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Synthesis and Characterization of Diethyl Fumarate-1,4-Cyclohexanedimethanol Polyesters for Use in Bioresorbable Bone Cement Composites

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Unsaturated polyesters are prepared by transesterification polymerization of diethyl fumarate and 1,4-cyclohexanedimethanol. The structure of the polyesters was characterized by FT-IR and ^{1}*H- and* ^{13}*C-NMR spectroscopy. Semicrystalline morphology of the polymers is suggested by DSC analysis with* T_g *at 21°C and melting at 140°C. The thermogravimetric analysis indicated that the onset of degradation takes place at 300°C. The polyester's structure has significant impact on the properties of the composites prepared by crosslinking the fumarate double bonds with N-vinyl pyrrolidone in the presence of an inorganic filler, calcium sulfate dihydrate, with the addition of a radical initiator, benzoyl peroxide, at ambient temperatures. The compressive strength and hydrolytic stability of the cement compositions was correlated with structure of the polyesters.*

Keywords fumarate polyesters, 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 by a number of workers as a potential matrix in bioresorbable composites and bone cement (3-6).

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-1,3-propanediol as well their crosslinkable composites (7).

In this paper we present synthesis and characterization of diethyl fumarate–1,4-cyclohexanedimethanol polyesters and their composites.

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Experimental

Materials

Diethyl fumarate (DEF), 1,4-cyclohexanedimethanol (CDM, 70/30% *trans/cis*), $ZnCl_2$, *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 polyesters were synthesized by the transesterification polycondensation of DEF and CDM. The reaction was catalyzed with $ZnCl_2$. 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 the 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 85 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 polymer (KBr) was determined with a Nicolet Avatar 360 FT-IR spectrometer. ^1H and ^{13}C-NMR spectra were obtained on 10% polymer solutions in $CDCl_3$ at ambient temperature using a Bruker WP270SY spectrometer operating at 200.13 MHz for ^1H and 50.33 MHz ^{13}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 an evolution delay of 3.704 ms to produce negative methylene and positive methine and methyl ^{13}C resonance signals. ^1H-^{13}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 700°C at 20°C/min. The molecular weight of polymers was determined relative to polystyrene standards in $CHCl_3$ 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.

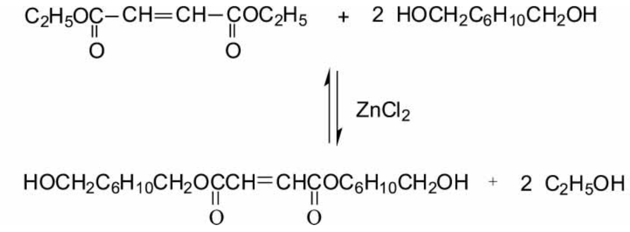
Composite Preparation and Characterization

In a typical preparation, a moldable, curable composition was prepared by mixing of 22.7 wt% polyester, 8.5 wt%, NVP, 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 a 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^2). 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

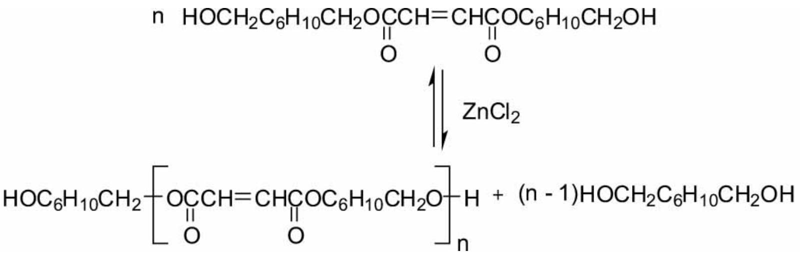
Polymer Synthesis

DEF-CDM polyesters were prepared via an ester exchange reaction. DEF first reacts with an excess of the diol (DEF/CDM = 0.67) liberating ethanol and forming a bis(hydroxyalkyl)ester (Equation 1).



$$C_2H_5O\underset{\overset{\|}{O}}{C}-CH=CH-\underset{\overset{\|}{O}}{C}OC_2H_5 + 2\ HOCH_2C_6H_{10}CH_2OH \xrightleftharpoons{ZnCl_2} HOCH_2C_6H_{10}CH_2O\underset{\overset{\|}{O}}{C}CH=CH\underset{\overset{\|}{O}}{C}OC_6H_{10}CH_2OH + 2\ C_2H_5OH \qquad (1)$$

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



$$n\ HOCH_2C_6H_{10}CH_2O\underset{\overset{\|}{O}}{C}CH=CH\underset{\overset{\|}{O}}{C}OC_6H_{10}CH_2OH \xrightleftharpoons{ZnCl_2} HOC_6H_{10}CH_2\left[O\underset{\overset{\|}{O}}{C}CH=CH\underset{\overset{\|}{O}}{C}OC_6H_{10}CH_2O\right]_n H + (n-1)HOCH_2C_6H_{10}CH_2OH \qquad (2)$$

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. A mixture of DEF and CDM with a polyesterification catalyst, $ZnCl_2$ is heated with stirring in an inert atmosphere at 150–200°C until the evolution of ethanol is complete. The process is then continued at higher temperature and under reduced pressure effect polymerization. The diol is 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 diol. The choice of final working temperature for the second stage (usually below 210°C) is governed by the need for the product to be kept molten during polymerization.

Polymer Characterization

The structure of the polyesters 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 3700–3100 cm^{-1} region, similarly to that of 1,4-cyclohexanedimethanol. This confirms the assumption that the resultant polymer is hydroxyl terminated since an excess of diol is used during the polymerization. The cycloaliphatic C-H stretch appears as a strong double peak at 2920, 2843 cm^{-1}and –CH_2 absorption appears at 1442 cm^{-1}. The strong ester carbonyl absorption peak is observed at 1716 cm^{-1}, as well as the broad absorbance due to the C-O bond centered between 1100-120 cm^{-1}.

Figure 1 shows the ^{1}H-NMR spectrum of the DEF-CDM polyester. The small absorption peak at 7.26 ppm is due to residual $CHCl_3$ in $CDCl_3$. In the proton NMR spectrum, a peak at 6.9 ppm is assigned to the fumarate *trans* olefinic hydrogens, similar to polypropylene fumarate (PPF) (8) and fumarate based polyesters (7). The double peaks at 4.15 and 4.0 ppm represent equatorial and axial methylene protons adjacent to oxygen atoms, respectively. The two proximate peaks result from the different environments of equatorial and axial protons in the *cis*- and *trans*-isomers of the 1,4-cyclohexanedimethyleneoxy group. Double peaks at 3.6 and 3.5 ppm are assigned to hydroxyl terminated CDM end of the chain. A weak multiplet absorption at 2.7 ppm is assigned to hydroxyl protons of the polyester's end-groups. The multiplets observed in the 1.3–2.0 ppm region and the peak at 1.1 ppm result from the different environments of equatorial and axial protons in the *cis*- and *trans*-isomers of the 1,4-cyclohexanedimethoxy group. The peaks at 1.9 and 1.7 ppm designate the equatorial

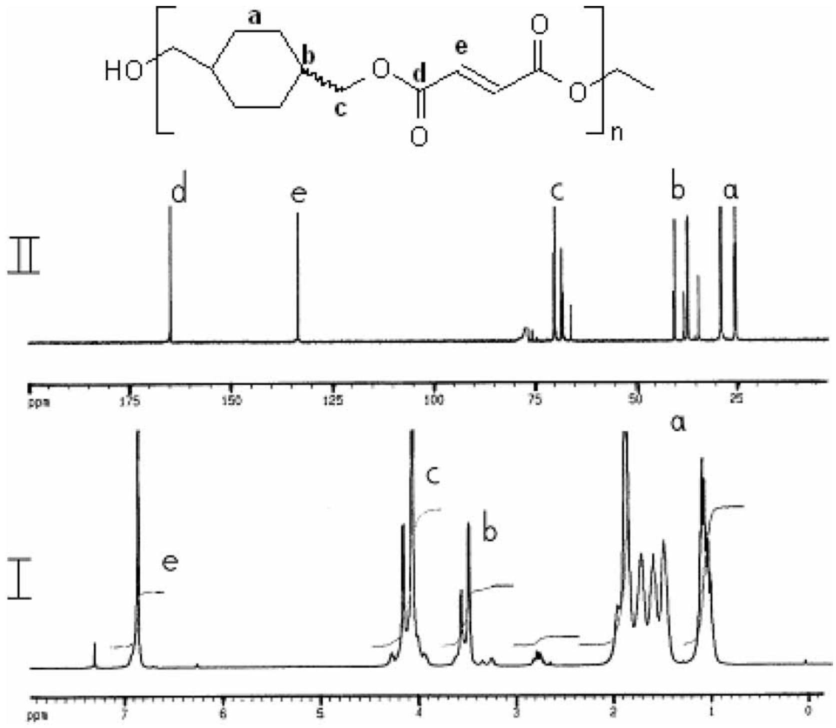


Figure 1. ^{1}H and ^{13}C-NMR spectra of DEF-CDM polyester in $CDCl_3$ solution.

and axial methine protons in the *cis*- and *trans*-isomers, respectively. The peaks at 1.8 and 1.5 ppm represent the equatorial and axial methylene protons in the *trans*-isomer whereas the peaks at 1.6 and 1.1 ppm represent the equatorial and axial methylene protons in the *cis*-isomer, respectively.

In the ^{13}C-NMR spectrum of the polymer (Figure 1) DEF residue is represented by a strong resonance signal at 165 ppm for the fumarate carbonyls and a peak at 134 ppm for olefinic carbons. A peak at 77 ppm is attributed to the solvent, $CDCl_3$. Main chain methylene carbons give signals in 65–72 ppm range. Methine and methylene carbons of the ring (*cis* and *trans*) absorb in 32-43 ppm and 22–30 ppm, respectively. The spectra are well resolved and indicate regular structure. Peaks assignments agree with calculated spectrum, spectra of model compounds, and CDM-based polyesters (9, 10).

Polymer Properties

The fumarate based polyesters formed by transesterification reaction of DEF and CDM have the number-average molecular weight 12×10^3 g/mol and the molecular weight distribution 1.8. Fumarate polyesters prepared from DEF and CDM according to results of DSC (Figure 2) are semicrystalline polymers with T_g at 21°C.

The crystallinity is associated with a more rigid main chain of the DEF-CDM polyester than polypropylene fumarate, which is amorphous (3, 7). The crystallization exotherm has a maximum at 90°C. The melting temperature of the polymer is observed to occur at ca. 140°C. The transition enthalpy of the polyester is 18.4 J/g. Glass transition temperature of the polyester was observed at 21.0°C.

Thermal stability of the polyester was analyzed by thermogravimetric analysis. At a heating rate of 10°C /min, the TGA scan (Figure 3) shows the onset of degradation to take place at 300°C. The decomposition products were not analyzed in this study and the mechanism has yet to be investigated.

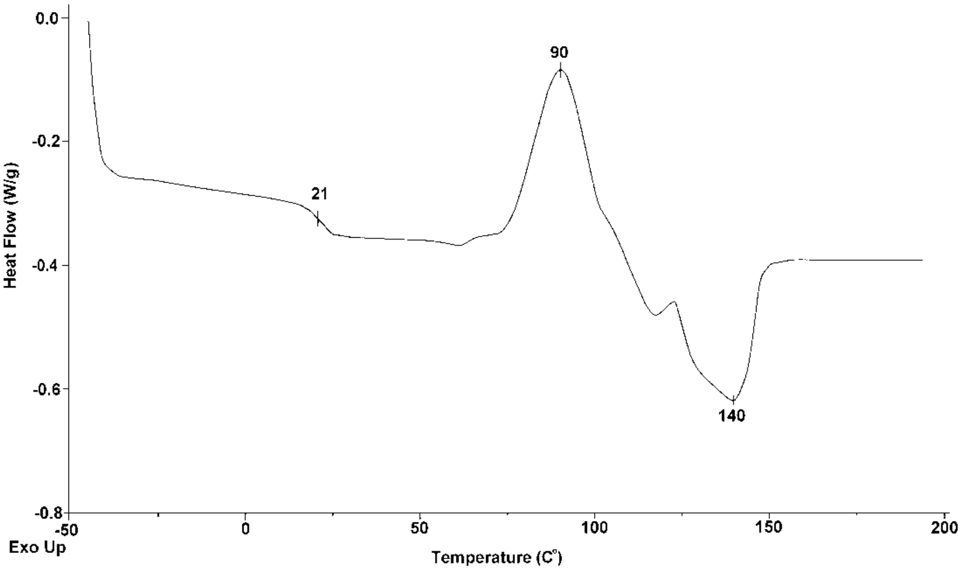


Figure 2. DSC of DEF-CDM polyester.

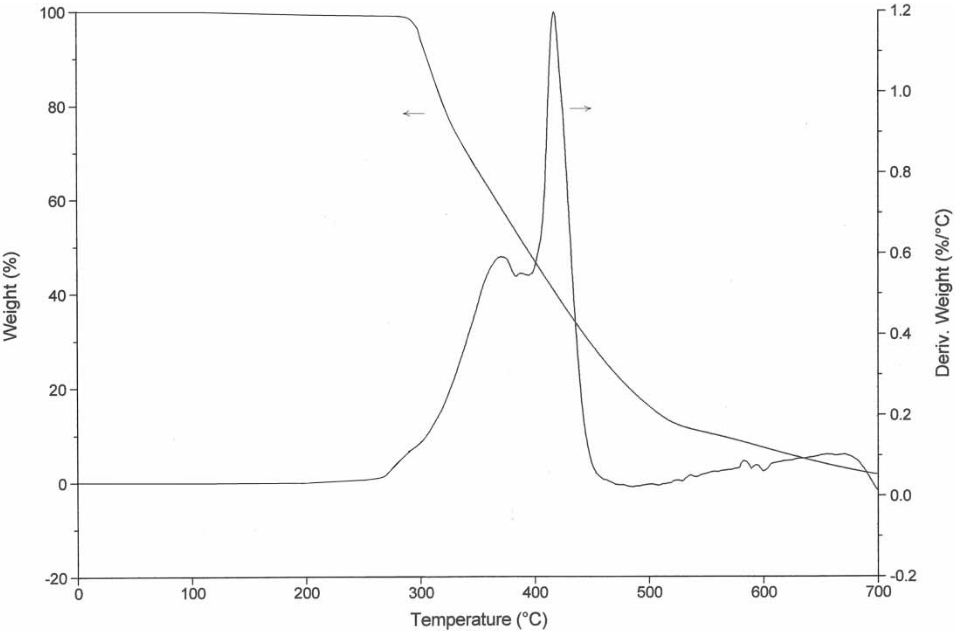


Figure 3. TGA of DEF-CDM polyester.

Composites

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, $CaSO_4$ $2H_2O$. The free radicals produced by benzoyl peroxide (2 wt% based on polyester and NVP) initiate cross-linking polymerization involving the fumarate groups in the polyester chains and the unsaturated NVP monomer. As a tertiary amine, NVP in conjunction with benzoyl peroxide apparently accelerates free radical formation at ambient temperatures (7). Cross-linking 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 in 15–20 min at body temperature (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 semi-flexible materials of modest strength and stuffiness. 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 (7). Calcium sulfate, both as the hemihydrate and dihydrate, has been used for many years to fill bone defects.

To maximize the cross-linking reaction, the weight ratio of DEF-CDM polyester to NVP was kept at 2.64, which correspond to a stoichiometric relationship of approximately

Table 1
Compressive strength of the DEF-CDM composites as compared with other fumarate-based polyesters (7)

Diol	Peak load (kg)	Compressive strength (MPa)	Modulus (MPa)
PG	70.2 ± 4.3	24.3 ± 8.7	839 ± 165
MPD	42.5 ± 3.9	14.7 ± 6.3	312 ± 87
DMD	23.8 ± 8.3	8.3 ± 3.5	217 ± 54
CDM	120 ± 10.2	50.2 ± 8.2	1452 ± 185

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 DEF-CDM based composites are compared (Table 1) with similarly prepared composites based on DEF–1,2-propanediol (DEF-PD), DEF–2-methyl-1,3-propanediol (DEF-MPD), and DEF–2,2-dimethyl-1,3-propanediol (DEF-DMD) (7). From the compressive testing of standardized cylindrical specimens, the highest tensile properties are shown by the DEF-CDM composite. It is apparently associated with the greater polyester backbone rigidity, as evidenced by the higher T_g of DEF-CDM polymer.

Degradation Studies

The biodegradability of aliphatic polyesters is attributed to their ability to undergo hydrolysis back to their respective monomeric carboxylic acids and diols. 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, $0.13M$ 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-CDM polyesters (Figure 4) was measured as the mass loss over time of exposure to the buffer solution. The results of hydrolysis of the DEF-CDM composites were compared with those obtained for DEF-PD, DEF-MPD, and DEF-DMD composites.

The polyesters' structural differences can account for different hydrolytic stability of their cured composites. Composites of CDM, DMD, and MPD polyesters have much higher stability than PD due to the more hydrophobic character of their backbones. The presence of substituted structures arising from the diols in the polyester backbone leads to hydrolysis resistance because of steric hindrance of these structures, which prevent the attack of ester linkages (12). The highest hydrolytic stability observed for CDM-based composite, apparently is related to its rigidity and hydrophobicity.

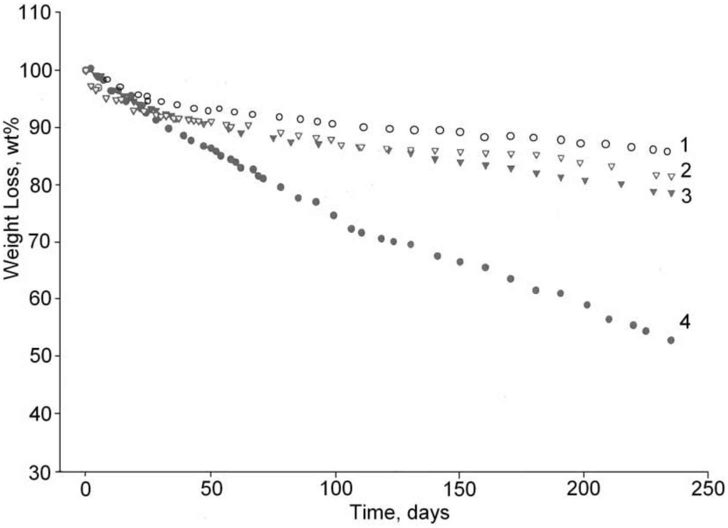


Figure 4. Weight loss of composites with DEF-based polyesters degraded in phosphate buffered saline (1) CDM, (2) DMD, (3) MPD, and (4) PD.

Conclusions

The transesterification polymerization of diethyl fumarate and 1,4-cyclohexanedimethanol results in polyesters. The structure of the polyesters was characterized by FT-IR and NMR spectroscopy. The polymer has the number-average molecular weight 12×10^3 g/mol and the molecular weight distribution 1.8. Semicrystalline morphology of the polymer is suggested by DSC analysis with T_g at 21°C and melting at 140°C. The thermogravimetric analysis indicated that the onset of degradation takes place at 300°C.

The polyester structure has a significant 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. From the compressive testing of standardized cylindrical specimens, the highest tensile properties are shown by the DEF-CDM composite in comparison with other fumarate-based polyesters, which is apparently associated with the greater polyester backbone rigidity. Hydrolytic stability of the composites can be correlated with the hydrophilic-hydrophobic composition of the polyesters.

Acknowledgements

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