (°C)	DC (%)
0	NA	6.5	81.8
20	1.89 (0.04)[a]	6.6	88.1
33	2.07 (0.11)	5.5	85.3
43	2.18 (0.09)	5.0	85.2
50	2.25 (0.04)	4.6	79.5
60	2.34 (0.09)	2.9	75.6
67	2.51 (0.08)	2.5	72.9
75	2.93 (0.12)	2.1	69.8

[a] Entries are mean values with standard deviations in parentheses.

Figures 7 and 8 show the degradation curves for eight materials, including one neat resin and seven composites with different filler contents. The degradation was evaluated based on loss of ultimate CS as a function of time. Figure 7 shows the entire degradation course of the tested experimental materials. Figure 8 represents only a partial degradation course within 21 days from Figure 7 because the data within 21 days were too crowded to see. From Figure 8, it is evident that all the tested materials exhibited a significant burst degradation behavior within the first 24 h. At Day 1, the neat resin lost almost 47% of its original CS (lost the most), followed by the composites with 33%, 20%, 43%, 50%, 60%, 67%, and 75% fillers (lost 35%, 21%, 11%, 10%, 11%, 9%, and 9%). The burst effect may be attributed to incomplete polymerization of the surface, since oxygen can easily inhibit the polymerization on the specimen surface. From Day 1 to Day 3, interestingly, all the materials showed an increase in CS. Among them, the composite with 33% filler showed the highest increase (45%), followed by the neat resin, the composites with 20, 50, 60, 43, 67, and 75% fillers (increased 15%, 15%, 9%, 7%, 5%, 4%, and 2% respectively). This increased CS can be attributed to the salt-bridge or ionic bond formation within the composites during the course of degradation. With increasing carboxylic acid groups (produced from the polymer backbone degradation), the salt-bridges start to form between the carboxyl groups on polymer fragments and calcium cations from the β-TCP, resulting in ''an ionomer.'' The ionic crosslinks combined with partially degraded polymer networks (still having relatively high molecular weight) resulted in an increase in CS.[10,17,18] This phenomenon is very similar to the setting mechanism in glass-ionomer cements.[26] At Day 7 (Fig. 8), only the neat resin showed a significant decrease (lost 42%) when compared with the CS measured at Day 3. The others showed either no change or a little change. At Day 14, the neat resin and two low filler-containing composites (20 and 33%) showed a significant decrease in CS (lost 69%, 46%, and 14%, compared with the CS at Day 7). The others showed either no change or a little increase. The absence of change or a little change means that the composites with a filler content higher than 33% still can retain their strengths up to Day 14. The actual remaining CS values at Day 14 were 32.8, 127.2, 166, 177, 144, 130, 121.2, and 109.7 MPa for the materials with 0, 20, 33, 43, 50, 60, 67, and 75% fillers. When compared with their original CS, these materials lost 89%, 52%, 23%, 3%, 9%, 0%, 11%, and 8% of their original strengths, respectively. Apparently, the higher the filler content in the composite, the slower the degradation. At Day 21, the materials with 0, 20, 33 43, and 50% fillers showed a significant decrease in CS but no statistical change was noticed for the composites with 60, 67, and 75% fillers. The results at Day 30 (Fig. 7) indicate that the materials continued to show a decreased tendency in CS. At Day 45, the neat resin and the composite with 20% filler completely lost their strengths (some specimens completely lost their integrity). The remaining composites showed a significant reduction in strength. The CS values were 25.4, 20.7, 36.9, 54.6, 86.1, and 75.8 MPa, for the remaining composites with 33, 43, 50, 60, 67, and 75% fillers, respectively. At Day 60, another three composites (33, 43, and 50%) lost their CS. The CS values for the remaining three composites (60, 67, and 75%) were 38.2, 53.0, and 58.3 MPa. At Day 75,

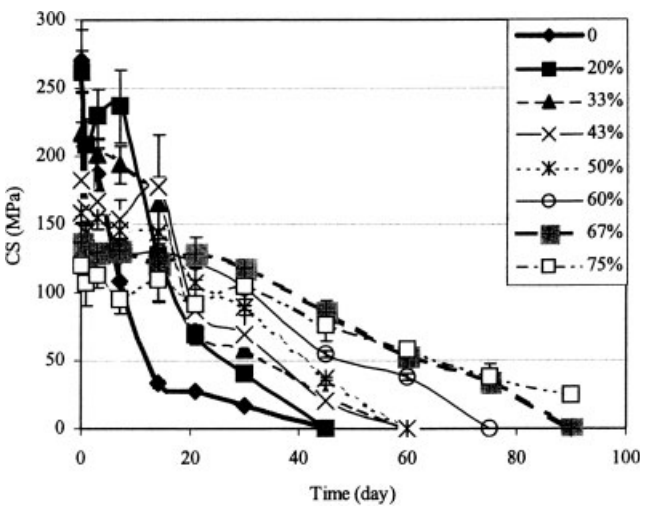

Figure 7 Compressive strengths of the cured resin and composites as a function of degradation time. Bar on each point = standard deviation.

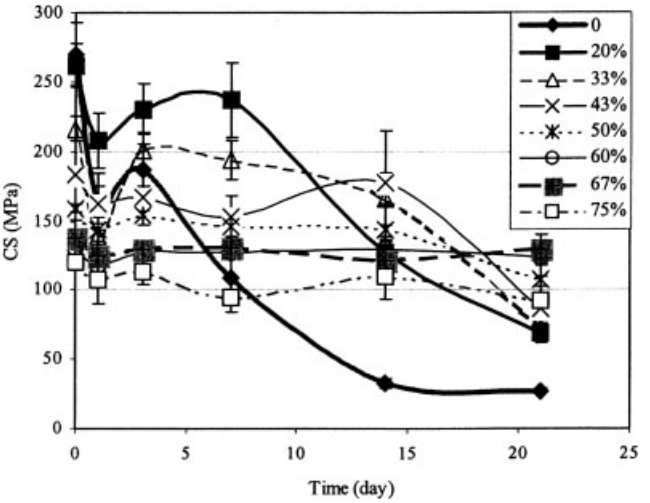

Figure 8 Compressive strengths of the cured resin and composites as a function of degradation time: Detailed duration from 0 to 21 days; bar on each point = standard deviation.

the composite with 60% filler completely lost its strength. Finally at Day 90, the composite with 67% filler lost its detectable CS. The composite with 75% filler still had 25.3 MPa left. The significant reduction in CS after either 14 or 21 days (depending on filler content) can be explained as follows: as degradation continues, the molecular weight of the polymer resin becomes lower and lower. Thus the formed salt-bridges are not able to offset the strength reduction caused by *in vitro* degradation. This proposed degradation mechanism is fairly consistent with those reported for linear high MW biodegradable polymers.[27] From the above study, we have also noticed two interesting phenomena, i.e., (1) a significant CS increase from Day 1 to 3 for the composites with 20 and 33% fillers; (2) no or little CS change between 1 and 30 days for the composites with 60, 67, and 75% fillers. We believe that these interesting behaviors are of particular and great importance to orthopedic clinics, because all the orthopedic restorations require high initial and sustained mechanical support during the recovery of bone tissues.[23] We might take an advantage of these particular properties for special needs in orthopedic and dental restorations.

CONCLUSIONS

Novel 3-arm methacrylate-endcapped biodegradable PGA prepolymer was synthesized and used to prepare the polymer composites with β-TCP fillers. The composites showed initial yield CS ranging from 20.1 to 92.3 MPa, modulus from 0.73 to 5.65 GPa, ultimate strength from 119.9 to 310.5 MPa, and toughness from 630 to 3930 N mm. Increasing filler content increased YS and modulus but decreased ultimate strength and toughness. Diametral tensile strength test shows the same trend as does CS test. Increasing filler content also increased curing time but decreased exotherm and degree of conversion. During the course of degradation, all the materials showed a significant burst degradation behavior within 24 h with more for the materials containing less fillers. All the composites exhibited an increase in strength between Day 1 and Day 3, which is probably due to salt-bridge formations. The composites with higher filler contents retained their strengths longer but those with lower filler contents lost their strengths at 45 or 60 days. The degradation rate is filler-content dependent. Future studies will focus on investigating MW effect, effect of different backbone components, biocompatibility, and other properties.

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