Synthesis and Characterization of Biodegradable Copolyesters and Copolyanhydrides Prepared from Fumaric and Succinic Acid Trimers and Oligomers

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Abstract. A series of new biodegradable copolymers and copolyanhydrides built of trimers of fumaric and succinic acid and propylene glycol, covering a wide range of compositions, were prepared and characterized for use as drug carriers. The polymers were found to degrade within a period of weeks. Polyanhydrides loaded with ibuprofen as a model drug released the drug for a period of one week, while the polyesters released the drug for more then 30 days. The biocompatibility and the rate of evacuation of trimer-based polymers of fumaric and succinic acids were investigated in rats. All polymers were found compatible when implanted in mice.

INTRODUCTION

Degradable polymers are of considerable interest for a variety of applications and have attracted significant attention for use in numerous medical and biomedical applications.[1,2] These polymers can help significantly to overcome many problems since they are biodegradable (being sensitive to hydrolysis), nontoxic, and biocompatible. Examples of their importance can be found in the field of drug delivery, releasing a dose of drug over an extended period of time.[3] Biodegradable polymers can stabilize the drug reservoir from premature inactivation; concurrently, the polymer can control the release of drug out of the reservoir, and finally the degradability of the material helps to overcome the need for any post-application removal. There have been only a few cases in recent years in which new degradable polymers were custom-made for application in humans. Polyanhydrides, a versatile family of biodegradable and biocompatible polymers, are one of these.

Biodegradable polyanhydrides based on aromatic and aliphatic dicarboxylic acids have been studied as carriers for therapeutic substances since the 1980s.[4–7] Studies on copolymers of several polyanhydride families have shown that varying co-monomer ratios produces erosion profiles ranging from days to years.[8] Syntheses of polyesters and polyanhydrides have been published for the controlled delivery of drugs providing a sustained release rate over a long period of time.[9–12] It has also been demonstrated by tissue-response and toxicology studies that polyanhydrides are not only degradable but also highly biocompatible.[13]

Oligomers are thought to accelerate the hydrolytic degradation of devices prepared from poly(lactide-co-glycolide), PLGA, due to their increased number of carboxylic end groups.[14,15] The oligomers increase the concentration of carboxyl groups, which results in an increased degradation rate and autocatalysis of ester hydrolysis. The formation of propylene fumarate oligomers was reported for use in bioerodible bone cement composites.[2,6] The effects of the oligomer molecular

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weight and end groups on the chemical and mechanical properties have been investigated.[2] Although oligomers and trimers play an important role in the complex bulk degradation mechanism, only a few works have studied their influence on degradation and their combination in copolymers and copolyanhydrides for use as drug carriers.

In this paper, we describe the preparation of new biodegradable copolyesters and copolyanhydrides using trimers and oligomers of fumaric and succinic acids. The copolymers were prepared by condensation without solvent in the requested molar or weight ratios. Their importance lies in their unique structure, which can be degraded by hydrolysis into nontoxic products that are easily eliminated from the body. The polymers were evaluated for their degradation properties and their potential use as controlled delivery carriers of drugs.

EXPERIMENTAL

Materials

Succinic anhydride, propane-1,2-diol, fumaric acid, maleic anhydride, and propylene oxide were obtained from Aldrich (Milwaukee, WI). Pyridine, toluene, dichloromethane, ether, and petroleum ether were purchased from Frutarom, Israel.

Instrumentation

Infrared (IR) spectroscopy was performed on an Anelect Instruments FT-IR model fx-6160 on samples cast on NaCl plates from solutions in CH_2Cl_2. Ultraviolet (UV) spectroscopy was performed on a Kontron Instruments Uvikon model 930. Thermal analysis was carried out on a Perkin Elmer DSC 7 differential scanning calorimeter, calibrated with Zn and In standards, at a heating rate of 20 ºC/min. Melting points were obtained on an electrothermal melting point apparatus (BDH, Poole, UK). Molecular weights of polymers were estimated on a gel permeation chromatography (GPC) system consisting of a Spectra Physics (Darmstadt, Germany) P1000 pump with UV detection (Applied Bioscience 759A Absorbance UV detector) at 254 nm, a Rheodyne (Coatati, CA) injection valve with a 20 µL loop, and a Spectra Physics Data Jet integrator. Samples were eluted with $CHCl_3$ through a linear Styrogel column (10-Å pore size) at a flow rate of 1 mL/min. Molecular weights were determined relative to polystyrene standards (Polyscience, Warrington, PA) with a molecular weight range of 400 to 1,500,000 with the aid of a WINner/286 computer program. ^{1}H NMR spectra ($CDCl_3$/TMS/d/ppm) were obtained on a Varian 300 MHz spectrometer.

Synthesis of Polyesters and Polyanhydrides based on Propylene Fumarate and Succinate

Preparation of bis(2-hydroxypropyl fumarate) trimer (PFP trimer)

PFP trimer was synthesized as previously described.[16] In brief, PFP trimer was prepared as follows: fumaric acid (1 mol, 116 g) was mixed with acetone (200 mL) and dry pyridine (3 mL) and heated to reflux with constant stirring. Propylene oxide (200 mL) was added dropwise over 14 h until a clear solution was obtained. The solvent was evaporated to dryness to yield the PFP trimer as a slightly yellow viscous oil. δ ^{1}H NMR ($CDCl_3$): 1.15 (d, 3, J = 6.3 Hz); 1.26 (d, 3, J = 6.6 Hz); 3.67 (m, 1); 4.07 (m, 2); 4.19 (m, 2); 5.03 (m, 1); 6.89 (d, 2, J = 8.1 Hz). IR data: 1630, 1720, 3380, cm^{-1}. Elemental analysis: ($C_{10}H_{16}O_6$) C, 51.67, H, 7.02 (Calcd. C, 51.72, H, 6.89). Titration with NaOH of PFP in acetone solution to the end point of phenolphthalein revealed the absence of acids.

Preparation of propylene-bis(hydrogen maleate) (MPM)

MPM trimer was synthesized by the reaction of propylene glycol (0.5 mol, 39 g) and maleic anhydride (1 mol, 98 g) in toluene (100 mL) at 100 ºC. Propylene glycol was added dropwise over 15 min into the solution of maleic anhydride in toluene. After 24 h at 100 ºC, the mixture was left to cool to room temperature, and a liquid oil was separated. Toluene was decanted, and the oily residue was evaporated to dryness to produce a viscous liquid. δ ^{1}H NMR (acetone d6): 1.31 (m, 3); 4.26 (m, 2); 5.14 (m, 1); 6.38 (d, 1, J = 6.0 Hz); 6.78 (d, 1, J = 6.0 Hz); 9.69 (s(br), 2). IR data: 1630, 1720, cm^{-1}. Elemental analysis: ($C_{11}H_{12}O_8$) C, 48.32, H, 4.61 (Calcd. C, 48.53, H, 4.41). Titration with NaOH confirmed the calculated acid content.

Preparation of propylene bis-(hydrogen succinate)trimer (SPS)

Succinic anhydride (1 mol, 100 g) was mixed with toluene (100 mL) in a bath at 110 ºC. Propane-1,2-diol (0.5 mol, 37.5 mL) was added dropwise during 30 min and the reaction was left overnight at 110 °C. The mixture was moved to a separatory funnel. The solvent was removed and the product was dissolved in ether (200 mL) and precipitated with petroleum ether (500 mL). δ ^{1}H NMR ($CDCl_3$): 1.225 (d, J = 6.9 Hz, CH**C**$\mathbf{H_3}$); 2.642 (m, $\mathbf{CH_2CH_2}$); 4.058 (dd, Jaa = 12.0 Hz, J''ab = 6.3 Hz, CH**C**$\mathbf{H''}$H′); 4.197 (dd, CH**C**$\mathbf{H'}$H″, Jaa = 12.0 Hz, J'ab = 3.0 Hz); 5.156 (ddq, J'ab = 3.0 Hz, J''ab = 6.3 Hz, Jac = 6.9 Hz, CH_3**C**$\mathbf{H}$CH′H″). δ ^{13}C NMR ($CDCl_3$): 178.2, 178.1, 171.9, 171.7, 68.6, 66.2, 28.9, 28.7, and 16.2 ppm. IR data: 2938, 1736, 1719, 1407, and 1165 cm^{-1}. Elemental analysis: C, 47.79; H, 5.88 (Calcd. C, 47.83; H5.60).

Preparation of poly(propylene succinate)-diol (PPS)

Succinic anhydride (0.5 mol, 50.0 g) and propane-1,2-diol (0.6 mol, 45 mL) were mixed together and remained overnight at 140 ºC. Afterward, 100 mL of toluene and 150 mL of concentrated H_2SO_4 were added. The reaction was connected to a system of Dean–Stark and was heated in a bath at 155 ºC for 12 h. The solvents were evaporated to give the crude product. The transparent yellow oligomer was dissolved in dichloromethane (150 mL) and precipitated with 600 mL of ether/petroleum ether (70:30), the upper layer was removed, and the solvent was evaporated to get PPS-diol with a molecular weight of Mw = 3100, Mn = 2030. δ ^{1}H NMR ($CDCl_3$): 1.232 (m, CH**C**$\mathbf{H_3}$); 2.620 (m, $\mathbf{CH_2CH_2}$); 4.039–4.188 (m, $\mathbf{CH_2}$CH); 5.133 (m, **C**$\mathbf{H}$$CH_3$). IR data: 3464, 2984, 1736, 1411, 1379, and 1161 cm^{-1}. Elemental analysis: ($C_{136}H_{179}O_{78}$) C, 53.79; H, 6.18 (Calcd. C, 53.75; H, 5.85).

Preparation of poly(propylene fumarate) di-succinate

A solution of PFP trimer (0.1 mol, 23.2 g) and succinic anhydride (0.2 mol, 20.0 g) in toluene (100 mL) was melt mixed at 100 ºC for 10 h. Afterward, the reaction mixture was dissolved in dichloromethane (200 mL) and filtered. The solvent was evaporated to dryness to get bis-(hydroxypropylene fumarate)-di-succinate with a molecular weight of Mw = 554, Mn = 482. δ ^{1}H NMR ($CDCl_3$): 1.231–1.346 (m, CH**CH_3**); 2.617–2.798 (m, **CH_2CH_2**); 4.100–4.408 (m, CH**CH_2**); 5.161–5.371 (m, **CH**CH_3); 6.211–6.388 and 6.807–6.910 (m, CH = CH). IR data: 3455, 2985, 1725, 1645, 1456, 1296, 1161, and 1079 cm^{-1}. Elemental analysis: ($C_{10}H_{16}O_6$) C, 51.67; H, 7.02 (Calcd. C, 51.72, H, 6.89).

Preparation of propylene bis(hydrogen maleate)di-acetate (MPMpp)

Pre-polymers of diacids were prepared as previously described.[17] In brief, MPM trimer (0.1 mol, 27.2 g) was added to boiling acetic anhydride (350 mL) for 30 min. The solvent was evaporated at 60 ºC, and the viscous liquid was dissolved in dichloromethane (100 mL) and washed in ether (500 mL). The lower layer was separated and the residue of solvent was evaporated. δ ^{1}H NMR ($CDCl_3$): 1.255–1.377 (m, CH**CH_3**); 2.217 (s, **CH_3**COOCO); 4.131–4.391 (m, CH**CH_2**OCO); 5.210–5.369 (m, O**CH**(CH_3)CH_2); 6.208–6.399 (m, **CH** = CHCOOCO); 6.751–6.920 (m, CH = **CH**COOCH_2). IR data: 2992, 1817, 1732, 1641, and 1096 cm^{-1}.

Bis-(2-hydroxypropyl fumarate)di-succinate (PFP-disuccinate)

δ ^{1}H NMR ($CDCl_3$): 1.211–1.335 (m, CH**CH_3**); 2.625 (sbr, **CH_2CH_2**); 4.011–4.391 (m, CH**CH_2**); 5.177–5.383 (m, $CHCH_3$); 6.814–6.868 (m, **CH** = **CH**). IR data: 2985, 1723, 1646, 1357, 1297, and 1159 cm^{-1}.

Poly(propylene fumarate)di-succinate (PPF-succinate)

δ ^{1}H NMR ($CDCl_3$): 1.231–1.346 (m, $CHCH_3$); 2.617–2.798 (m, **CH_2CH_2**); 4.100–4.408 (m, CH**CH_2**); 5.161–5.371 (m, **CH**CH_3); 6.211–6.388 and 6.807–6.910 (m, CH = CH). IR data: 3455, 2985, 1725, 1645, 1456, 1296, 1161, and 1079 cm^{-1}.

Propylene bis-(hydrogen succinate)pre-polymer (SPSpp)

δ ^{1}H NMR ($CDCl_3$): 1.220–1.241 (m, CH**CH_3**); 2.200 (s, **CH_3**COCO); 2.592–2.798 (m, CH_2**CH_2**COO); 4.014–4.205 (m, **CH_2**CH); 5.145 (m, **CH**CH_3). IR data: 2988, 2943, 1822, 1737, 1412, 1316, 1179, and 1081 cm^{-1}.

Poly(propylene fumarate)di-succinate pre-polymer

δ ^{1}H NMR ($CDCl_3$): 1.260–1.348 (m, CH**CH_3**); 2.221 (s, **CH_3**COOCO); 2.722–2.798 (m, CH_2OCOOC**CH_2**CH_2); 2.8721–2.964 (m, CH = CHOC**CH_2**CH_2); 4.128–4.391 (m, CH**CH_2**); 5.169–5.370 (m, $CHCH_3$); 6.244, 6.387 and 6.847 (m, CH = **CH**). IR data: 2988, 1823, 1787, 1725, 1646, 1297, 1260, and 1080 cm^{-1}.

Preparation of copoly(anhydride-ester)

All polymers were prepared by the same method. The pre-polymers were polymerized by condensation without solvent. The pre-polymer mixtures in the requested molar or weight ratios were polymerized at a temperature of 160 ºC or 180 ºC under a pressure of 0.1–0.5 mmHg for 30 to 180 min. Characterization of the copolyesters was carried out by GPC, ^{1}H NMR, IR, and DSC.

P(MPM-SA): δ ^{1}H NMR ($CDCl_3$): 1.243 (m, CH**CH_3**); 1.311 (m, **$(CH_2)_4$**CH_2CH_2COOCO); 1.643 (m, **CH_2**CH_2COO-CO); 2.435 (t, *J*ab = 7.2 Hz, **CH_2**COOCO); 4.187–4.381 (m, CH**CH_2**); 5.214–5.330 (m, **CH**CH_2); 6.329 (m, CH = CH-anhydride); 6.873 (m, **CH** = CH, ester). IR data: 2930, 2851, 1812, 1741, 1473, 1412, and 1043 cm^{-1}.

P(MPM): δ ^{1}H NMR ($CDCl_3$): 1.242–1.398 (m, CH**CH_3**); 4.218–4.371 (m, CH**CH_2**); 5.277 (m, **CH**CH_3); 6.384 (m, CH = **CH**COOCO anhydride); 6.818–7.004 (m, CH = **CH**COO ester). IR data: 2990, 1803, 1732, 1639, 1454, 1386, 1230, and 1074 cm^{-1}.

P(SPS): δ ^{1}H NMR ($CDCl_3$): 1.241 (d, *J*a = 6.6 Hz, CH**CH_3**); 2.726 (m, CH_2CH_2); 4.085 (dd, *J*aa = 11.7 Hz, *J*″ab = 6.6 Hz, CH**CH**″H′); 4.196 (dd, *J*aa = 11.7 Hz, *J*′ab = 3.3 Hz, CH**CH**′H″); 5.156 (ssq, *J*′ab = 3.3 Hz, *J*′ab 6.6 Hz, *J*ac = 6.6 Hz, CH_3**CH**CH′H″). IR data: 2942, 1822, 1737, 1411, 1358, 1181, and 1051 cm^{-1}.

P(SPS-SA): δ ^{1}H NMR ($CDCl_3$): 1.245 (d, *J* = 6.6 Hz, CH**CH_3**); 1.307 (m, **$(CH_2)_4$**CH_2CH_2COOCO); 1.640 (m, **CH_2**CH_2COOCO); 2.423 (t, *J* = 7.5 Hz, **CH_2**COOCO); 2.644 (m, CH_2CH_2); 2.746 (m, CH_2CH_2); 4.090 (dd, *J*aa = 12.3 Hz, *J*″ab = 6.6 Hz CH**CH**″H′); 4.202 (dd, *J*aa = 12.3 Hz, *J*′ab = 3.3 Hz, CH**CH**′H″); 5.132–5.192 (ddq, *J*′ab = 3.3 Hz, *J*″ab = 6.6 Hz, *J*ac = 6.6 Hz, CH_3**CH**CH′H″). IR data: 2931, 2852, 1815, 1741, 1472, 1413, and 1045 cm^{-1}.

P(PPF-SUCC-SA): δ ^{1}H NMR ($CDCl_3$): 1.315 (m, **$(CH_2)_4$**CH_2CH_2COOCO); 1.647 (m, **CH_2**CH_2COOCO); 2.437 (t, *J* = 7.2 Hz, **CH_2**COOCO); 2.714 (m, CH_2**CH_2**); 4.061–4.390 (m, **CH**CH_2); 5.179–5.388 (m, **CH**CH_3); 6.844 (m, **CH** = CH). IR data: 2930, 2851, 1810, 1739, 1472, 14212, 1360, 1286, and 1044 cm^{-1}.

Preparation of triblock copolymer of poly(propylene fumarate) or succinate-ester with lactones (PLA, PCL, PTMC, and PLGA

Poly(propylene fumarate) diol (2.0 g) was dissolved in 60 mL dry toluene. The solution was heated to 135 ºC, and 8.0 g of cyclic monomer was added. The system was boiled for 60 min and afterward a stannous octoate (1% in toluene, 0.2% in ratio with the cyclic monomer) was added. The reaction mixture was heated and stirred for > 5 h. The solvent was evaporated with argon for 2 h following vacuum of 1–0.5 mmHg for 15 min. The yellow viscous polymer was stored in dry conditions. The copolyesters in Table 2 were prepared using the same procedure.

PPF-PCL: δ ^{1}H NMR ($CDCl_3$): 1.281 (m, CH**CH_3**); 1.358 (m, CH_2CH_2**$(CH_2)_2$**CH_2COO); 4.038 (t, *J* = 6.6 Hz, CH_2**CH_2**COO); 4.208–4.365 (m, **CHCH$_2$**); 5.163 (m, **CH**CH_3); 6.218 (m, CH = CH); 6.856 (m, CH = CH). IR data: 2946, 2867, 1727, 1367, 1295, 1244, and 1191 cm^{-1}.

PPF-PTMC: δ ^{1}H NMR ($CDCl_3$): 1.314 (m, CH**CH_3**); 2.041 (p, *J* = 6.3 Hz, CH_2**CH_2**CH_2COOCO); 4.229 (t, *J* = 6.3 Hz, CH_2**CH_2**OCOO); 4.266 (m, CH**CH_2**); 5.216 (m, **CH**CH_3); 6.241 (m, CH = CH); 6.830 (s(br), CH = CH). IR data: 2972, 2909, 1798, 1747, 1460, 1407, 1331, 1248, and 1034 cm^{-1}.

PPF-PLA: δ ^{1}H NMR ($CDCl_3$): Multiplates at 1.339, 1.553, 4.277, 5.161, 6.227, and 6.817 ppm. IR data: 2994, 1753, 1453, 1382, 1268, 1189, 1131, 1092, and 1052 cm^{-1}.

PPS-PLA: δ ^{1}H NMR ($CDCl_3$): Multiplates at 1.240, 1.561, 2.628, 4.122, and 5.153 ppm. IR data: 2993, 2945, 1745, 1454, 1381, 1269, 1188, and 1091 cm^{-1}.

Preparation of copolymers of fumaric or muconic acid with sebacic acid

Sebacic acid (5.0 g) and fumaric or muconic acid (5.0 g) were stirred with 70 mL acetic anhydride at 180 ºC for 40 min. The residue of the acetic anhydride was removed by evaporator and the mixture was polymerized at 180 ºC for 30 min.

Copoly(fumaric acid-co-sebacic acid) P(PA-SA): δ ^{1}H NMR ($CDCl_3$): 1.305 (m, $\mathbf{CH_2CH_2}CH_2CH_2COO$); 1.636 (m, $\mathbf{CH_2}CH_2COO$); 2.625 (t, J = 7.2 Hz, CH_2CO); 6.891 (s, CH). IR data: 2918, 2879, 1812, 1778, and 1171 cm^{-1}.

Copoly(muconic acid-co-sebacic acid) P(MA-SA)

δ ^{1}H NMR ($CDCl_3$): 1.311 (m, $\mathbf{CH_2CH_2}CH_2CH_2CO$); 1.642 (m, $\mathbf{CH_2}CH_2CO$); 2.434 (t, J = 7.4 Hz, CH_2CO); 6.260 (d, J = 5.4 Hz, **CH**CHCO); 7.0404 (d, J = 5.4 Hz, CHO). IR data: 2935, 2859, 1809, 1748, and 1125 cm^{-1}.

In Vitro Hydrolytic Degradation

Rectangular polymer specimens prepared by melt molding were placed in 20 mL of 0.1 M phosphate buffer, pH 7.4, at 37 ºC with continuous shaking (100 rpm). At each time point, as requested, a polymer sample was removed from the buffer and dried at room temperature under high vaccum for 2 h. The hydrolysis of the polymer was monitored in terms of weight loss of the sample (GPC) and disappearance of the anhydride bonds (IR spectroscopy).

In Vitro Drug Release

The drug, 5 wt% ibuprofen, was dispersed in the polymer solution, and the solvent was removed under vacuum. Tablets were prepared by melt casting of the polymer–drug mixture into 3 × 5 × 8 mm slabs. In vitro drug release was determined in 0.1 M phosphate buffer, pH 7.4, at 37 ºC. Ibuprofen concentrations in the solutions were determined by UV absorption at 287 nm.

In Vivo Biocompatibility and Polymer Elimination

The biocompatibility and the rate of evacuation of trimer-based polymers of fumaric and succinic acids, P(MPM-SA) 50:50, P(SPS-SA) 50:50, and 1:1:1 PPS-PLGA, were investigated in rats. Three representative polymers from the above series were chosen for in vivo evaluation. Smooth disks of 2 × 5 × 10 mm were prepared in clean conditions. The disks were sterilized in γ irradiation (2.5 Mrad) and were examined in GPC to confirm that there is no influence on their molecular weight as well as on their mechanical and spectral properties.

The clean samples of the polymers and the synthetic surgery wire Vicryl, used as control, were implanted subcutaneously in two different sites at the dorsal side of the rats. In these studies 20 rats were used and 2 samples of polymers were implanted in each rat simultaneously and in sterilized conditions. Table 3 describes the different groups of rats and their scarifying time in days.

The implantation areas and the residues of the polymers were removed and examined by light microscopy following routine tissue processing and hematoxylin and eosin slide preparation, as described elsewhere.[17]

RESULTS AND DISCUSSION

Preparation and Characterization of Polymers

Trimers and oligomers of fumaric and succinic acids were used for the preparation of new polyesters and polyanhydrides. The polymers were prepared from trimers and oligomers composed of propane-1,2-diol, succinic and maleic anhydride, and were polymerized to give copolyanhydrides and copolyesters. Propylene bis-(hydrogen succinate) trimer (SPS) was prepared by condensation reaction between propane-1,2-diol with succinic anhydride in a molar ratio of 2:1 (Fig. 1). Changing the ratio to 1:1.1 led to the poly(propylene succinate)-diol (PPS) with molecular weight of Mw = 3100, Mn = 2030 (Fig. 1).

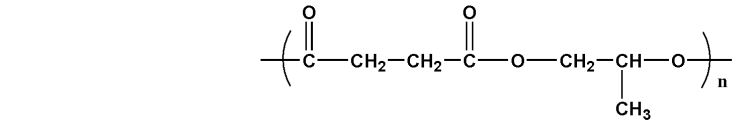
For the preparation of polyanhydride acetate anhydride derivatives of the carboxylic acid end were prepared from the reaction with acetic anhydride. Homo- and copolyanhydrides based on trimers of succinate and fumarate, poly(propylene succinate) and poly(propylene fumarate)anhydrides and their copolymers with sebacic acid were synthesized by melt condensation (Table 1). Characterization of the copolyanhydride esters was carried out with GPC, NMR, IR, and DSC. The polymers obtained from PPF-dicarboxylate and HPM were dark colored due to the presence of double bonds in the polymeric chain and conjugation between these bonds and the anhydride bonds. In order to obtain light polymer, the PPF-disuccinate was prepared in various molecular weights leading to an unconjugated system. The units were prepared by reaction between PPF-diol or propylene fumarate (PFP) with an equivalent amount of succinic anhydride (Fig. 2). These diacid derivatives were polymerized to get light polyanhydrides.

The oligomers of PPS and PPF can also be used for the synthesis of copolyesters. The oligomers contain two terminal hydroxyl groups that can react with cyclic monomer, such as lactide, glycolide, caprolactone, and trimethylene carbonate in coordinative catalysis and ring-opening polymerization, while the hydroxyl groups are initiating the polymerization (Fig. 3). In that way we obtained ABA triblock copolyesters from type in different molecular weights (Table 2).

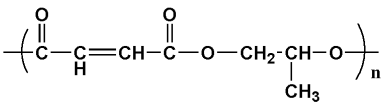
In Vitro Degradation Properties and Drug Release of the Polymers

The polymer degradation for several synthetic polyanhydrides was evaluated following the decrease in

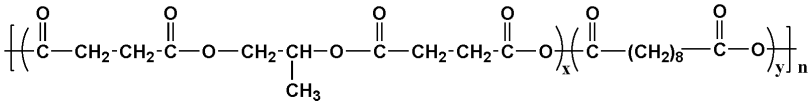
Table 1. Polyanhydrides based on propylene fumarate or succinate and fumaric or muconic acids



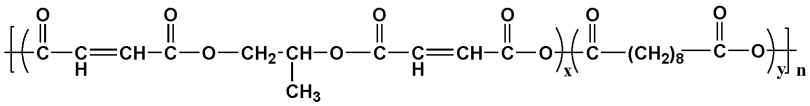
PPS



PPM



P(SPS-SA)



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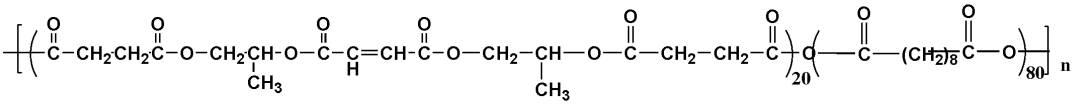

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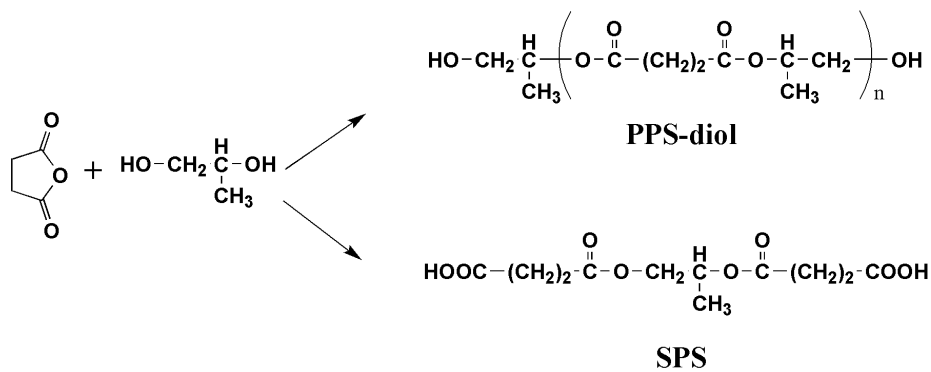

Fig. 1. Schematic description for the preparation of bis-(hydrogen succinate) (SPS) and poly(propylene succinate)-diol (PPS) trimers.

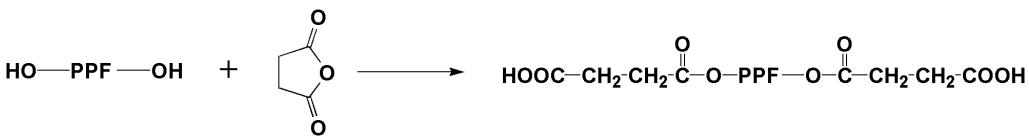

Fig. 2. Reaction between poly(propylene fumarate)-diol (PPF-diol) and succinic anhydride for the preparation of poly(propylene fumarate)-di-succinate (PPF-succinate).

molecular weight (GPC), weight loss, loss of anhydride bonds (IR), and absorption of water. Penetration of water into the polymer matrix leads to hydrolysis of anhydride and ester bonds and results in a decrease in molecular weight.[18–20] The rate of loss in the anhydride bonds in copolymers that contain sebacic acid increased with the rise in sebacic acid content in the polymer. Water absorption of copolyanhydride of P(SPS-SA) and P(MPM-SA) in phosphate buffer was found to act similarly. With higher sebacic acid content in the copolymer, water absorption increased (Fig. 4). Hydrolytic degradation of the polyanhydrides, P(SPS-SA) and P(MPM-SA), at the same conditions, present the typical profile reported in the literature for polyanhydride[5] (Fig. 5a,b). As shown in Fig. 5, decrease in the molecular weight from 110,000 to about 5,000 and weight loss of up to 55% occurred during the first 48 hours of the polymer degradation. It is possible also to conclude that a higher percentage of the trimers SPS and MPM in the polymer leads to a faster weight loss of the respective polymer resulting from the water solubility of these trimers. The release of ibuprofen from the polymers was examined and showed complete correspondence between the water absorption and drug release (Fig. 6). Fast water absorption

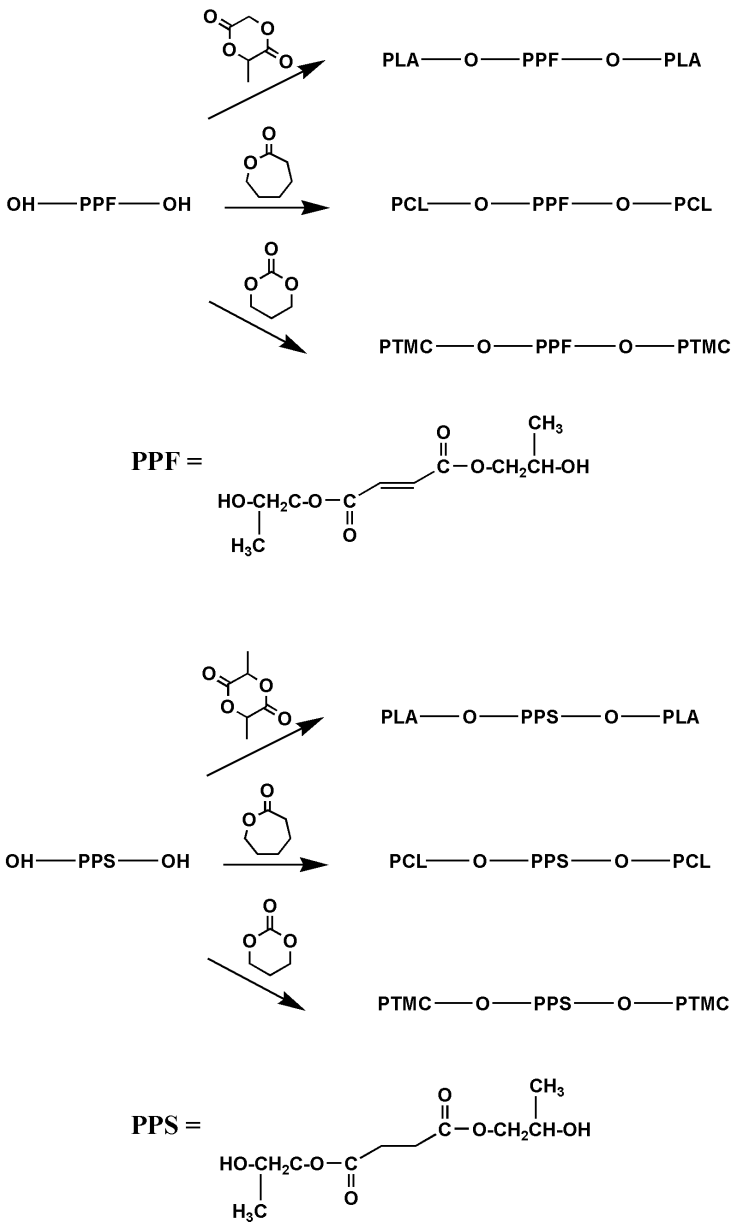

Fig. 3. Preparation of triblock copoly(propylene fumarate or succinate) with cyclic monomers.

Table 2. Structures of copolyesters based on PPS and PPF

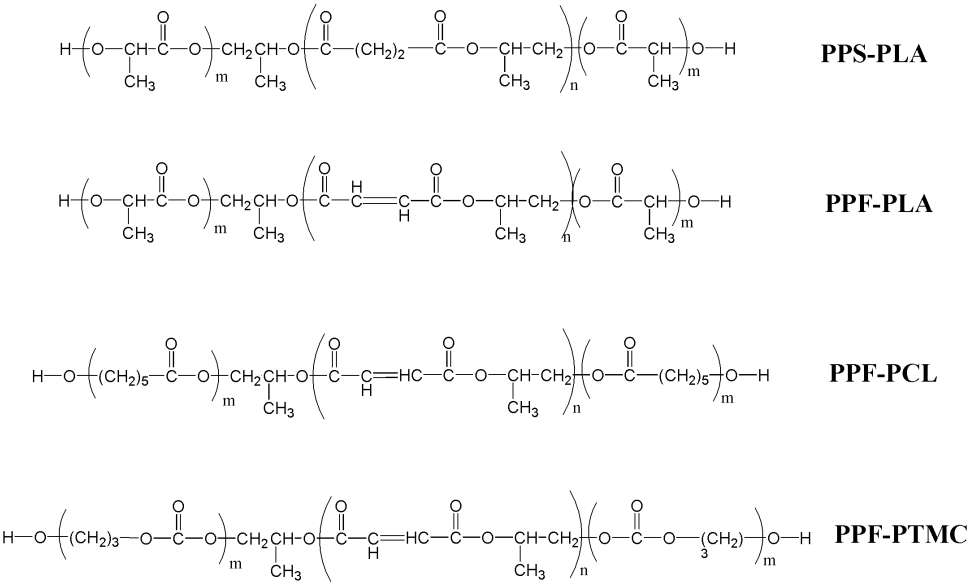

Table 3. Groups of rats and their scarifying time in days. The experiment was conducted for 21 days, 6 animals were sacrificed at 3, 7, and 21 days after the implantation. The final group was sacrificed at the 21st day

group	number of animals	test-article	sacrifice time, days (no. of animals)
A	6(3 × 2)	P(MPM-SA) 50:50 (Left and right sides)	3 (2), 7 (2), 21 (2)
B	6(3 × 2)	P(SPS-SA) 50:50 (Left and right sides)	3 (2), 7 (2), 21 (2)
C	6(3 × 2)	PPS-PLGA (1:1:1) (Left and right sides)	3 (2), 7 (2), 21 (2)
D	2(1 × 2)	Vicryl (Left and right sides)	21 (2)

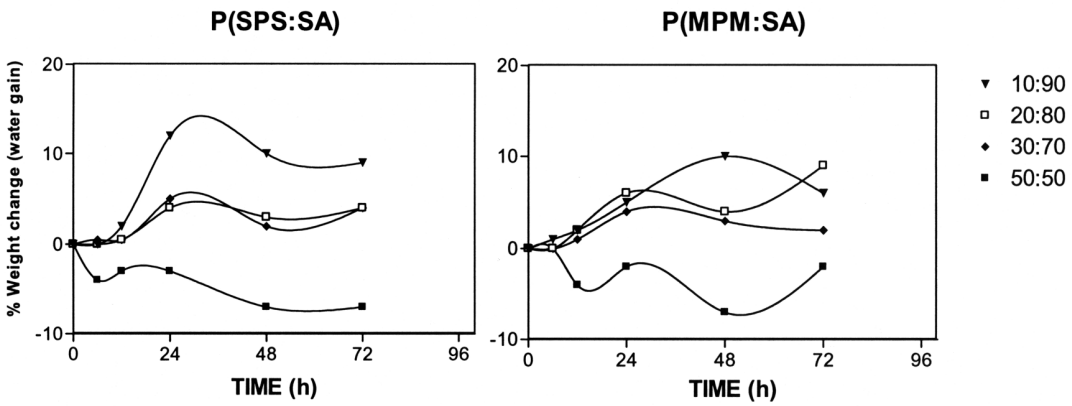

Fig. 4. Water gain, described by weight change of copolyanhydride esters in different ratio mixtures during hydrolysis. Molecular weight was determined by GPC. Hydrolysis was conducted in phosphate buffer, pH 7.4, at 37 ºC. SD ± 5%.

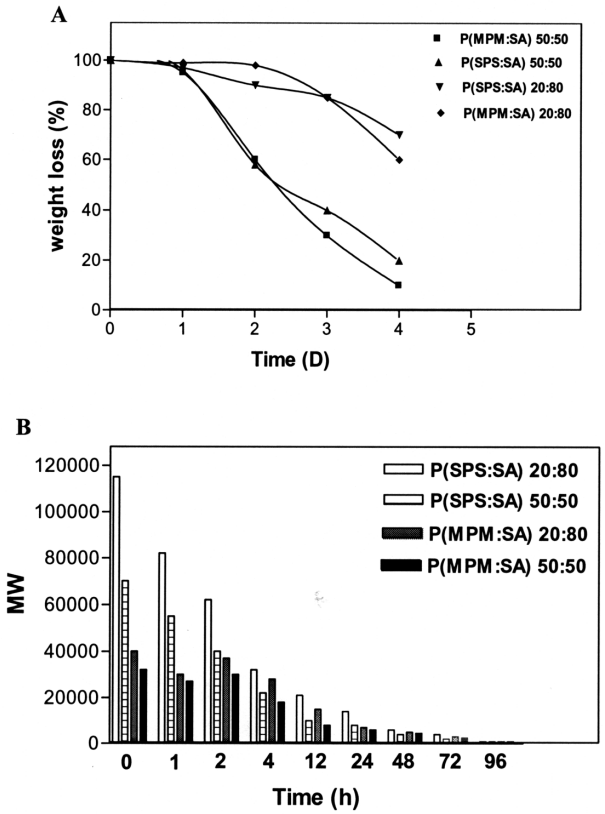

Fig. 5. Degradation studies at different ratios. (A) Weight loss of copolyanhydride esters. (B) Change in molecular weight during hydrolytical degradation of copolyanhydride esters. Molecular weight was determined by GPC. Hydrolysis was conducted in phosphate buffer, pH 7.4, at 37 ºC. SD ± 5%.

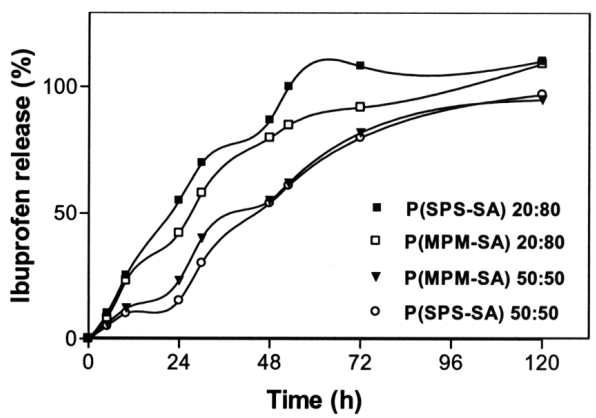

Fig. 6. In vitro ibuprofen release from mixtures of copolyanhydride esters in different ratios. Release from 5 wt% loaded ibuprofen in polymer tablets was conducted in phosphate buffer, pH 7.4, at 37 ºC and determined by UV at 287 nm. SD ± 5%.

leads to rapid hydrolytic degradation of the polymer matrix and hence to solubility and secretion of the drug by diffusion.

Similar in vitro experiments were performed for the copolyesters and copolycarbonate esters under the same conditions. The selected polymers were PPS-PLA, PPS-PLGA, and PPS-PTMC in diverse ratios. The decrease in the molecular weight for the copolyesters PPS-PLA and

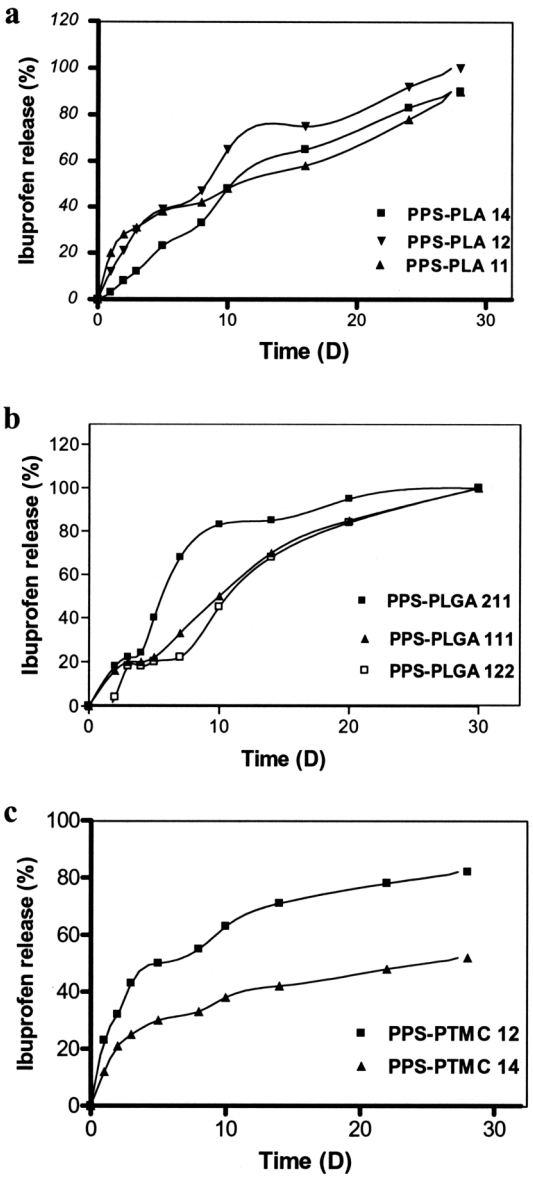

Fig. 7. (a) Ibuprofen release from polymer tablets of PPS-PLA in different ratios. (b) Ibuprofen release from polymer tablets of PPS-PLGA in different ratios. (c) Ibuprofen release from polymer tablets of PPS-PTMC in different ratios. Release from 5 wt% loaded ibuprofen in polymer tablets was conducted in phosphate buffer, pH 7.4, at 37 ºC and determined by UV at 287 nm. SD ± 5%.

PPS-PLGA was found to be the same, up to 4000 after 4 weeks in phosphate buffer (data not shown). Figure 7 a,b describes the total release of the ibuprofen from the copolyesters (PPS-PLA and PPS-PLGA) for 4 weeks, and Fig. 7c describes the release of the drug from the triblock copolycarbonate esters (PPS-PTMC) for the same period. The polymer PPS-PTMC in a ratio of 1:2 showed release of 80% of ibuprofen, while in a ratio of 1:4 it showed release of 50%, after 4 weeks of the experiment (Fig. 7c). In this way it is possible to accelerate the degradation rate of polycarbonates that are known for their high hydrolytical stability. This stability was the major obstacle to using the polycarbonates as degradable polymers.

Biocompatibility and Elimination

All animals implanted with polymer were in good health and gained weight throughout the study. Macroscopic examination of the implant site indicated no swelling or pathological signs during the experiment or at time of sacrificing. The implantation sites were clean and normal, without inflammatory or swelling signs. The residues of the polymers were removed easily with almost complete elimination at day 21. Improvement in the tissues over time was found in all the groups and in biocompatibility at the implantation site.

In general, the degree of severity in the tissues 21 days after implantation, for groups (A), P(MPM-SA), and (B), P(SPS-SA), were essentially equal to those obtained for group D, the synthetic surgery wire Vicryl. The degree of inflammation severity for group C (PPS-PLGA) was clear and without any specific findings relative to those observed for groups (A) and (B) at all times (Table 4).

Histopathology examinations of tissues at the implant site, showed slight inflammation at a degree of 1–2, on a scale of 1–5, where 5 is determined as severe damage.

Table 4. Degree of inflammation at the closest areas to the tissues that were in contact with the implanted polymers: (A) Shem (control) and Vicryl after 21 days of implantation. (B) The polymers at all scarifying times

(A)

	Shem	Vicryl
Implants (n)	2	2
Lesion		
Hemorrhage	0	0
Edema	0	0.5
Necrosis	0	0
Vascular inflammation	0	1.5
Acute inflammation	0	0
Subcutaneous inflammation	0	2.0
Giant cells	0	2.0
Fibrosis	0	2.0
Foreign material	0	2.0
Thickness of inflammatory layer (mm)	0	0.1

(B)

	P(SPS-SA)			P(MPM-SA)			PPS-PLGA		
Implants (n)	4	4	3	4	4	3	2	4	4
Sacrifice day	4	7	21	4	7	21	4	7	21
Lesion									
Hemorrhage	0.75	0	0	0.5	0.5	0	0	0	0
Edema	1.0	1.0	1.0	1.0	1.25	0.6	0.5	1.0	0
Necrosis	0	0	0	0	0.5	0	0	0	0
Vascular inflammation	0.25	1.75	1.0	0.25	1.5	1.3	1.0	0.5	0
Acute inflammation	1.5	0.75	0.6	1.5	1.75	1.0	1.0	1.0	0
Subcutane inflammation	2.6	2.0	2.0	2.0	2.25	2.0	1.0	1.0	1.25
Giant cells	0	0.75	1.6	0.25	1.0	2.0	0	1.0	1.5
Fibrosis	1.0	1.5	2.0	0.75	1.5	1.6	1.0	1.0	2.0
Foreign material	2.0	1.25	1.6	3.0	2.25	2.0	2.0	2.0	1.75
Thickness of inflammatory layer (mm)	0.38	0.6	0.32	0.4	0.65	0.3	0.08	0.21	0.2

Toxicity rating: 0—no remarkable change; 1—minimal change; 2—moderate change, and 3—marked change.

This level of inflammation is similar to that of the clinically used PLA-based polymers (Vicryl). In all cases no encapsulation of the polymer by the tissue was found.

CONCLUSIONS

This work describes the formation of a range of polyanhydrides and polyesters made from trimers of fumaric and succinic acid and propylene glycol. All polymers were found to degrade within a period of weeks. Polyanhydrides loaded with ibuprofen as model drug released the drug for a period of one week, while the polyesters released the drug for more then 30 days. All polymers were found compatible and degradable when implanted in mice.

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