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Synthesis and Characterization of Biodegradable Aromatic Anhydride Copolymers

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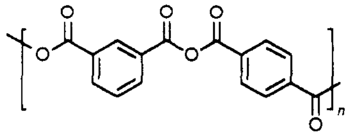
ABSTRACT: Aromatic copolyanhydrides based on the common diacids isophthalic acid (IPA), terephthalic acid (TA), 1,3-bis(*p*-carboxyphenoxy)propane (CPP), and fumaric acid (FA) were synthesized and characterized. The copolymers were highly soluble in chloroform or dichloromethane (>20% w/w) and melted at temperatures between 80 and 130 °C. In comparison, the respective homopolymers are insoluble and melt at temperatures above 250 °C. The copolymers were amorphous and had a weight-average molecular weight between 17 000 and 35 000. The thermal and solubility properties of the aromatic copolymers were dependent upon the copolymer composition. Copolymers of isophthalic acid or fumaric acid containing between 15 and 60 mol % CPP were highly soluble in dichloromethane or chloroform and melted at temperatures below 120 °C. The copolymers containing more than 60% CPP were less soluble and melted at progressively higher temperatures as the fraction of CPP was increased. Copolymers of IPA containing 10–90% fumaric acid were soluble and melted at temperatures below 100 °C. The copolymers of terephthalic acid, however, were soluble and melted at relatively low temperatures (<100 °C) only in the range of 10–35% TA content. The hydrolytic degradation of IPA and CPP copolymers was homogeneous with initial release of the IPA monomers and slower erosion of the CPP residues. Increasing the CPP content in the copolymer further slows the degradation and drug release. These polymers were stable upon storage at 25 °C and exposure to 2.5 Mrad of γ-irradiation. Biocompatibility, as compared to implantable polymers currently in clinical use, was good.

Introduction

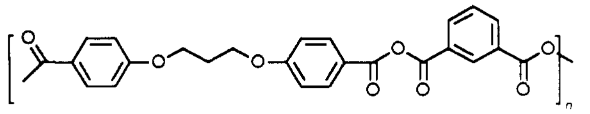
Polyanhydrides of aromatic diacids offer several advantages over aliphatic polymers, including longer release and degradation times[1] and higher mechanical strength and stability.[2,3] However, aromatic polyanhydrides are insoluble in common organic solvents and melt at high temperatures.[4,5] These properties limit the uses of purely aromatic polyanhydrides since they cannot be fabricated into films or microspheres using solvent or melt techniques. Because of these limitations, only soluble polyanhydrides based on aliphatic diacids and copolymers with aromatic diacids have been used for drug delivery.[2,6]

The objective of this study was to synthesize and characterize copolymers of common aromatic diacids, such as isophthalic and terephthalic acid, and to investigate their use for controlled drug delivery applications. Copolymerization of aromatic monomers will introduce irregularity to the polymer chains, resulting in a decrease in the cohesive forces between the polymer chains and a subsequent change in the polymer properties.

Very little has been reported on the synthesis and properties of anhydride copolymers of aromatic diacids.[4,5] In this study, copolymers of isophthalic acid (IPA), terephthalic acid (TA), 1,3-bis(*p*-carboxyphenoxy)propane (CPP), and fumaric acid (FA) were synthesized and characterized. Fumaric acid was used in this study because it forms a crystalline, insoluble, and high melting homopolymer.[7] The structures of isophthalic acid copolymerized with terephthalic acid and CPP are



Poly(TA–IPA)



Poly(CPP–IPA)

The hydrolytic behavior, drug release, and biocompatibility in intramuscular and subcutaneous implantation of these polymers are also reported.

Experimental Section

Materials. Isophthalic acid (IPA), terephthalic acid (TA), fumaric acid (FA), sebacic acid (SA), cadmium acetate dihydrate, and acetic anhydride were purchased from Aldrich Chemical Co. (Milwaukee, WI). 1,3-Bis(*p*-carboxyphenoxy)propane (CPP) was synthesized as previously described.[8] Analytical grade solvents were purchased from J. T. Baker Inc. (Phillipsburg, NJ).

Instrumentation and Methods. Infrared spectroscopy was performed on a Perkin-Elmer 1310 spectrophotometer (Norwalk, CT). Polymeric samples were film cast onto NaCl plates from a solution of the polymer in chloroform. The melting points of acids and prepolymers were determined on an Electrothermal IA8100 digital melting point apparatus (Curtin Matheson Science, Inc., Houston, TX). Thermal properties of polymers were determined using differential scanning calorimetry (DSC) and thermal mechanical analysis (TMA) on a Perkin-Elmer DSC-7 scanning calorimeter (Norwalk, CT). Samples of 4–6 mg were analyzed at a 10 °C/min heating rate in a nitrogen atmosphere. The molecular weight distributions of the polymers were determined on a Waters HPLC/GPC system (Milford, MA) consisting of a Waters 510 pump and a Waters 490E programmable multiwavelength detector at 254-nm wavelength. Samples were eluted in dichloromethane through a Waters Linear Styrogel column (Milford, MA) at a flow rate of 1.0 mL/min. Molecular weights of polymers were determined relative to polystyrene standards (Polysciences, Inc., Warrington, PA; molecular weight range, 400–1 500 000) using the Waters Maxima 820 computer program. Viscosity of polymers was determined on a Cannon 50 Ubbelohde viscometer (Thomas Scientific, Swedesboro, NJ) at 25 °C. ^{1}H NMR spectra were obtained on a Varian 300-MHz spectrophotometer (Palo Alto, CA) using $CDCl_3$ containing tetramethylsilane (TMS) or deuterated water as solvent. UV absorbances were determined on a Perkin-Elmer Lambda 3B spectrophotometer.

Preparation of Polymers. Acetic acid mixed-anhydride prepolymers of CPP, sebacic acid, and fumaric acid were prepared as previously described.[7,8] Isophthalic acid prepolymer was prepared by the addition of 50 g of the acid powder to 500 mL of refluxing acetic anhydride with constant stirring. After 10

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min at reflux, the prepolymer product in solution was filtered to remove unreacted isophthalic acid and rotoevaporated to dryness at 65 °C. The remaining liquid was mixed with 20 mL of dry toluene and allowed to crystallize at room temperature for 24 h. The white precipitate was filtered and washed with 200 mL of isopropyl ether to yield 40 g of the product. The melting point of the resultant prepolymer product was 105–120 °C; M_n = 580 and M_w = 820. Infrared absorption frequencies (film on NaCl, cm^{-1}) were $\nu_{C=O}$ 1790 (s, s) and 1720 (s, s), $\nu_{C=C}$ 1600 (s, w); ^{1}H NMR chemical shifts (CDCl$_3$, ppm) were δ 8.7 (d, 6 Hz, 1 H), 8.3 (m, 2 H), 7.6 (t, 4 Hz, 1 H), and 2.4 (s, 6 H).

Attempts to prepare terephthalic acid prepolymers under similar conditions yielded a high melting point product (>300 °C), which was not useful for polymerization at 180 °C. Therefore, mixed prepolymers containing terephthalic acid were prepared and used for polymerization.

Mixed prepolymers containing terephthalic acid were prepared from the reaction of 50 g of the mixture of acids in 500 mL of refluxing acetic anhydride for 10 min following the procedure for the synthesis of IPA prepolymer. The data analysis for the mixed prepolymers is as follows.

IPA–TA 80:20 mixed prepolymer: mp 90–120 °C; IR (film on NaCl, cm^{-1}) $\nu_{C=O}$ 1790 (s, s) and 1720 (s, s), $\nu_{C=C}$ 1600 (s, w); molecular weight (by GPC) M_n = 640, M_w = 910.

TA–FA 45:55 mixed prepolymer: mp 80–85 °C; IR (film on NaCl, cm^{-1}) $\nu_{C=O}$ 1790 (s, s) and 1720 (s, s), $\nu_{C=C}$ 1600 (s, w); molecular weight (by GPC) M_n = 540, M_w = 850.

TA–CPP 30:70 mixed prepolymer: mp 105–120 °C; IR (film on NaCl, cm^{-1}) $\nu_{C=O}$ 1790 (s, s) and 1720 (s, s), 1600 (s, w); molecular weight (by GPC) M_n = 720, M_w = 1050.

TA–SA 30:70 mixed prepolymer: mp 65–71 °C; IR (film on NaCl, cm^{-1}) $\nu_{C=O}$ 1800 (s, s) and 1730 (s, s), $\nu_{C=C}$ 1600 (s, w); molecular weight (by GPC) M_n = 810, M_w = 1550. All prepolymers were white solids, soluble in dichloromethane or chloroform.

Polymers were synthesized by melt condensation using the appropriate mixtures of acetic acid mixed-anhydride prepolymers. Polymerizations were carried out at 180 °C under a vacuum of 0.1 mmHg for 90 min.[8] When catalyst was used, 2% by weight of finely powdered cadmium acetate dihydrate was mixed with the prepolymers prior to polymerization.

Solubility Test. A 10-mg sample of polymer powder was added to 10 mL of solvent (0.1% w/v) and allowed to dissolve for 2 h at room temperature with constant stirring. Solubility was determined as the polymer completely dissolved in solution. Polymers that were soluble were tested for a higher solubility by dissolving various amounts of polymer in 10 mL of solvent. The solubility of the polymers was determined in dichloromethane, chloroform, carbon tetrachloride, ethyl acetate, butyl acetate, toluene, hexanes, and diethyl ether. As used here, "practically insoluble" is defined as less than 0.5% (w/v) and "highly soluble" as greater than 15% (w/v).

Stability Studies. Polymer samples (200 mg), sealed in glass ampules under dry argon, were kept at 4 and 25 °C and the molecular weights were followed by GPC over a 6-month period. The stability of the polymers to γ-irradiation was conducted on 200-mg compression-molded circular wafers irradiated in dry ice with a 2.4-Mrad dose (^{60}Co, Isomedix Inc., Morton Grove, IL). The samples were analyzed by IR, ^{1}H NMR, and GPC to determine possible chemical changes.

Degradation and Release Studies. Polymer disks, weighing 200 mg and 1 × 14 mm in size, were prepared by compression molding the polymer powder at 30 000 psi and 50 °C for 1 min using a Carver laboratory press (Menomonee Falls, WI). Alternatively, disks were prepared by molding the melted polymer into a Teflon mold. The disks were placed in a 100 mL of 0.1 M phosphate buffer (pH 7.4) at 37 °C with constant orbital shaking at 75 rpm. The solution was replaced periodically with fresh buffer. Polymer degradation was estimated from the weight loss of the sample and quantitation of the degradation products by UV absorption at 254 nm. The compositions of the degradation products and the polymers were determined by ^{1}H NMR analysis after lyophilization of the solutions [CPP: (K$_2$CO$_3$ in D$_2$O, ppm) δ 7.86 (d, 9 Hz, 4 H), 7.04 (d, 9 Hz, 4 H), 4.30 (t, 6 Hz, 4 H), 2.80 (t, 6 Hz, 2 H); IPA (K$_2$CO$_3$ in D$_2$O, ppm) δ 8.29 (s, 1 H), 7.98 (d, 7 Hz, 2 H), 7.53 (t, 7 Hz, 1 H)]. For incorporation of indomethacin, 5% by weight of indomethacin powder was mixed with the polymer powder and compressed into disks. Indomethacin release was monitored by HPLC.[9]

Animal Biocompatibility Studies. Poly(CPP–IPA) (1:1) was tested for its potential irritation in comparison to clinical grade poly(CPP–SA) (20:80), Biodel (Nova Pharmaceutical Corp., Baltimore, MD) and Vicryl (Ethicon, Inc., Somerville, NJ) synthetic absorbable surgical suture. A sham procedure was used as control. The test articles were cut into approximately 10 × 1 × 1 mm sections and sterilized under UV light for 30 min prior to implantation.

Twelve male New Zealand white rabbits were placed on study and assigned to four subgroups of three rabbits each. The test articles were implanted into the paravertebral muscle on one side of the spine and into the subcutaneous tissue on the other side of the spine utilizing sterile surgical technique. The rabbits received a total of eight implants each. Each test article was implanted once intramuscularly and once subcutaneously in each subgroup and was evaluated a total of three times by each route at each sacrifice interval. Detailed observations for overt toxicity and signs of bleeding, swelling, or infection of the incision site were conducted daily. At 1, 2, 3, and 4 weeks following implantation the appropriate rabbits were sacrificed and gross necropsy examination of the tissues surrounding the implant sites was conducted. All implant sites were then labeled and fixed in 10% neutral buffered formalin and histological examination of the implant sites was conducted.

Results

Copolymers of isophthalic acid, terephthalic acid, 1,3-bis(*p*-carboxyphenoxy)propane, and fumaric acid were synthesized by melt condensation.[8] The optimal polymerization conditions were 180 °C under a vacuum of 0.1 mmHg or less for 90 min. Longer reaction times or higher reaction temperatures did not increase the polymer molecular weight. The properties of various copolymers are summarized in Table I. For comparison, the properties of the corresponding aromatic homopolymers are given in Table II. The homopolymers were insoluble and melted at temperatures above 250 °C. However, copolymerization with as little as 10 mol % of a second aromatic diacid resulted in a drastic change in the properties of the polymer. These polymers became amorphous, were highly soluble in dichloromethane, and had melting points below 125 °C. The polymers had molecular weights of up to 35 000 and intrinsic viscosities of 0.41 dL/g.

The effect of cadmium acetate, a known catalyst in polyanhydride synthesis,[8] on the polymerization is shown in Table III. Polymerization in the presence of a catalyst resulted in higher molecular weight polymers in shorter times; longer polymerization times did not affect the polymer molecular weight.

The polymers described in Table I formed transparent films when cast from solution or melt compressed. The terpolymers containing sebacic acid (Table IV) had a higher molecular weight and were more pliable than the aromatic copolymers.

Stability. Samples of poly(CPP–IPA) (33:67 and 11:89), poly(TA–IPA) (20:80), and poly(CPP–IPA–SA) (16:66:18) were used for the storage and γ-irradiation studies. Polymer samples were stored in glass ampules under argon at 4 and 25 °C. Insignificant changes in the molecular weight of the polymers were observed after 6 months at 4 °C. The 25 °C samples show a small decrease in molecular weight and in the solubility of the polymers in dichloromethane. IR analysis of the samples revealed partial hydrolysis of the polymers as noted from the appearance of a small peak at 1700 cm^{-1}, attributed to the carbonyl group of the resultant carboxylic acid.

Table I
Physicochemical Properties of Aromatic Copolyanhydrides[a]

polymer	mp, °C	heat capac, J/g	solubility,[b] % w/v	molecular weight M_n	molecular weight M_w	$[\eta]$, dL/g
P(CPP-IPA) (11:89)	110–115	2.59	>20	13 700	34 500	0.41
P(CPP-IPA) (33:67)	95–104	3.50	>20	12 800	31 600	0.39
P(TA-IPA) (20:80)	105–112	1.06	>20	10 200	24 700	0.35
P(IPA-FA) (75:25)	120–126	0.37	>20	8 100	19 500	0.31
P(IPA-FA) (50:50)	75–80	0.84	>20	9 400	22 100	0.34
P(IPA-FA) (20:80)	100–107	2.10	>20	7 800	17 300	0.28
P(CPP-FA) (35:65)	72–77	0.96	>20	7 200	14 800	0.24
P(TA-FA) (45:55)	200–205	43.20	<0.5	[c]	[c]	[c]
P(TA-FA) (20:80)	130–137	3.45	>20	7 500	22 300	0.28

[a] The melting points and the heat capacities were determined by DSC and verified by TMA. Molecular weights were estimated by GPC relative to polystyrene standards. Intrinsic viscosities were measured in dichloromethane at 25 °C. [b] Solubility in dichloromethane or chloroform at 25 °C. [c] The polymer was insoluble.

Table II
Physical Properties of Aromatic Polymers

polymer	mp, °C	crystallinity, %	solubility[d]
TA	400[a]	60	<0.1
CPP	256[a]	61[c]	<0.1
IPA	259[a]	50	<0.1
FA	246[b]	60[c]	<0.1
CPP–SA (70:30)	203	crystalline	<0.5
IPA–SA (70:30)	198	crystalline	<0.5
TA–SA (70:30)	340	crystalline	<0.5
FA–SA (70:30)	148	crystalline	<0.5

[a] Reference 5. [b] Reference 7. [c] Reference 10. [d] Solubility (% w/v) was determined in dichloromethane, chloroform, and carbon tetrachloride.

Table III
Cadmium Acetate Catalysis in the Polymerization of Aromatic Copolymers[a]

reactn time, min	no catalyst M_w	no catalyst M_n	with catalyst[b] M_w	with catalyst[b] M_n
	Poly(CPP-IPA) (11:89)			
20	11 200	5 600	24 300	11 600
40	14 800	7 800	24 800	12 200
60	17 400	7 900	24 400	12 300
90	18 700	8 970	25 100	12 100
	Poly(TA-IPA) (20:80)			
20	7 800	4 600	13 400	8 100
40	10 300	5 700	13 100	8 900
60	11 700	6 400	14 500	8 200
90	12 900	6 700	12 900	8 300

[a] CPP and IPA prepolymers (11:89 molar ratio), or terephthalic–isophthalic mixed prepolymer (20:80 ratio), polymerized at 180 °C under vacuum of 0.1 mmHg. Molecular weight was determined by GPC. [b] Cadmium acetate dihydrate (2% by weight) was mixed with the prepolymers and polymerized.

Polymer samples were γ-irradiated, and changes in the polymer molecular weight and the IR and ^{1}H NMR spectra were studied. No changes were observed in the molecular weight or the IR and ^{1}H NMR spectra. This indicates that the polymers can be sterilized for biomedical purposes using γ-irradiation.

Solubility and Thermal Properties. The thermal and solubility properties of aromatic copolymers are described in Figures 1 and 2. The crystallinity of these polymers was estimated from their heat capacities, which were determined by DSC.[10] As expected, a decrease in crystallinity resulted in a decrease in melting point and an increase in solubility. All copolymers were practically insoluble in the common solvents, carbon tetrachloride, ethyl acetate, butyl acetate, toluene, hexanes, and diethyl ether.

Table IV
Physicochemical Properties of Aromatic Terpolymers[a]

polymer	molecular weight M_n	molecular weight M_w	mp, °C	heat capac, J/g
CPP-IPA-TA (50:40:10)	10 700	25 200	111	2.54
CPP-IPA-TA (25:60:15)	12 500	27 800	115	2.73
FA-TA-IPA (55:9:36)	6 600	15 400	68	0.85
FA-TA-SA (56:16:28)	7 900	16 300	98	2.97
FA-CPP-SA (55:25:20)	8 200	15 900	47	0.24
TA-CPP-SA (24:48:28)	12 700	31 800	153	6.70
CPP-IPA-SA (15:58:27)	14 600	39 700	56	2.13
CPP-IPA-SA (17:66:16)	15 200	36 100	83	0.43
TA-IPA-SA (17:66:16)	10 800	27 500	133	0.45

[a] Molecular weights were determined by GPC relative to polystyrene standards; the melting points were determined using DSC/TMA analysis. All polymers were soluble in dichloromethane (>15% w/v).

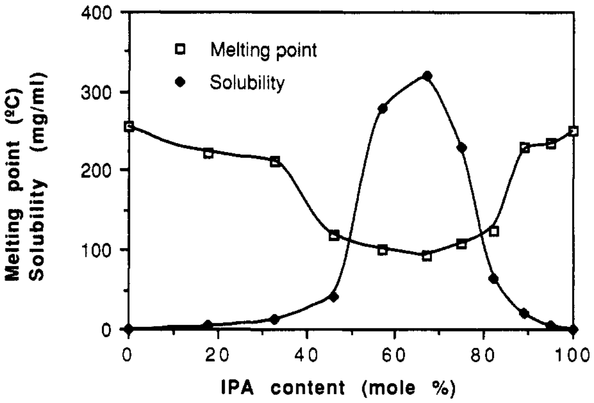

Figure 1. Solubility and melting point of CPP–IPA copolymers in dichloromethane.

Copolymers of isophthalic acid or fumaric acid containing between 10 and 60 mol % CPP were amorphous, highly soluble in dichloromethane or chloroform, and melted at temperatures below 120 °C. The copolymers containing progressively more than 60% CPP were more crystalline, had a higher melting point, and were less soluble than those containing lower fractions of CPP. Alternatively, copolymers containing 15–40% terephthalic acid were soluble and melted at relatively low temperatures. Copolymers of IPA containing 10–90% fumaric acid were soluble and melted at temperatures below 100 °C. The copolymers containing FA were dark and decomposed at temperatures above 230 °C. Similar properties were reported for copolymers of FA with aliphatic diacid monomers.[7]

All copolymers had a single broad transition temperature with a low heat capacity (Table I), indicative of amorphous polymers.[10] X-ray diffraction of several of

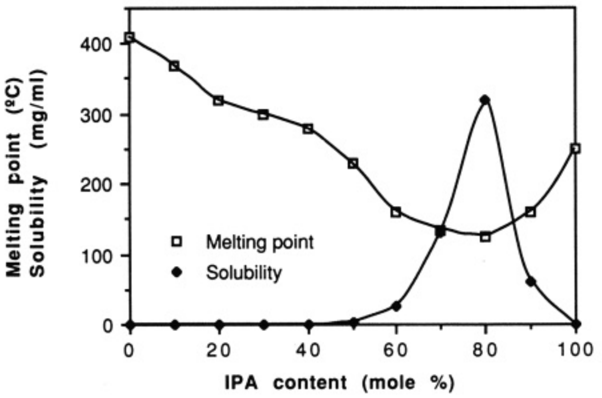

Figure 2. Solubility and melting point of TA–IPA copolymers in dichloromethane.

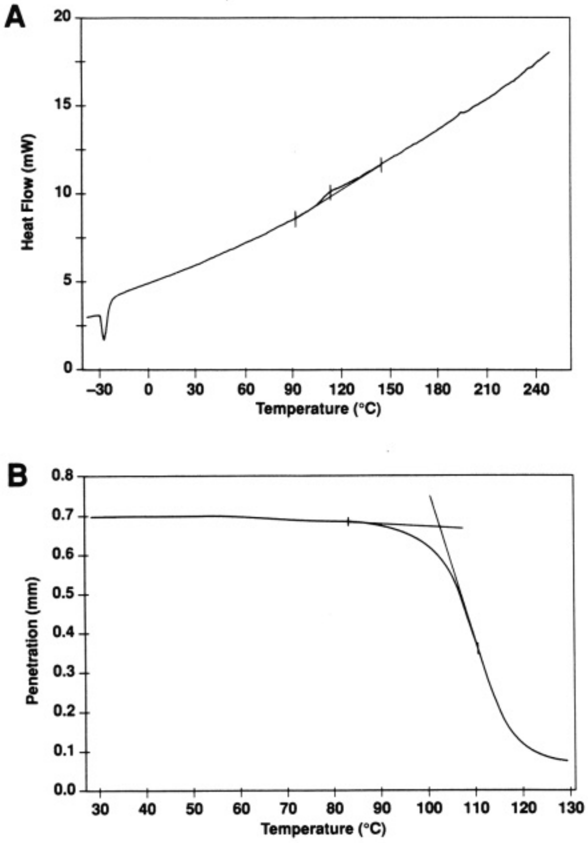

Figure 3. Thermal analysis of poly(CPP–IPA) (11:89): (A) DSC chromatogram; (B) TMA chromatogram.

these copolymers verified low crystallinity (<5%). As seen in Figure 3, the aromatic copolymers show a small transition change in the DSC at 100–120 °C with no other transitions up to 350 °C. However, the copolymers show a significant change in the thermomechanical properties at 100–120 °C as determined by TMA (Figure 3). At these temperatures the polymer is transformed from a glassy hard material to a viscous mass.

Adding a third monomer to form terpolymers further decreases the melting temperatures and crystallinity and increases the solubility of the polymers (Table IV). Terpolymers containing 10–25% sebacic acid are pliable, soluble, and melt at low temperatures. In comparison, the respective copolymers of CPP, IPA, or FA and 30 mol % sebacic acid are insoluble and melt at high temperatures (Table II).

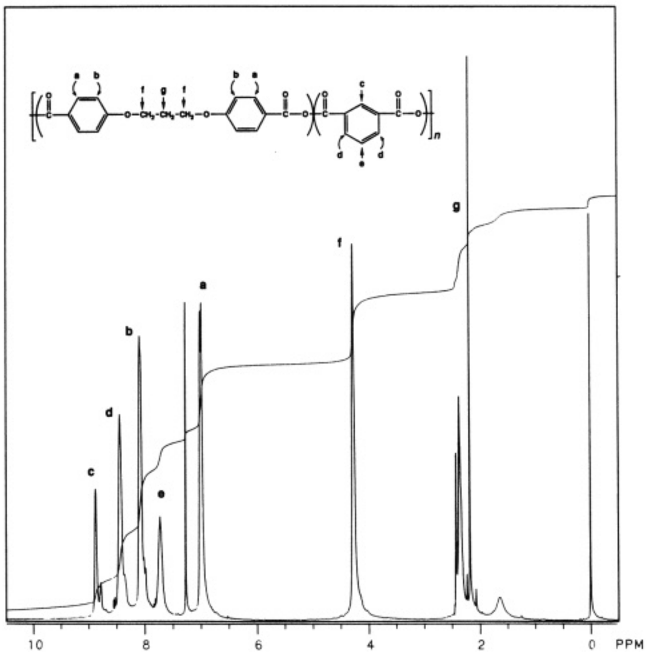

Figure 4. ^{1}H NMR spectrum of poly(CPP–IPA) (43:57).

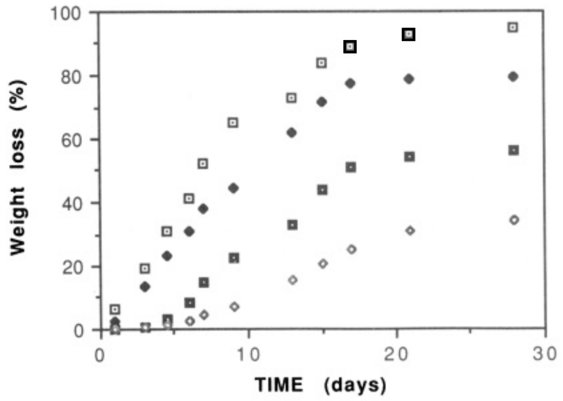

Figure 5. Hydrolytic degradation of CPP–IPA copolymers. Degradation in phosphate buffer (pH 7.40) at 37 °C: ⊡, 89% IPA; ◆, 67% IPA; ■, 46% IPA; ◇, 18% IPA.

Spectral Analysis. The aromatic copolymers are characterized by peak absorbances at 3070 (C–H stretching of unsaturated bonds), 1790 and 1720 (aromatic anhydride carbonyls), and 1600 cm^{-1} (aromatic ring). Polymers containing aliphatic residues, such as CPP and aliphatic diacids, also show absorbancies at 2920 cm^{-1} with a shoulder at 2840 cm^{-1}, characteristic for aliphatic methylene groups.

The composition of the copolymers was determined by ^{1}H NMR analysis. The ratio of CPP and IPA units in poly(CPP–IPA) is determined from the peak integrations at 7.77 (1 H; IPA) and 4.26 ppm (4 H; CPP) (Figure 4). The composition of copolymers containing fumaric acid is determined from the peak ratios of the FA unsaturated protons at 6.1 ppm and the representative peak of the respective aromatic comonomer. The ^{1}H NMR analysis of the 20:80 terephthalic–isophthalic copolymer is (CDCl$_3$, ppm) δ 7.77 (m, 1 H), 8.26 (m, 1 H), 8.52 (m, 2 H), and 8.88 (m, 1 H). The ratio of the peak integrations at 8.26 and 7.77 ppm, representing terephthalic acid and isophthalic acid, respectively, fits the copolymer compositions.

Hydrolytic Degradation and Drug Release. The hydrolytic degradation as a function of time of several CPP–IPA copolymers is shown in Figure 5. Poly(IPA) is completely degraded and eliminated in 4 weeks, whereas during the same time only 4% of the poly(CPP) is eliminated. The copolymers containing up to 25 mol %

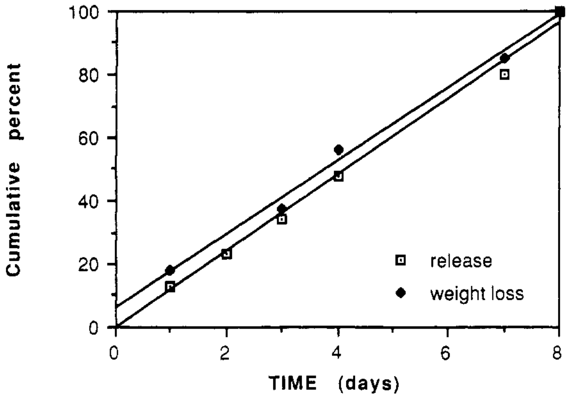

Figure 6. Degradation and indomethacin release from poly(TA-IPA) (20:80) (linear curve fit, r = 0.995).

Table V
Analysis of the Remaining CPP-IPA Copolymers After 4 Weeks of Degradation[a]

IPA-CPP, mol %	wt loss, %	CPP content,[b] %	anhydride bonds,[c] %
100:0	100	0	0
95:5	97	100	0
89:11	85	100	32
82:18	80	100	51
75:25	75	100	50
67:33	67	100	48
57:43	44	100	49
33:77	34	100	48

[a] Degradation of injection-molded disks in phosphate buffer (pH 7.4) at 37 °C. The weight loss, composition, and anhydride bond content were determined on the remaining polymer after 4 weeks of degradation. [b] Determined by ^{1}H NMR of the remaining polymer after a complete hydrolysis in 1 M K_2CO_3. [c] Determined by IR from the ratio of the acid and anhydride peak heights at 1700 and 1780 cm^{-1}, respectively; % anhydride bonds = 100[1 − (acid peak/(acid peak + anhydride peak))].

CPP degrade at the same rate as the poly(IPA). Analysis of the remaining polymers after 4 weeks of degradation showed significant absorption in the IR spectra at 1720 and 1780 cm^{-1}, attributed to intact anhydride bonds (Table V). The remaining polymers contained only CPP monomers and oligomers, as determined by ^{1}H NMR.

The degradation of poly(TA-IPA) (20:80) is shown in Figure 6. The polymer degrades linearly in 8 days as compared to 4 weeks and several months for the respective IPA and TA homopolymers. The increase in the degradation rate of this polymer is probably due to the decrease in crystallinity[12] and the higher water solubility of its degradation products.

The degradation rate of IPA-FA copolymers decreased as the IPA content increased and was intermediate between the degradation times for IPA and FA homopolymers, which were 3 and 28 days, respectively. Drug release from these polymers is shown in Figures 6 and 7. For both polymers the drug release follows the degradation of the polymers.

Biocompatibility of Aromatic Copolymers. A preliminary implantation test in male New Zealand white rabbits was conducted to evaluate the tissue irritation potential (biocompatibility) of test articles of poly(CPP-IPA) (50:50) and poly(CPP-IPA-SA) (50:34:16) in direct contact with muscle and subcutaneous tissue. Clinical grade poly(CPP-SA) (20:80) and Vicryl absorbable surgical suture were used for comparison, and a sham procedure was used as control.

There were no significant clinial signs or abnormalities of the incision site observed during the study period. There were no remarkable changes or differences observed in the body weights during the study.

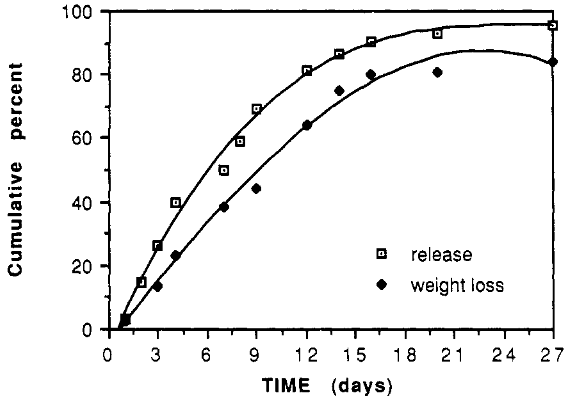

Figure 7. Degradation and indomethacin release from poly(CPP-IPA) (33:67).

Macroscopic pathology shows no difference between the various test materials with respect to grossly observable reactions at the implantation sites. No abscesses were observed in any sites of implantation. Microscopic pathology of the sites of implantation shows that at 1 week postimplantation all articles produced trace to mild necrosis and inflammation at the intramuscular implantation site, whereas Vicryl produced less inflammation or necrosis. For any given material, more necrosis was produced at the intramuscular site than at the subcutaneous site. At the 2-week interval, there was generally less response than at 1 week, and at 3 weeks the test articles were less irritating than the same materials at 2 weeks. At 4 weeks, no meaningful differences could be seen between the various implants or the sham procedure.

The aromatic copolymers were slightly more irritating than Vicryl after 1 week postimplantation, but this irritation decreased at 2 weeks, with no irritation at 4 weeks.

Discussion

Aliphatic polyanhydrides usually melt at temperatures below 100 °C and are highly soluble in dichloromethane or chloroform. Aromatic homopolyanhydrides are practically insoluble in common organic solvents and melt at higher temperatures. Both aliphatic and aromatic homopolyanhydrides possess high crystallinity, usually above 50%.[10] Copolymers of aliphatic and aromatic diacids are, in general, soluble in dichloromethane and chloroform; however, the solubility decreases with increase in the aromatic content and polymers containing 70 mol % or more of the aromatic comonomer are practically insoluble (Table II).

Four monomers were used in this study to demonstrate the utilization of the copolymerization approach to develop new and useful bioerodible polymers from common unsaturated and aromatic monomers. The physical properties of the copolymers are dependent on the copolymer composition, particularly the monomer structure. Table VI summarizes the range of soluble and low-melting copolymers prepared from the studied monomers. As expected, the tendency of the monomers used for form an insoluble and crystalline polymer is in the following order: TA > CPP > FA > IPA, where copolymers containing terephthalic acid with the "rigid" structure are the most crystalline and insoluble, and copolymers of isophthalic acid with the nonsymmetric structure are the least crystalline. Assuming random copolymers, as found for the aliphatic copolymers,[12] one can estimate the probability for forming a soluble copolymer for a given pair of

Table VI
Soluble and Low-Melting Aromatic Copolymer Compositions[a]

copolymer	monomer content, %	copolymer	monomer content, %
TA–CPP	20–30 TA	IPA–FA	10–90 IPA
TA–FA	10–35 TA	TA–SA	0–30 TA
TA–IPA	10–40 TA	CPP–SA	0–65 CPP
CPP–IPA	10–60 CPP	IPA–SA	0–70 IPA
CPP–FA	15–50 CPP	FA–SA	0–70 FA

[a] Polymers in this range have a solubility of >1% in dichloromethane and melting points below 150 °C. The estimated range is in mole percent with an error of ±5%.

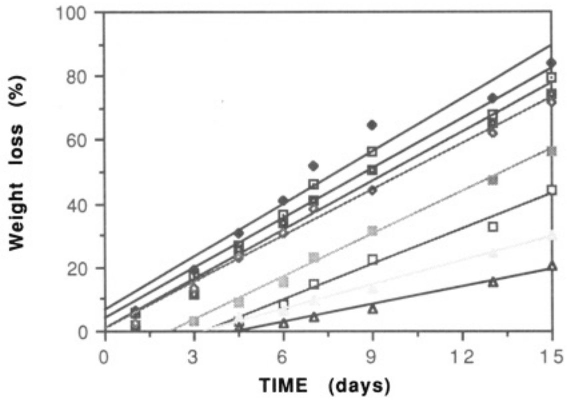

Figure 8. Degradation rate of CPP–IPA copolymers. Degradation in phosphate buffer (pH 7.4) at 37 °C: ◆, poly(IPA); □, 89% IPA; ■, 75% IPA; ◇, 67% IPA; ▣, 57% IPA; □, 46% IPA; ▲, 33% IPA; △, 18% IPA.

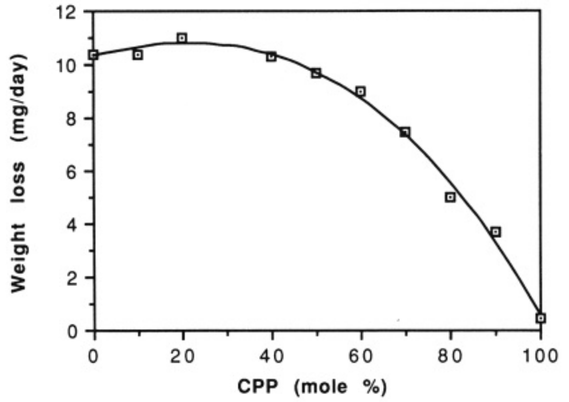

Figure 9. Degradation rate of poly(CPP–IPA) as a function of CPP content. Degradation in phosphate buffer (pH 7.4) at 37 °C (polynomial curve fit $y = 10.356 + 0.064X - 0.0029X^2 + 0.0000128X^3$, $r = 0.995$).

monomers with structures similar to the monomers used in this study (Table VI). For aromatic monomers to form a soluble polymer, it seems that at least 1 out of 10 monomer units in the polymer must be different.

The hydrolytic degradation properties of the aromatic copolymers were demonstrated using various compositions of IPA and CPP copolymers. Increasing the CPP content in the copolymer slows the degradation of the polymer (Figures 8 and 9). The degradation profile can be divided into two phases, attributed to the two different regions in the polymer matrix, the CPP region and the IPA region. In the first phase, the copolymers are degrading at a nearly constant rate for about 15 days (Figures 8 and 9, $r > 0.98$). During that time the IPA region is degraded and released from the matrix, leaving the CPP region, which is slowly degrading much like the CPP homopolymer. ^{1}H NMR analysis of the composition of the degradation products in solution with time shows that the polymer is homogeneously degrading and for the first 10 days is releasing exclusively the isophthalic acid, after which the CPP monomer is released (Figure 10). Similar data were reported for the degradation of the copolymers of CPP and sebacic acid.[11] The drug release from these polymers is a result of the degradation of the polymer and diffusion of the drug through the polymer matrix.

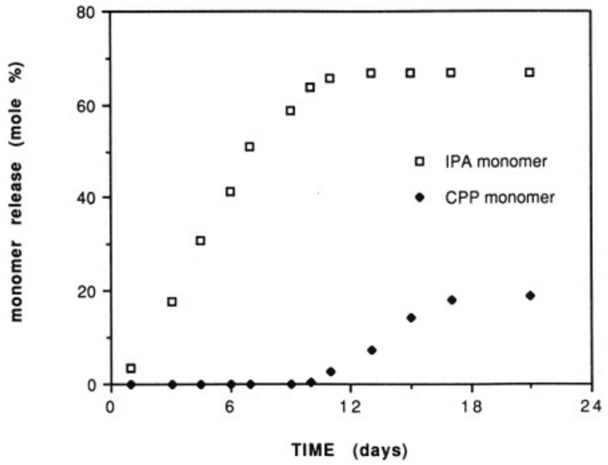

Figure 10. Composition of poly(CPP–IPA) (33:67) degradation products. Degradation in phosphate buffer (pH 7.4) at 37 °C.

In summary, a new class of purely aromatic polyanhydrides based on common aromatic diacids has been synthesized and characterized. Various polymers with desired physical properties have been produced from two or more aromatic acid monomers. These polymers are soluble in common organic solvents and melt at relatively low temperatures which makes them suitable candidates as carriers for drug delivery applications. Copolymers of IPA and CPP degrade in a homogeneous fashion to degrade and release IPA monomer, leaving the CPP to slowly degrade. The drug release from these polymers follows their degradation. Preliminary irritation tests show these polymers to have good biocompatibility.

The mechanical properties of the aromatic anhydride copolymers and its effect on the development of medical devices and drug delivery systems will be addressed in a subsequent publication.

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