Copolymerization and Polymer Blending of Trimethylene Carbonate and Adipic Anhydride for Tailored Drug Delivery

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ABSTRACT: The copolymerization in bulk and solution of trimethylene carbonate (TMC) with adipic anhydride (AA) as well as the blending of homopolymers are described. We show experimentally that the components are not copolymerizable but partially miscible, forming a microscopic dispersion without any visible signs of phase separation. Poly(adipic anhydride) (PAA) functions as a plasticizer, permitting an increase in the erosion rate by increasing the porosity and hydration. Drug delivery from the blends was evaluated. A statistical factorial model was designed to explore the influence of three important blend parameters and their interactions, making it possible to predict the erosion and drug-release behavior of the blend matrices. The PAA:poly(trimethylene carbonate) (PTMC) ratio and molecular weight of the polycarbonate component significantly influence the drug-release performance, mass loss, and degree of plasticization. The interaction among these factors also influences the blend properties. Plasticization of PTMC enhances the drug release to an extent that is dependent on the amount of PAA used. We demonstrate that blending offers a convenient alternative to copolymerization for the preparation of polymer matrices with predictable drug delivery. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 72: 227–239, 1999

Key words: screening design; poly(trimethylene carbonate); poly(adipic acid); drug delivery; degradable blend; copolymerization

INTRODUCTION

In the last decade, a variety of biocompatible polymers have been investigated for use as medical implants and for drug-delivery applications.[1] The use of degradable polymers has been favored because they eliminate the need for surgical removal after depletion. Linear aliphatic polycarbonates, such as poly(trimethylene carbonate) (PTMC), have been shown to be suitable for these applications, being biocompatible and degradable by simple hydrolysis, promoted *in vivo* by enzymatic activity.[2] PTMC displays high elasticity at room temperature but degrades slowly in aqueous solution, showing little molecular weight loss, sample weight loss, or change in morphology after several months.[3] Attempts to alter the degradation rate have been made by changing the chemical composition by copolymerization of trimethylene carbonate (TMC) with ε-caprolactone or D,L-lactide or by blending PTMC with other degradable homopolymers.[4–6]

This study describes the combination of TMC and adipic anhydride (AA) as a possible route to control the drug-release behavior of PTMC matrices. AA yields a fast-degrading, surface-eroding polyanhydride, the anhydride bond being more susceptible to hydrolysis than are the ester or

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carbonate bonds. Like other biocompatible polyanhydrides, it has been shown to be useful for drug-delivery applications, for example, microspheres used for ocular drug delivery.[7–9]

TMC and AA were copolymerized in bulk and solution to obtain block copolymers and statistical copolymers. Blends of homopolymers of PTMC and PAA were also prepared. The blending of polymers is an excellent means of combining desirable properties of different polymers, the process being superior to copolymerization in terms of simplicity and speed. Studies show that by blending polymers one can modify drug-release profiles[10–13] and prepare matrices with properties different from those of the original polymers.[14,15] When adding a low molecular weight polymer to a high molecular weight polymer, the former may plasticize the matrix.[6,16]

However, when dealing with blends, one always has to take into account the compatibility or, more often, the lack of compatibility. Two polymers, giving rise to a blend with properties analogous to those of a single-phase material, are considered totally miscible. When a blend shows signs of nonuniformity, for example, phase separation or opacity, it is termed noncompatible.[17] In some cases, the polymers give rise to a macroscopically uniform but microscopically heterogeneous material, thus showing partial miscibility. If the miscibility of polymers is hard to achieve, the reliable prediction of miscibility is more difficult still. A number of studies of polymer blending have been performed, showing that similarities in the chemical nature between two polymers or their monomers do not necessarily lead to miscibility.[10,18]

The performance of a polymer blend or a copolymer as a drug-delivery device depends on several variables, the most important being the ratio of the components: Other factors are the molecular weight, morphology, preparation technique, drug size and loading, sample geometry, pH, and temperature of the release medium. To detect variable interaction effects, a factorial design can be used, where the response is measured for all possible combinations of factors at two or more levels.[19] The factorial design needs fewer measurements than does the classical approach to give the same precision. These features have made factorial design an important tool for exploring organic synthesis.[20] This article describes a screening study for investigating variables likely to control the release and degradation characteristics and their influence on the polymer matrix properties and drug-delivery performance.

The objective of this study was to obtain a controllable drug-delivery matrix by polymer blending or copolymerization of TMC and AA. A statistical screening experiment was designed to identify the influential blend parameters and whether there are important interaction effects.

EXPERIMENTAL

Materials

The catalysts used in this work were *n*-BuLi, aluminum–isopropoxide, and $Sn(oct)_2$ from Aldrich Chemical Co. (Milwaukee, WI) and BF_3OEt_2 and Et_3N from Merck-Schuhardt (Darmstadt, Germany). Methanol, hexane, toluene, 1,2-dichlorobenzene, and CH_2Cl_2 from Merck-Schuhardt and THF from Riedel-de Haën (Seelze, Germany) were used as solvents.

For the preparation of PTMC, 1,3-propanediol (p.a.) was purchased from Merck-Schuhardt and diethyl carbonate (p.a.) was purchased from Aldrich Chemical Co. For the poly(adipic anhydride) (PAA) preparation, adipic acid (p.a.) was purchased from Merck-Schuhardt, and acetic anhydride (p.a.) from Riedel-de Haën. Amitryptiline served as a model drug and was obtained from Sigma Chemical Co. (St. Louis, MO).

Homopolymerization

PTMC was prepared by ring-opening polymerization of 1,3-dioxan-2-one (TMC) which was synthesized according to a method published by our group.[3] The monomer was polymerized in a dried, sealed 25-mL septum vial flushed with argon through a syringe. High molecular weight (HMW) and medium molecular weight (MMW) PTMCs were synthesized at 130 and 80°C for 5 and 24 h, respectively, using $Sn(oct)_2$ as an initiator ($M/I = 250$). Low molecular weight (LMW) PTMC was synthesized in toluene (5 mL/g monomer) at 80°C for 24 h using $AlCl_3$ as an initiator ($M/I = 250$). The polymers were recovered by dissolving them in CH_2Cl_2, precipitating in cold methanol, and filtering. They were dried to a constant weight *in vacuo*.

We previously reported on the synthesis of the cyclic monomer oxepan-2,7-dione from which PAA was prepared.[21] Polymerization was carried out in a dried, sealed 25-mL septum vial flushed with

argon through a syringe. The reaction continued for 2 h at ambient temperature using Et_3N as an initiator ($M/I = 250$). The product was isolated by dissolving the product in CH_2Cl_2 and precipitating in cold hexane. After filtration, the polymer was dried to a constant weight *in vacuo*.

Copolymerization

All polymerizations were carried out in dry vessels with continuous stirring. The molar ratio of the monomers was in every case 1 : 1. Aluminum isopropoxide, $Sn(oct)_2$, *n*-BuLi, BF_3OEt_2, and Et_3N were used as catalysts.

For the block copolymerizations, TMC was first added to a 50-mL glass flask together with the catalyst and, in some cases, a solvent. TMC was allowed to react in an inert atmosphere for some time before adding the AA. After the reaction had taken place, the products were dissolved in CH_2Cl_2 and isolated by precipitation in methanol, filtration, and drying to a constant weight *in vacuo*.

The statistical copolymerizations were carried out in dried and sealed septum vials, flushed with argon. Both monomers were added together with the catalyst, and sometimes with a solvent, through a syringe. The products were recovered as described for the block copolymerization.

Preparation of Blends

Blends were prepared using a solvent-mixing technique.[10] A 20 w/v % solution of each polymer in methylene chloride was prepared as well as a 10 w/v % solution of the drug in methylene chloride.

Five milliliters of the PTMC solution was then mixed with various amounts of the PAA solution and the drug solution to obtain the desired ratios of polymers and drug concentration in each blend. The organic solvent was removed by evaporation with constant stirring. The blends were subsequently dried to a constant weight *in vacuo.* The drug content in the dry blends varied from 5 to 15 wt %.

Factorial Design for Statistical Variable Analysis

Multilinear regression of a two-level three-factor screening model was used to study the PTMC–PAA blends. Three blend parameters likely to influence significantly the blend degradation behavior and drug-release rate were identified: (x_1) the PAA-to-PTMC weight ratio in the blend, (x_2) the molecular weight of PTMC, and (x_3) the content of the drug incorporated into the blend. Blends were varied from a high (+) to a low (−) level according to the plan shown in Table I. All experiments were duplicated. The response data, y_i, that is, the experimental results, were related to the experimental variables, x_k, using an interaction model[19]:

Table I Factorial Design for Statistical Variable Analysis

	Factors		
Exp. No.	PAA Content (%)	M_n(PTMC) (g/mol)	Drug Load (wt %)
b1	20	17,000	5
b2	80	17,000	5
b3	20	150,000	5
b4	80	150,000	5
b5	20	17,000	15
b6	80	17,000	15
b7	20	150,000	15
b8	80	150,000	15
b9	50	63,500	10
b10	50	63,500	10
b11	50	63,500	10

$$y_i = \beta_0 + \sum \beta_k x_k + \sum\sum \beta_{km} x_k x_m + \sum \beta_{kk} x_k^2 + \varepsilon_i \qquad k \neq m$$

The model lack of fit and confidence intervals were sufficiently small to determine what factors are significant, synergistic effects, and in which direction variables influence the result. *Modde 3.0* software (developed by Umetri AB) was used for the modeling and calculations.

In Vitro Degradation

The blends were pressed into 0.5-mm thin films using a Schwabenthan Polystat 400S. Circular samples, ∅ 5 mm, were punched, weighed, and immersed in 20 mL of 0.1*M* phosphate buffer solution (pH 7.4). Degradation was then allowed to proceed at 37°C with gentle shaking motions. The buffer was changed four times a day to keep the pH constant and to maintain sink conditions. Samples were removed from the degradation medium at various time intervals, dried to a constant weight, and weighed prior to analysis.

Polymer Characterization

UV-Vis Spectroscopy

The buffer solution was analyzed for release of the model drug by measuring the extinction at 240 nm using a 8451A diode array spectrophotometer from Hewlett–Packard.

Composition Analysis

A Bruker Avance DMX 500 ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrometer was used to analyze the compositions. Samples were dissolved in deuterochloroform (Aldrich Chemical Co.) in 5-mm-o.d. sample tubes.

Infrared Spectroscopy

All polymers were characterized using a Perkin–Elmer Spectrum 200 FTIR spectrometer with an ATR (golden gate) sample probe.

Differential Scanning Calorimetry

For the thermal analyses, a Mettler Toledo DSC 820, connected to an RP100 cooling unit from Labplant, England, was used. Samples were sealed into 40-μL aluminum pans and spectra were recorded from -35 to 110°C at a heating rate of 10°C min^{-1}. The second heating scan was used for the calculations.

Size-Exclusion Chromatography

The molecular weight prior to and after degradation was monitored with a Waters apparatus. A Waters 6000A pump with five Ultrastyralgel® columns (10^5, 10^4, 10^3, 500, and 100 Å pore sizes) and chloroform as the eluent, with a flow rate of 1.0 mL/min, were used at 25°C with a Waters RI 401 refractive index detector. Polystyrene standards with narrow molecular weight distributions (M_w/M_n = 1.06) were used to calibrate the system.

Surface Morphology

The surface morphology of the films was examined by scanning electron microscopy (SEM) using a JEOL JSM 5400 scanning microscope. Samples were mounted on metal stubs and sputter-coated with gold–palladium (Denton Vacuum Desc II).

RESULTS AND DISCUSSION

Homopolymerizations

PTMC was prepared by ring-opening polymerization of TMC. ^{1}H-NMR ($CDCl_3$): δ = 2 ppm (qv), δ = 4.25 ppm (t). HMW PTMC, M_n = 150,000 g/mol, appeared hard, white, and nonsticky with a T_g of -14°C. MMW PTMC, M_n = 63,500 g/mol, was white and nonelastic with a T_g of −16.8°C. LMW PTMC, M_n = 17,000 g/mol, was soft and somewhat sticky with a T_g of −20.9°C. FTIR spectroscopy showed a carbonyl absorption at 1736 cm^{-1}.

Anionic ring-opening of oxepan-2,7-dione yielded a white powder of PAA. The polymer is semicrystalline, T_m = 75.8°C and ΔH = 85.8 J/g. ^{1}H-NMR ($CDCl_3$): δ = 1.75 ppm (m), δ = 2.5 ppm (m). The polymer has LMW, M_n = 1320 g/mol, due to rapid termination during polymerization.[21] An absorption doublet at 1800 and 1741 cm^{-1}, characteristic of the anhydride bond in aliphatic polyanhydrides, was revealed by FTIR spectroscopy.

Copolymerizations

TMC and AA were copolymerized in bulk and solution with aluminum isopropoxide, Sn(oct)$_2$, n-BuLi, BF_3OEt_2, and Et_3N as catalysts. For the block copolymerizations, the TMC monomer was reacted first, since the anionic chain end formed during the ring-opening of TMC is expected to be more reactive than the resonance-stabilized propagating chain end of AA. The results from block copolymerizations are given in Table II. No formation of a copolymer was detected, although the synthesis conditions were varied over a broad range in terms of temperature, solvent, reaction time, and type of initiator. The absence of bond formation between the anhydride and carbonate units was verified by FTIR, ^{1}H-NMR, and SEC characterization of the products. SEC chromatograms showed two separated peaks arising from a fraction of HMW PTMC mixed with a fraction of LMW PAA. ^{1}H-NMR spectra of the copolymerization products showed that only homodiads corresponding to PTMC and PAA, respectively, are present in the spectrum. No peaks from AA–TMC or TMC–AA heterolinkages were detected. FTIR analysis sustained that the product consists of a mixture of homopolymers rather than a copolymer. The molecular weight of the PTMC fraction is, however, lower at longer reaction times, showing a tendency to degradation. Obviously, the PTMC chain cannot function as a macroinitiator for AA as was reported for ε-caprolactone and AA in toluene.[22] The monomers frequently do not reach full conversion. Detectable amounts of unreacted monomer, especially TMC, are present in the products.

The results from statistical copolymerizations are given in Table III. In contrast to the block

Table II Conditions and Results of the Block Copolymerization of Equimolar Amounts of 1,3-Dioxan-2-one (TMC) and Oxepan-2,7-dione (AA)

Exp. No.	Initiator	$[M]/[I]$[a]	Solvent	T (°C)	t (h)[b]	M_w	M_w/M_n	Total Yield (%)	IR Analysis	NMR Analysis
1	*n*-BuLi	250	Toluene	25	2 + 2	700	1.2	—	PAA + PTMC	PAA + PTMC
						10,400	1.4			
2	*n*-BuLi	250	THF	25	2 + 2	2200	3.1	—	PAA + TMC	PAA + TMC
3	*n*-BuLi	250	Toluene	0	2 + 2	118,000	1.8	—	PTMC	PTMC + PAA
4	Aluminum isopropoxide	250	—	100	2 + 2	1600	1.5	—	PTMC + PAA	PTMC + PAA
						244,000	2.3	67		
5	Aluminum isopropoxide	250	CH_2Cl_2	25	20 + 2	600	1.8		PTMC + PAA	—
						17,400	2.1	53	+ AA	
6	Sn-oct	250	—	100	2 + 2	2979	1.16		PTMC + PAA	PTMC + PAA +
						19,389	1.25	79		TMC monomer
7	Et_3N	250	Toluene	25	3 + 1.5	1600	1.6	86	PAA + TMC	—
8	BF_3EtO_2	250	1,2-Dichlorobenzene	80	2 + 22	669	1.53		PTMC +	—
						33,545	1.53	46	PAA traces	

[a] Monomer-to-initiator ratio with respect to [TMC].
[b] Polymerization time for each monomer.

Table III Conditions and Results of the Statistical Copolymerization of Equimolar Amounts of 1,3-Dioxan-2-one (TMC) and Oxepan-2,7-dione (AA)

Exp. No.	Initiator	$[M]/[I]$[a]	Solvent	T (°C)	t (h)[b]	M_w	M_w/M_n	Total Yield (%)	IR Analysis	NMR Analysis
11	Sn-oct	250	—	85	5	3300	1.6	36	PAA	PAA + TMC
12	Sn-oct	250	—	100	24	1100	1.6	90	PAA + TMC	—
13	Sn-oct	250	1,2-Dichlorobenzene	100	24	900	1.5	98	PAA + TMC	—
14	Et_3N	136	—	25	0.5	1660	1.2	88	PAA + TMC	PAA + TMC
15	Et_3N	136	Toluene	25	22	1450	1.4	86	PAA + TMC	PAA + TMC
16	Al-isoprop.	530	—	80	48	2150	1.33	38	PAA	—
17	BF_3OEt_2	250	1,2-Dichlorobenzene	80	120	763	1.73	83.5	PAA	—

[a] Monomer-to-initiator ratio with respect to [AA].

copolymerizations, the monomers were added simultaneously to the vessel. This procedure favors the conversion of the AA monomer, being kinetically faster. The products contain only homopolymers of AA and essentially unreacted TMC monomer. No copolymer formation was observed in the bulk or in solution as verified by FTIR, ^{1}H-NMR, and SEC characterization of the products. The same has been reported for random copolymerizations of AA and ε-caprolactone, where the former rapidly precipitates as a homopolymer, leaving the ε-caprolactone unreacted.[22]

Preparation of PTMC–PAA Blends

Film samples with different relative amounts of PAA, PTMC (of different M_n values), and the drug were prepared by solvent evaporation. The films obtained were in every case opaque but macroscopically uniform, showing no signs of phase separation, thus implying partial miscibility.[18] The components were evidently evenly distributed in the films, since the same peak ratios for the PAA and PTMC absorbencies of the IR-spectra were obtained for different areas of the films.

Degradation of PTMC–PAA Blends

Samples of the PTMC–PAA blends were immersed in phosphate buffer (pH 7.4) at 37°C. PAA is known to undergo rapid hydrolytic chain cleavage under these circumstances, yielding adipic acid in a surface-eroding fashion.[6–8, 21]

Like polyesters and polyanhydrides, PTMC degrades by random chain scission. This process is, however, inherently slow, the carbonate linkage being less susceptible to hydrolysis than the corresponding ester and anhydride linkages. Complete hydrolysis of PTMC can take years.[3] As with other polyesters, PTMC is bulk-eroding, meaning that a homogeneous loss of the material occurs from the entire cross section of the matrix. Consequently, an increase in the degradation rate can be achieved by enhancing the bulk porosity and water permeability.[12,14] This can be brought about by blending PTMC with LMW PAA.[6] When hydrated, PAA rapidly degrades into monomer which diffuses out of the matrix. The diffusion process opens up pores and cracks further facilitating water penetration, which, in turn, will enhance bulk erosion. The development of pores was monitored by SEM. Prior to immersion, the film surfaces are dense and smooth. In contrast with films of pure PTMC, films of the blends do show

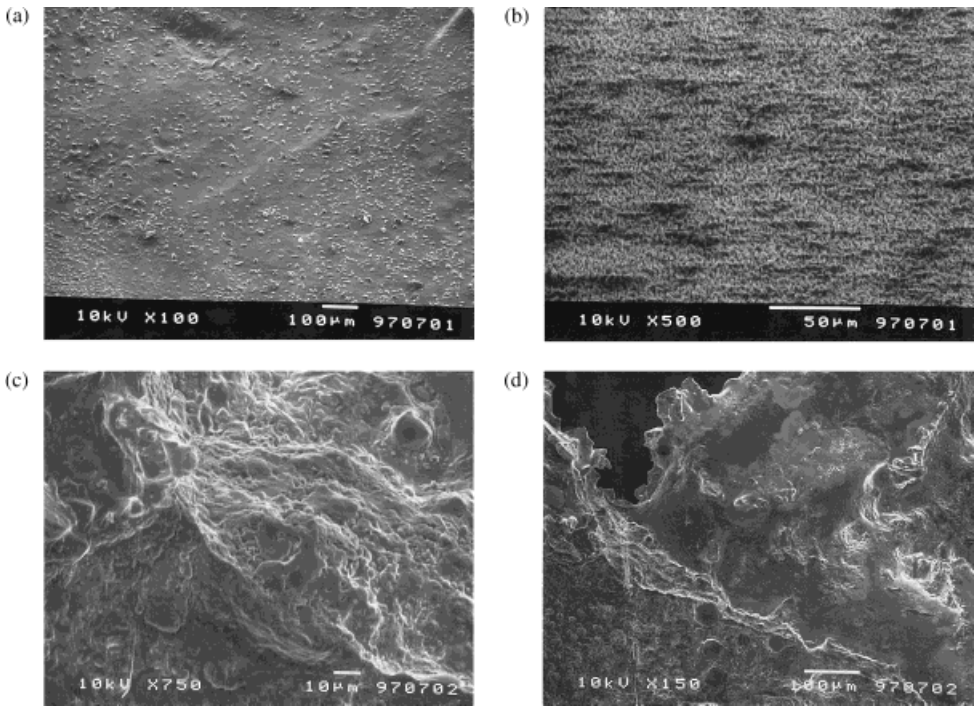

Figure 1 SEM pictures showing the topology of PTMC–PAA films at different stages of erosion: (a) blend of 50% PTMC (MMW) and 50% PAA before incubation; (b) the same material after 2 days of water exposure; (c) the same material after 3 weeks; (d) blend of 20% PTMC (LMW) and 80% PAA after 3 weeks.

some porosity, probably introduced during film preparation. Crystalline drug particles are visible, sparsely distributed about the surface [Fig. 1(a)]. Small cracks begin to show on the surface within 1 day of immersion; with time, the surface will take on a more granular appearance [Fig. 1(b)]. After 3 weeks, a considerable number of cracks and cavities are seen on the remains of the films [Fig. 1(c,d)]. A film containing a high amount of PAA tends to become weaker and more fragmented than films containing mostly PTMC. This is expected: The more material leaving the bulk, the more thinned-out is the matrix remaining. No visible difference in porosity was seen between films with different drug loading.

The matrix compositional changes with time were monitored by ^{1}H-NMR, confirming the degradation and erosion of PAA as illustrated in Figure 2. A clear diminution of the PAA peaks at 1.75 and 2.5 ppm is observed after 12 h. Complete disappearance of PAA occurs within 48 h. Small, multiple peaks at 2.4 and 1.6 are seen to develop within this period. Other small peaks, in the range 1.45–1.65 ppm, are also seen, assigned to drug and oligomeric degradation products. Extraction of these species is significantly slower than the degradation of PAA. Their peak areas steadily decline, but after 3 weeks, there are still remains of the degradation product trapped in the bulk. Blends containing a high amount of PAA would be expected to result in a higher amount of accumulated degradation products. The screening model confirms that the PAA content has a significant effect, whereas the other factors are relatively insignificant. Additionally, a significant interaction effect between the M_n (PTMC) and the PAA content can be seen to influence the results.

FTIR analysis gives complementary information on the compositional changes associated with the blend hydrolysis. Initially, the blends show absorption at 1800 and 1740 cm^{-1} stemming from PAA and PTMC, respectively. Figure 3 shows that a sharp peak at 1690 cm^{-1} is developed in the spectrum during blend degradation. This peak originates from the carboxylic end groups formed by chain cleavage of PAA,[9] its presence confirming the entrapment of degradation products in the matrices. The spectra for further-eroded matrices were identical to that for pure PTMC.

Mass loss from the films is apparent immediately after incubation, as seen in Figure 4. Erosion proceeds rapidly for 2 days, after which the rate of

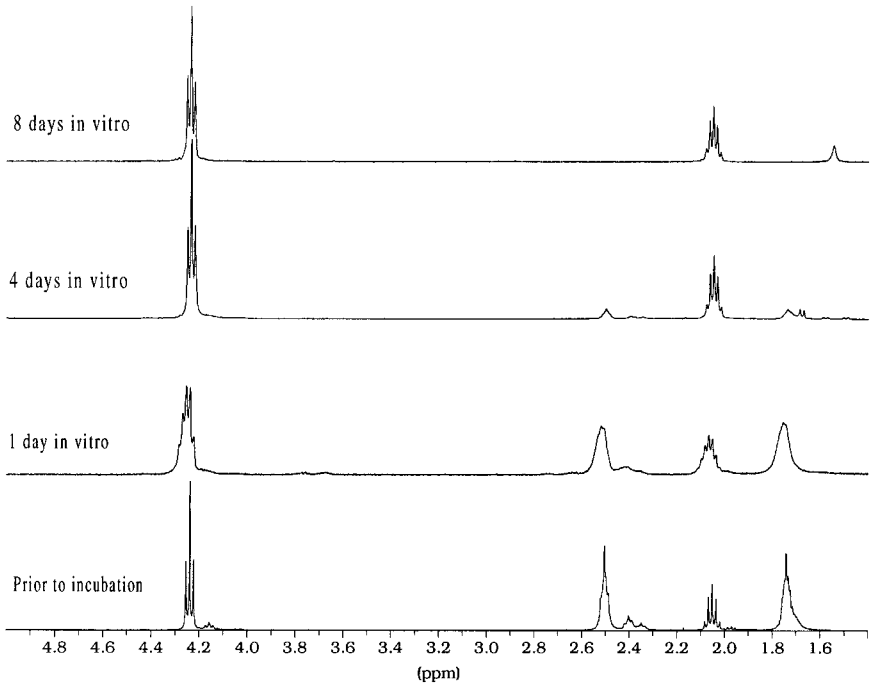

Figure 2 Compositional changes of a PTMC–PAA (20/80) blend as monitored by ^{1}H-NMR.

mass loss levels out and mass loss slows down until it becomes negligible. Polyesters are known to display an initial period of zero mass loss, during which time degradation into water-soluble oligomers takes place, followed by a period of continuous mass loss.[23] The same is observed for PTMC, a bulk-eroding polymer.[3] Hence, mass loss of films is most likely to stem from the loss of PAA degradation products and drug particles diffusing out of the matrix. ^{1}H-NMR results confirm this. The point in

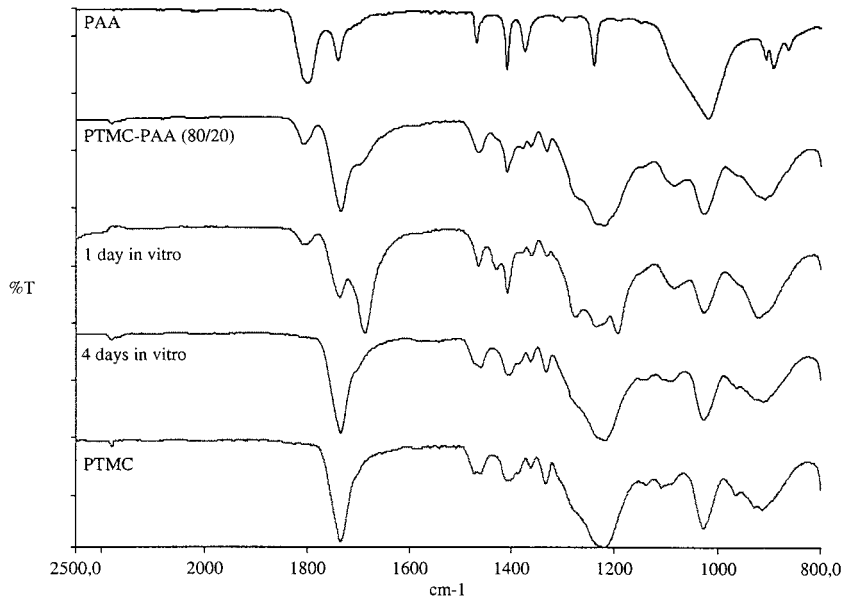

Figure 3 Compositional changes of a PTMC–PAA (80/20) blend as monitored by ATR–FTIR.

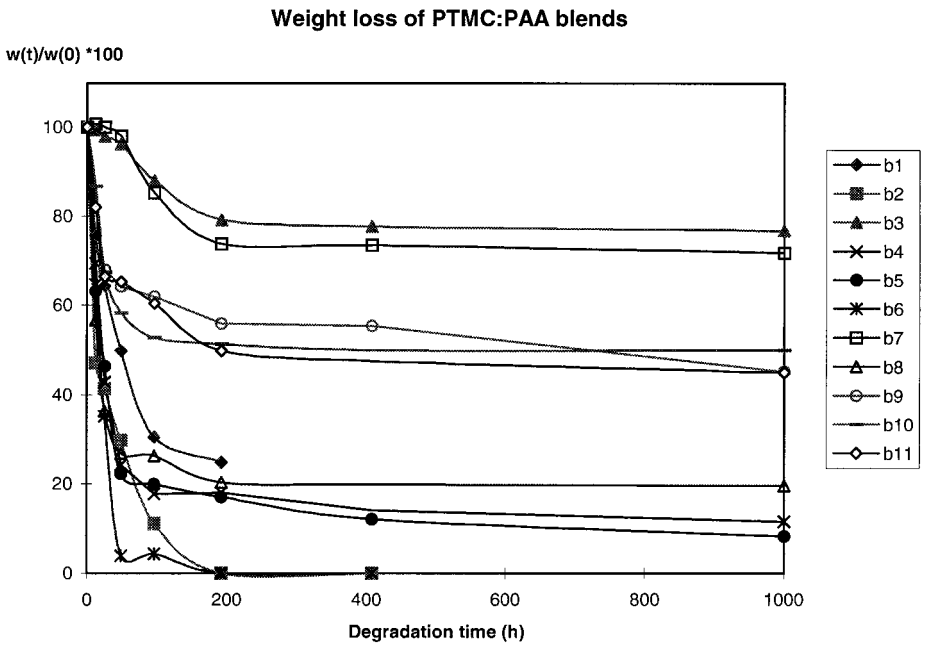

Figure 4 Weight loss (%) from 11 individual PTMC–PAA blends, prepared according to the experimental design shown in Table II.

time at which cessation of mass loss occurs is consistent with the depletion of degradation products of the films. Furthermore, Figure 4 shows that the weight percentage remaining after erosion retardation is in good agreement with the PTMC ratio of the individual blends, except for those samples containing LMW PTMC, where mass loss is more extensive. A mass loss of 100 % observed in two cases occurs because those samples disintegrated completely. The screening model predicts an important influence of the PAA content and M_n (PTMC) factors on weight loss. A high level of PAA will promote sample weight loss, whereas the M_n(PTMC) factor works in the opposite direction. An interaction effect (PAA $\times$ M_n) is also significant. Figure 5 illustrates these relationships by means of a contour plot.

Only a slight change in the molecular weight of the PTMC was detected on the time scale of this experiment, as seen in Figure 6. Earlier work of our group[3,4] showed that the molecular weight decrease of PTMC is indeed very slow in aqueous solution and also that it is independent of the nature of the aqueous medium and of the temperature of the aqueous medium. The molecular weight distribution (MWD = M_w/M_n) is constant for the HMW PTMC and MMW PTMC samples. LMW PTMC, however, shows a slight decrease in MWD from 1.5 to 1.3 over 1 month. Water-soluble oligomers, being polymerization residuals, may be lost by diffusion as the porosity of the matrix increases, explaining why mass loss for these samples is larger than could be accounted for by the PAA degradation products. The molecular weight of PAA decreased markedly the first day. Degradation is more or less complete after 2 days.

DSC analysis of undegraded films shows a melting endotherm at 76°C, corresponding to the melting of PAA crystallites. PTMC is amorphous, showing a glass transition in the region -14 to -21°C, depending on the molecular weight. Two distinct peaks were obtained, supporting the notion that PAA and PTMC do not form a true blend but a microscopic dispersion of one component in the other.[17]

Blending of PAA is associated with a melting-point depression, revealed by the DSC measurements. This is expected because of interference with the crystalline regions. Initially, one single melting endotherm at 75.8°C is observed in the thermograms. Figure 7 illustrates how this peak broadens and shifts to higher values, in the range 78–82°C, within 1 day of incubation. These changes are accompanied by an increase of ΔH, indicating an overall increase of the crystallinity. The presence of water increases the chain mobility, facilitating recrystallization of previously amorphous material. Also, chain scission of PAA

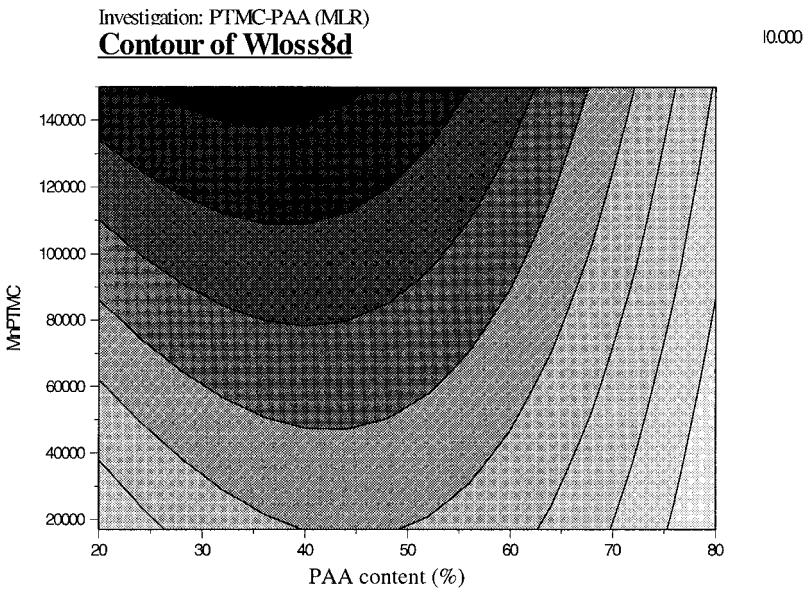

Figure 5 A contour plot showing the influence of M_n(PTMC) and PAA content on the extent of weight loss from the blend. Lighter colors denote increasing weight loss.

is followed by a large release of adipic acid into the matrix pores.[3] As the compositional analysis showed, erosion is a slower process than is degradation, leading to some accumulation of degradation products in the films. Crystallization of this material contributes to an increasing crystallinity. After 2 days, the peak starts to diminish. Disappearance of the melting endotherm correlates well with the leveling out in the rates of mass loss.

Figure 8 shows that blending lowers the T_g of PTMC in every case, suggesting that the PAA component acts as a plasticizer. The largest decrease is observed for samples containing HMW PTMC. The effect of M_n (PTMC) is clearly the dominant influence on the T_g depression, according to the screening model. Interaction effects and PAA content exert a minor influence, while the effect of drug content is insignificant. After incubation, the T_g steadily increases and reaches its final value in 4–8 days, the longer time being required for samples containing HMW PTMC. By this time, almost all adipic acid has left the matrix, but for samples containing LMW or MMW PTMC, the T_g will continue to rise, but at a slower rate. We attribute this to the leakage of oligomers, an effect also causing the MWD to increase, as discussed earlier.

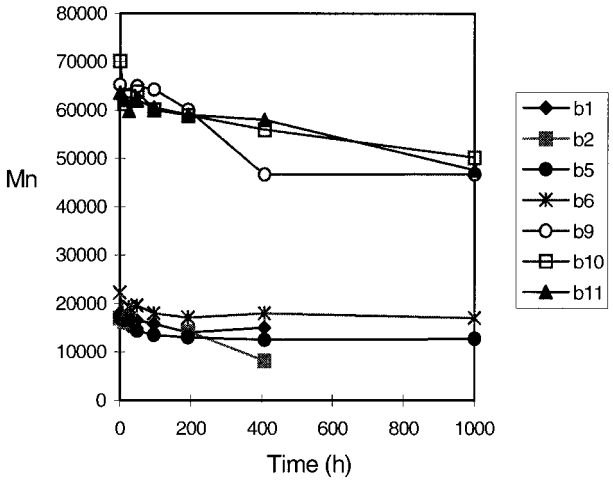

Figure 6 Molecular weight of the PTMC component as a function of incubation time.

Release of Drug from PTMC–PAA Blends

Drug release from pure PTMC is slow. Approximately 40% of the drug incorporated is released in 1 month. Given that the decrease of molecular weight is small, loss of the drug is likely to stem largely from diffusion. Chain scission is slow and erosion delayed, thus restraining the delivery. Figure 9 shows that drug release is speeded up when PAA is introduced into the PTMC matrix.

The extent of drug release is in good agreement with the amount of PAA in the blend, implying that the drug particles are evenly distributed in the matrix. The drug is released rapidly, in a

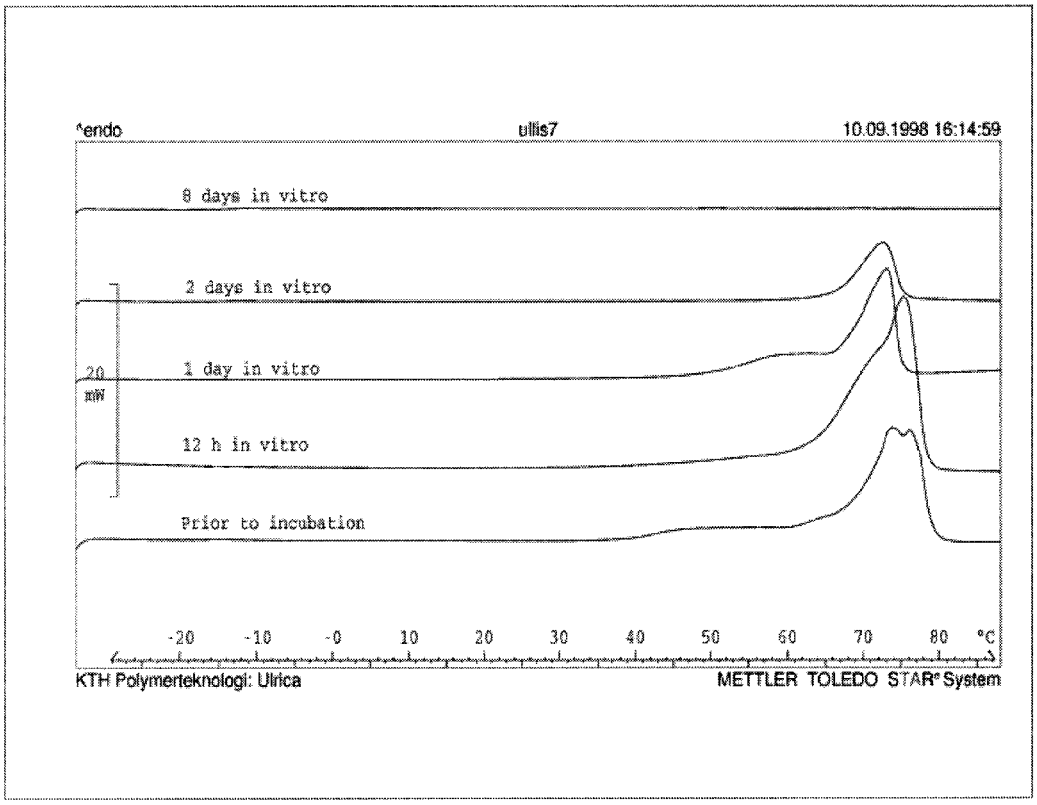

Figure 7 Thermograms of a PTMC–PAA (20/80) blend at different stages of degradation.

linear fashion, close to that observed for pure PAA, during the first few days. The release rate then levels off, after which the release proceeds more slowly but still with a linear time dependence of the rate of release.

The screening model confirms that the PAA content exerts a strong influence on the rate of drug release, so that a larger proportion of PAA in the blend will shorten the time scale for drug delivery. This holds true for the drug content as well, which is a significant factor in this case. M_n(PTMC) works the opposite way: A HMW matrix is predicted to retard the drug release. In addition to the main factor effects, there are two interaction effects which will influence the observed result. Figure 10 illustrates the relationship between the effects of PAA and M_n(PTMC). From an understanding of these relationships, we can control the rate of the drug release from the blend matrices.

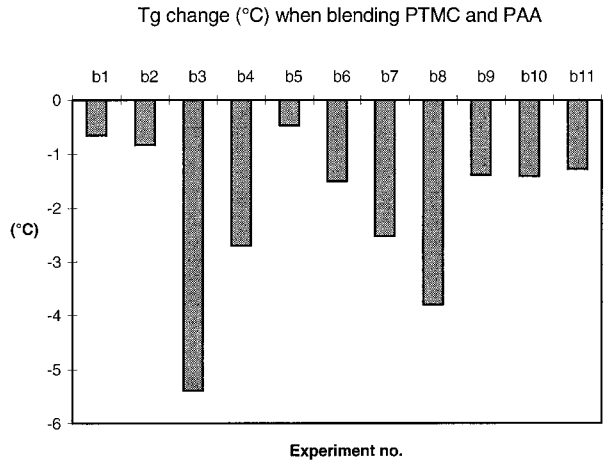

Figure 8 T_g depression (°C) of the PTMC component observed in sample b1–b11 as a result of blending.

CONCLUSIONS

We have shown that blending PTMC with LMW PAA provides a simple and convenient alternative to copolymerization, where tailored drug-delivery matrices are needed. The components were not copolymerizable in the bulk or in solution under a broad range of reaction conditions. However, the components show partial miscibility in each other. No sign of phase separation is observed in the blends. The resulting material is

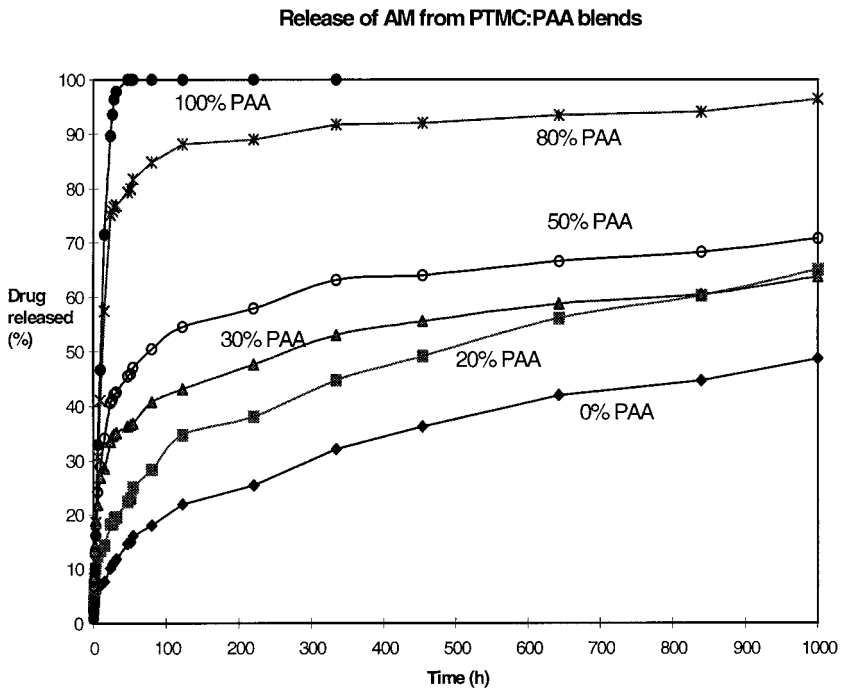

Figure 9 Release of model drug (amitryptiline) from blends having different proportions of PAA.

macroscopically uniform but opaque, having two separate T_g's, corresponding to those of the individual components.

A statistically designed factorial experiment was used to formulate a model capable of predicting the influence on blend properties of three important blend parameters—the PAA content, the M_n of PTMC, and drug loading. The model takes into account interaction effects among these parameters. A good fit to the model was obtained,

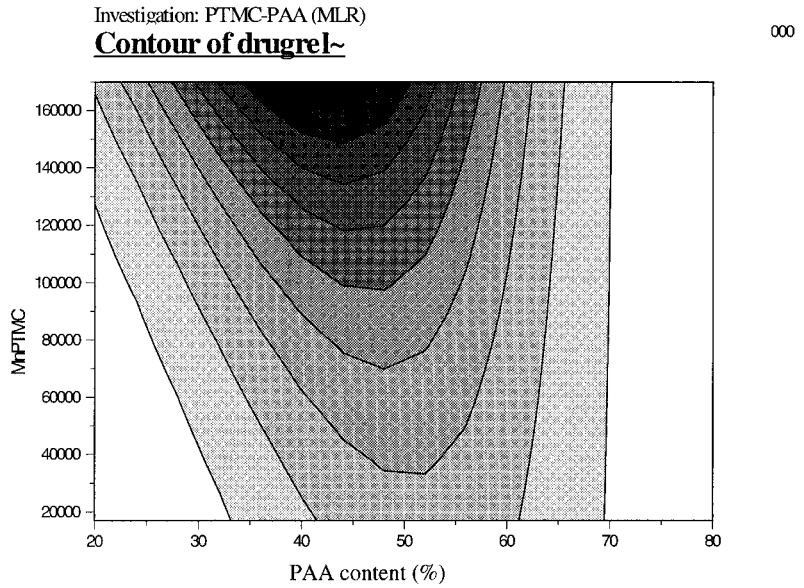

Figure 10 Contour plot showing the influence of M_n(PTMC) and PAA content on the extent of drug release from the blend. Lighter colors denote shorter times required to release 50% of the drug.

allowing the erosion and drug-delivery rate to be controlled.

Blending will bring about plasticization of PTMC. The degradation and erosion of PAA degradation products, confirmed by compositional analysis, are connected to increasing mass loss, porosity, and water permeability of the bulk, thus enhancing the hydration and degradability of PTMC. The molecular weight of the PTMC component was virtually unchanged on the time scale of this experiment, whereas the PAA component was completely degraded within a few days.

The potential of PTMC–PAA blends for use in controlled drug-release applications was demonstrated. Compared to pure PTMC, drug release from PTMC–PAA is increased to an extent that depends on the amount of PAA incorporated into the blend. The screening design shows that two factors are the principal variables influencing the drug-release rate: the extent of mass loss and the matrix plasticization. Synergistic effects will also influence the resulting blend performance. Given knowledge of these relationships, it is possible to achieve the desired rates of drug release and erosion.

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