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### Synthesis and Characterization of Fumarate Copolyesters for Use in Bioresorbable Bone Cement Compositions

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## Synthesis and Characterization of Fumarate Copolyesters for Use in Bioresorbable Bone Cement Compositions

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*Unsaturated amorphous copolyesters of varied composition were prepared by transesterification copolymerization of diethyl fumarate, and two diols, 1,2-propanediol and 2-methyl-1,3-propanediol. The copolyesters were characterized by IR, <sup>1</sup>H- and <sup>13</sup>C-NMR, GPC, DSC, and TGA. The glass transition is changing with composition from 0°C to 19°C as the content of 1,2-propanediol residue in the copolyester increases. The copolyester structure and composition have an impact on the compressive strength and hydrolytic stability of the composites prepared by crosslinking the fumarate double bonds with N-vinyl pyrrolidone in the presence of inorganic filler, calcium sulfate dihydrate, with the addition of a radical initiator, benzoyl peroxide, at ambient temperatures.*

**Keywords** fumarate copolyesters, bioresorbable bone cement compositions

### Introduction

Synthetic linear polyesters have proven to be effective biodegradable polymers in several surgical applications, including sutures, bone plate, and controlled release systems (1, 2). Poly(propylene fumarate) (PPF) has been considered as a potential matrix in bioresorbable composites and bone cement (3–6). The use of fumaric derivatives in the polyester synthesis allows introduction of an unsaturated site into the polymer. Here, there is the additional feature of chemical activation of the double bond by the adjacent carbonyl group, which permits ready crosslinking.

In our attempt to expand the range of fumarate-based resorbable polymers, we have prepared polyesters from diethyl fumarate, 2-methyl-1,3-propanediol and 2,2-dimethyl-1,2-propanediol (7), and diethyl fumarate and 1,4-cyclohexanedimethanol (8), as well their crosslinkable composites.

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In this paper, we present synthesis and characterization of novel copolyesters of diethyl fumarate and two diols, 1,2-propanediol and 2-methyl-1,3-propanediol and their composites.

## Experimental

### Materials

Diethyl fumarate (DEF), 1,2-propanediol (PD), 2-methyl-1,3-propanediol (MPD),  $\text{ZnCl}_2$ , *N*-vinyl pyrrolidone (NVP), calcium sulfate dihydrate, and benzoyl peroxide (BP) were obtained from Aldrich (Milwaukee, WI) and used as received.

### Polymer Synthesis

Fumarate-based copolyesters were synthesized by the transesterification polycondensation of DEF, PD, and MPD (9). The reaction was catalyzed with  $\text{ZnCl}_2$ . A typical two-stage polymerization involved heating the reagents under a nitrogen sweep to 230–240°C for 6–8 h. A vacuum (1 torr) was then applied at 210°C for 6–8 h to remove any remaining by-products. Precipitation from methylene chloride solution into diethyl ether resulted in a suspension of a polyester that was filtered, washed with fresh diethyl ether, and dried under vacuum at room temperature. The yield of the polymer was 80 wt% determined as final weight of the polymer compared with the weight of initial reaction mixture less the weight of the distillate collected.

### Polymer Analysis

Infrared spectrum of the polymers (KBr) were determined with a Nicolet Avatar 360 FT-IR spectrometer.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were obtained on 10% polymer solutions in  $\text{CDCl}_3$  at ambient temperature using a Bruker WP270SY spectrometer operating at 200.13 MHz for  $^1\text{H}$  and 50.33 MHz  $^{13}\text{C}$ . Relaxation times were at least 5 times the longest  $T^1$  value in each spectrum. The distortionless enhancement by polarization transfer (DEPT) NMR spectra were obtained with evolution delay of 3.704 ms to produce negative methylene and positive methine and methyl  $^{13}\text{C}$  resonance signals.  $^1\text{H}$ - $^{13}\text{C}$  correlation spectra were run using the standard XHCOR Bruker program. Thermal transitions were measured using a TA Instruments model DSC 2010 with a heating rate of 10°C in the –50 to 200°C range. Two cycles of heating and cooling were used in all runs.  $T_g$  was taken as a midpoint of a straight line between the inflexion of the peak's onset and endpoint. The thermal stability of the polymers was measured by a thermogravimetric analyzer TA Model 2090 from ambient temperature to 600°C at 20°C/min. The molecular weight of polymers was determined relative to polystyrene standards in  $\text{CHCl}_3$  solutions with sample concentrations 0.8% (wt/vol) by gel permeation chromatography using an Alltech 526 HPLC pump at an elution rate of 1.0 ml/min through Styragel HR 0.5, 1, 3, and 4 columns (Waters) at 25°C, a Model 410 refractive index and Viscotek T50A differential viscometer detectors.

### Composite Preparation and Characterization

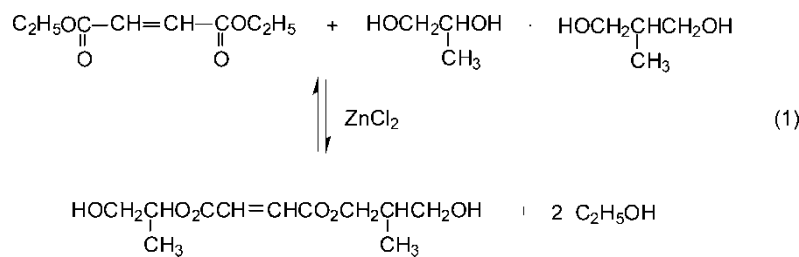
A moldable, curable composition was prepared by mixing of 22.7 wt% polyester, 8.5 wt% *N*-vinyl pyrrolidone, 0.7 wt% benzoyl peroxide, and 68.1 wt% calcium sulfate dihydrate.

When mixed together, the composition becomes a putty-like mixture, which remains moldable for 15–30 min, and then cures to a rigid state. Compressive testing for strength and modulus was conducted according to ASTM standard F 451–756 for acrylic bone cement with the MTS (Q-TEST) materials test system. Samples for testing were prepared by placing the curing composition in cylindrical Teflon molds (6 mm in diameter and 12 mm length specimens) and allowed to harden for 48 h at 37°C. Uniaxial compression tests were conducted at a crosshead rate of 20 mm/min. Compressive strengths were determined from the maximum loads achieved divided by the original cross-sectional area (ca. 28 mm<sup>2</sup>). Polymers and composites were degraded in phosphate buffered saline pH 7.4 in an incubator at 37°C. To determine mass loss during degradation preweighed disks (6 mm in diameter and 3 mm length) were each placed into a tarred scintillation vial. Periodically, the samples were removed from the incubator, rinsed with distilled water, dried *in vacuo* until a constant mass and the mass loss was recorded as the average of the three individually degraded samples. The percentage mass loss was determined for each sample by comparing the dry weight ( $m_d$ ) remaining at a specific time with the initial weight ( $m_0$ ), % mass loss =  $(m_0 - m_d)/m_0 \times 100$ .

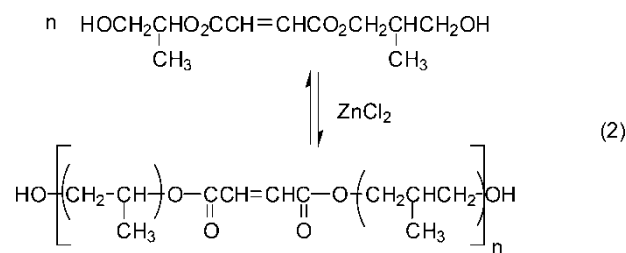
## Results and Discussion

### Polymer Synthesis

DEF-PD-MPD copolyester was prepared via an ester exchange reaction (Table 1). DEF first reacts with an excess of the diols (DEF/PD + MPD = 0.67) liberating ethanol and forming a bis(hydroxyalkyl)ester (Equation 1):



In a second stage, the ester is subjected to polycondensation by alcoholysis, forming the copolyester (Equation 2):



Both stages are inherently reversible, but the conditions are chosen to drive each reaction in forward direction by removal of the low molecular product as it is formed.

**Table 1**  
Synthesis and characterization of DEF-PD-MPD copolyesters

| Sample | PD/MPD in Feed (mol%) | PD/MPD in Polym. (mol%) | GPC $M_n$ | MWD | DSC $T_g$ ( $^{\circ}\text{C}$ ) |
|--------|-----------------------|-------------------------|-----------|-----|----------------------------------|
| BC 11  | 100/0                 | 100/0                   | 7400      | 1.8 | 21                               |
| BC 16  | 98/2                  | 92/8                    | 6600      | 1.7 | 19                               |
| BC 15  | 95/5                  | 89/11                   | 6400      | 1.9 | 16                               |
| BC 14  | 90/10                 | 75/25                   | 6800      | 1.9 | 13                               |
| BC 5   | 85/15                 | 71/29                   | 7700      | 2.0 | 11                               |
| BC 6   | 75/25                 | 52/48                   | 6800      | 1.9 | 9                                |
| BC 7   | 50/50                 | 23/77                   | 6800      | 1.9 | 5                                |
| BC 8   | 25/75                 | 6/94                    | 7000      | 2.0 | 1                                |
| BC 9   | 15/85                 | 4/96                    | 7600      | 1.8 | 0                                |
| BC 10  | 0/100                 | 0/100                   | 8300      | 1.8 | -2                               |

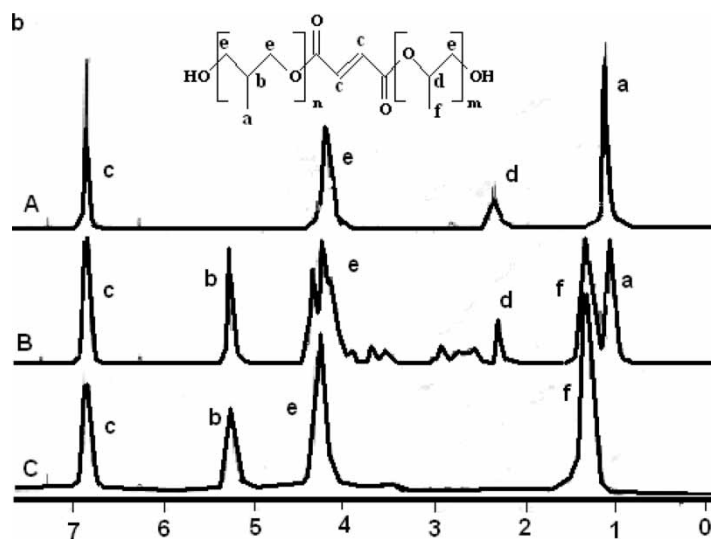
A mixture of DEF, PD and MPD with a polyesterification catalyst,  $\text{ZnCl}_2$  is heated with stirring in an inert atmosphere at 150–200 $^{\circ}\text{C}$  until the evolution of ethanol is complete. The process is then continued at higher temperature and under reduced pressure effect polymerization. The diols are used in excess over the theoretical requirement of the first step in order to force the ester-exchange reaction toward completion and to compensate for losses of the diols. The choice of final working temperature for the second stage (usually below 210 $^{\circ}\text{C}$ ) is governed by the need for the product to be kept molten during polymerization.

### Polymer Characterization

The structure of the polyester was characterized by FT-IR and NMR spectroscopy. In the IR analysis of the polymer, terminal hydroxyl groups appear as a broad absorption in the 3600–3200  $\text{cm}^{-1}$  region, similarly to those of the diols. This confirms the assumption that the resultant polymer is hydroxyl terminated since an excess of diols is used during the polymerization. Stretching absorptions of fumaric group are observed in the 3040–3010  $\text{cm}^{-1}$  region. The strong ester carbonyl absorption peak is observed at 1716  $\text{cm}^{-1}$ , as well as the broad absorbance due to the C–O bond centered between 1100–1200  $\text{cm}^{-1}$ .

The structure and composition of the copolyesters were determined from the analysis of proton NMR spectra (Figure 1). The assignment of the resonances is given in (7). The spectra show relatively well-resolved resonances of methyl protons (0.8–1.8 ppm), methine protons of MPD (2.0–2.5 ppm) and PD (5.0–5.5 ppm), methylene protons (3.8–4.8 ppm), and fumarate protons (6.7–7.6 ppm). Small resonances in the 2.5–3.8 ppm result from the reactions of hydroxyl end groups with fumarate double bonds (7). Integration of the PD and MPD methine protons gave quantitative information on composition of the copolyesters (Table 1). Based on compositional data, reactivity ratios,  $r_1 = 0.23$ , and  $r_2 = 1.13$  for PD ( $M_1$ ) and MPD ( $M_2$ ) were estimated using Fineman and Ross method (10).

A  $^{13}\text{C}$ -NMR spectrum of the copolyester shows both resonances of PPF, DEF-PD and DEF-MPD polyesters (7). The DEF residue is represented by resonance signals



**Figure 1.** Proton NMR spectra of DEF-MPD (A), BC-5 (B) and DEF-PD (C).

at 164–165 ppm for the fumarate carbonyls and peaks at 134 ppm for olefinic carbons. Methylene carbons of PD residue give signals at 65 and 67 ppm, whereas those of MPD absorb at 69 (CH<sub>2</sub>O) and 66 (CH<sub>2</sub>OH) ppm. Methine carbons of both residues, PD and MPD show signals at 16 and 13 ppm, respectively. Methyl carbons of PD and MPD absorb at 16 and 13 ppm, respectively.

### Polymer Properties

The fumarate based copolyesters have the number-average molecular weight 6.4–8.3 × 10<sup>3</sup> g/mol and the molecular weight distribution 1.8–2.0. The copolyesters according to DSC results (Figure 2) are amorphous polymers as their corresponding homopolymers (7). The glass transition (*T*<sub>g</sub>) is changing with composition from –2°C for DEF-MPD polyester to 21°C for DEF-PD (Table 1).

Thermal stability of the copolyester was analyzed by thermogravimetric analysis. At a heating rate of 10°C/min, the TGA scan (Figure 2) shows the onset of one-step degradation at 282°C (Figure 3).

Polymer-ceramic composites represent recent advances in resorbable bone cements (3) which are designed to mimic the viscoelastic properties of bone, improve fracture toughness (i.e., reduce brittleness), resulting in better performance in mixed stress modes, and improve initial moldability. In preparing moldable bone replacement material from the fumarate based unsaturated polyester, the polymer was mixed with a vinyl monomer, N-vinyl pyrrolidone (NVP), a radical initiator, benzoyl peroxide, and inorganic filler, CaSO<sub>4</sub>·2H<sub>2</sub>O. The free radicals produced by benzoyl peroxide (2 wt% based on polyester and NVP) initiate cross-linking polymerization involving the fumarate groups in the copolyester chains and the unsaturated NVP monomer. As a tertiary amine, NVP in conjunction with benzoyl peroxide apparently accelerates free radical formation at ambient temperatures (3). Crosslinking proceeds rapidly and establishes the structure of the three dimensional network in which the polyester and NVP are immobilized in an inorganic matrix. The mixture is workable by hand and solidifies

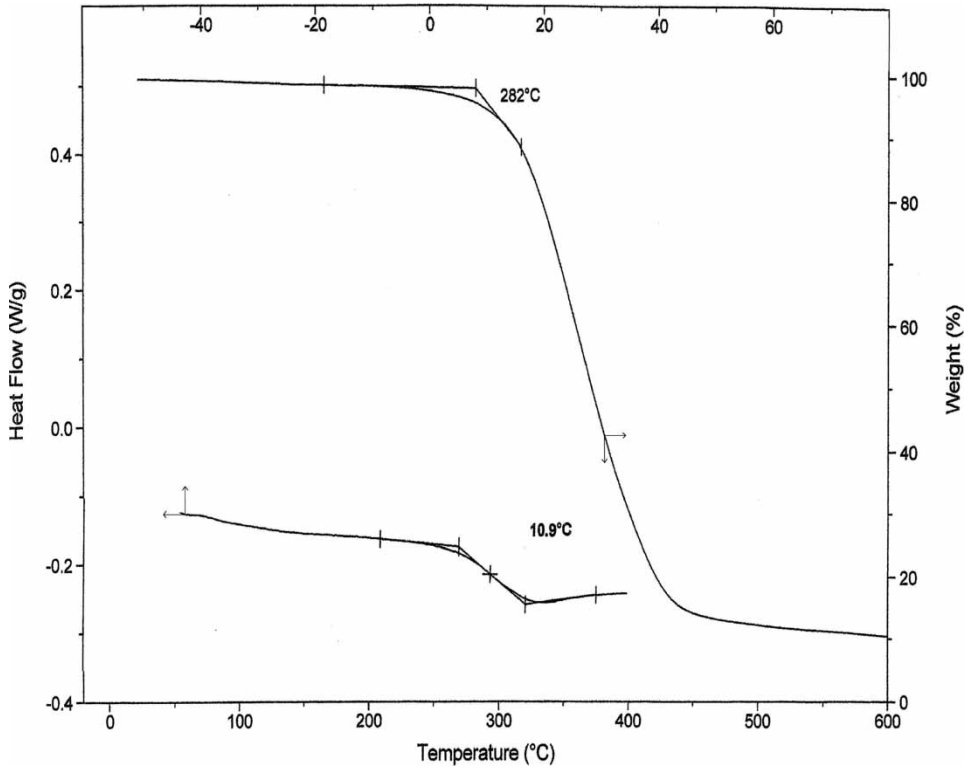


Figure 2. DSC and TGA traces of BC-5 copolyester.

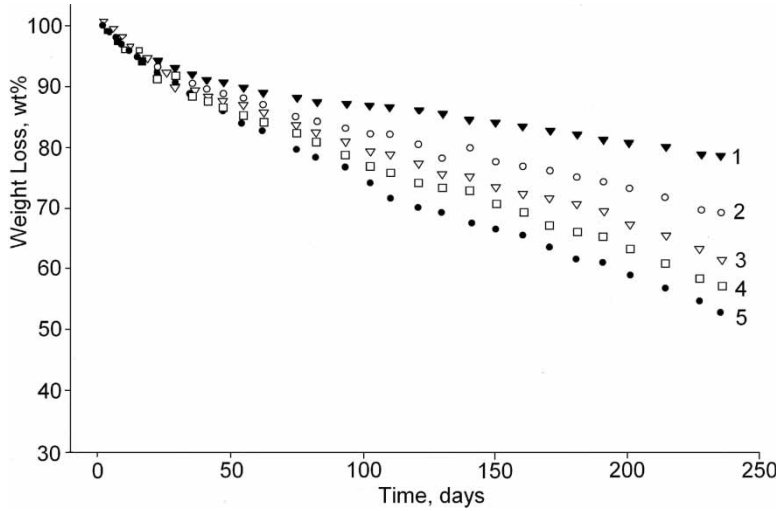


Figure 3. Weight loss of composites with DEF-based polyesters degraded in phosphate buffered saline (1) DEF-MPD, (2) BC-7, (3) BC-6, (4) BC-14 and (5) DEF-PD.

in 15–20 min at body temperatures (37°C) to give a cured composite. Unlike the PMMA systems, setting is only mildly exothermic, with maximum cure temperatures of 45°C for 20 g material. This is because a much lower percentage of liquid monomer is undergoing polymerization than in the commercial acrylic systems. The unmodified, cured fumarate based polyesters are semiflexible materials of modest strength and stiffness. Therefore, in bone cement applications, reinforcing inorganic fillers are required to improve strength and modulus. Additionally, the inorganic filler may act to dissipate some of the polymerization heat and reduce shrinkage of the cement, eliminating internal voids and cracking. Calcium sulfate, both as the hemihydrate and dihydrate, has been used for many years to fill bone defects (3).

To maximize the cross-linking reaction, the weight ratio of the copolyesters to NVP was kept at 2.64, which correspond to a stoichiometric relationship of approximately 1.2 NVP units for each fumarate unit. PNVP is a water-soluble polymer, which was used for decades as a blood-plasma extender, and is currently used in various pharmaceutical compositions. PNVP induces only minor storage-related functional changes in organs and its cytotoxicity is extremely low (11).

Mechanical properties of the cured copolyester based composites are compared with similarly prepared composites based on DEF–PD and DEF–MPD (7) (Table 2). From the compressive testing of standardized cylindrical specimens, the tensile properties do not change significantly with change of the copolyester composition and remain intermediate between the homopolyesters.

### Degradation Studies

The biodegradability of aliphatic polyesters is attributed to their ability to undergo hydrolysis back to their respective monomeric carboxylic acids and diols (1). Hydrolysis can occur via the ester bond, resulting in the formation of alcohol and carboxylic acid end groups. These monomers in turn, are shunted to metabolic pathways where they are enzymatically transformed into carbon dioxide and water.

*In vitro* demonstration of biodegradation requires experimental conditions mimicking the physiological characteristics of living media especially constant osmolarity, and neutral pH. Thus, 0.13 M phosphate buffer (pH 7.4) at 37°C was used as *in vitro* medium in order to provide isoosmolarity and to neutralize the generated carboxyl groups without changing the pH of the medium.

The degradation rate by hydrolysis of cured composites of DEF-PD-MPD copolyesters (Figure 3) was measured as the mass loss over time of exposure to the buffer solution.

**Table 2**  
Compressive strength of the equimolar copolyester composite as compared with other homopolyesters (7)

| Diol | Peak load (kg) | Compressive strength (MPa) | Modulus (MPa) |
|------|----------------|----------------------------|---------------|
| PD   | 70.2 ± 4.3     | 24.3 ± 8.7                 | 839 ± 165     |
| MPD  | 42.5 ± 3.9     | 14.7 ± 6.3                 | 312 ± 87      |
| BC-6 | 62.6 ± 9.2     | 18.2 ± 4.7                 | 564 ± 93      |



The results of hydrolysis of the DEF-PD-MPD copolyesters composites were compared with those obtained for DEF-PD and DEF-MPD polyesters composites. The copolyesters structural differences can account for different hydrolytic stability of their cured composites. Composites of the copolyesters have intermediate hydrolytic stability between those of homopolyesters, DEF-PD and DEF-MPD. The presence of substituted structure arising from the MPD diol in the polyester backbone leads to an increase in hydrolysis resistance because of steric hindrance of these structures, which prevent the attack of ester linkages (12).

## Conclusions

The transesterification polymerization of diethyl fumarate, 1,2-propanediol, and 2-methyl-1,3-propanediol at various feed results in copolyesters with different contents of the diols residues. Reactivity ratios,  $r_1 = 0.23$ , and  $r_2 = 1.13$  for PD ( $M_1$ ) and MPD ( $M_2$ ) were estimated using the Fineman and Ross method. The structure of the polyesters was characterized by FT-IR and NMR spectroscopy. The fumarate-based copolyesters have the number-average molecular weight  $6.4\text{--}8.3 \times 10^3$  g/mol and the molecular weight distribution 1.8–2.0. Amorphous morphology of the polymer is suggested by DSC analysis with  $T_g$  at increasing from  $0^\circ\text{C}$  to  $19^\circ\text{C}$  as PD/MPD ratio in the copolyester increases. The thermogravimetric analysis indicated that the onset of one-step degradation takes place at  $282^\circ\text{C}$ . The copolyester structure and composition has an impact on the properties of the composites prepared by crosslinking the fumarate polyesters with NVP in the presence of an inorganic filler, calcium sulfate dihydrate, with the addition of a radical initiator, benzoyl peroxide, at ambient temperatures. Hydrolytic stability of the composites can be correlated with the composition of the copolyesters.

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