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Research Paper

Hydrophilic Absorbable Copolyester Exhibiting Zero-Order Drug Release

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Purpose. A novel absorbable hydrophilic copolyester developed in our laboratory, amorphous 40/60 poly(ethylene diglycolate-co-glycolide), exhibits outstanding physical properties. Films made from this material appear fully transparent, colorless, soft and slightly elastic, but relatively strong and durable materials so that they can be potentially used as stand-alone devices in various *in-vivo* medical applications. In this study, *in-vitro* drug release characteristics of this copolyester were examined.
Methods. High Performance Liquid Chromatography was used to generate release profiles on selected non-steroidal anti-inflammatory agents, NSAIDs. In addition, dielectric relaxation spectroscopy, as well as mid- and near infrared spectroscopy, were used to study specific polymer chain interactions in water and buffer solution as a function of aging time at 37°C.
Results. This copolyester, compression molded into a film, exhibited nearly constant *in-vitro* release of various hydrophilic and hydrophobic drugs. The release profile showed minimal or, in most cases, no burst effect. The effect was observed with the three NSAIDs that were tested as model compounds; however, this system may prove generally useful for other drug entities. *In-vitro* hydrolysis conducted at 37°C on this hydrophilic copolyester revealed an unusually long induction period (no hydrolysis for up to 6 days), followed by the relatively rapid hydrolysis. Data from dipole relaxation spectroscopy indicated that the water molecules do not structurally associate with the polymer chains in phosphate buffer during initial hydrolysis period.
Conclusions. The results suggest unique dynamics of water diffusion through the polymer matrix that may play a critical role in achieving controlled release properties. Furthermore, we suspect that the molecular interactions associated with this new synthetic absorbable material may find a critical utility in important medical applications.

KEY WORDS: absorption; adhesion prevention; copolyester; drug delivery; zero-order drug release.

INTRODUCTION

With many drugs, the basic goal of a drug carrier is to provide a dosage form that is capable of achieving steady-state blood levels or tissue levels that are therapeutically effective while maintaining this level without encountering any safety concerns. A basic objective is to optimize the delivery of drugs to maintain a level of efficacy in spite of fluctuations that may take place in the environment where they are released. Sustained or controlled release formulations are designed to achieve a prolonged therapeutic effect by continuously releasing a medication over an extended period after administration of a single dose. This approach improves patient compliance and makes the product more convenient. An additional benefit is the reduction of high peak blood levels for medications that are highly bioavailable. Controlled release dosage forms are able to achieve therapeutic levels with more control, as opposed to those that exhibit a burst affect that in some cases is deleterious.

There are a number of technologies currently available that are being used as controlled release systems, some of which are able to provide constant release kinetics for certain drugs. These include osmotic-based approaches (1,2), liposomal systems (3,4), multilayer systems (5,6), and bioerodible polymers. However, there remain many drugs that could benefit from a constant delivery system, but many do not have the capability of being delivered at a constant rate with the other technologies that exist today.

With respect to bioerodible systems, one of the early polymeric systems recognized for zero-order release potential

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ABBREVIATIONS: Cap, ε-caprolactone; DI, deionized (water); DRS, dipole relaxation spectroscopy; FTIR, Fourier transform infrared (spectroscopy); Gly, glycolide; GPC, gel permeation chromatography; HPLC, high-performance liquid chromatography; kGy, kilograys (0.1 Mrad); Mil, a length measurement corresponding to 1/1000 of an inch; MIR, mid-infrared (spectroscopy); NIR, near-infrared (spectroscopy); NSAID, nonsteroidal anti-inflammatory drug; PDS, poly(*p*-dioxanone); PEDG, poly(ethylene diglycolate); PLGA, poly(lactide-*co*-glycolide).

were the polyanhydrides (7–10). These systems have a very high water reaction rate, which, coupled with a very low rate of diffusion of water into the polymeric device, lead to advantageous release properties when the device is fashioned in the form of a sheetlike structure. However, these hydrophobic and, in most cases, highly crystalline materials (11) were generally very stiff, which limited their suitability in soft tissue. Due to their high moisture sensitivity, the polymer stability is also of concern (12). Other biodegradable systems include poly(ortho esters) that have been under examination for over 30 years (13,14). These materials erode from the surface only if additives are included in the matrix (15). The acid-sensitive nature of ortho ester linkages allows for pH-dependent cleavage: Surface erosion is obtained by either addition of basic substances to suppress degradation in the bulk or incorporation of acidic catalysts to promote degradation on the surface.

A variety of hydrophilic polymers and hydrogels have been developed for the controlled delivery of drugs, peptides, and proteins (16–19). The new class of "swelling-controlled release systems," which exhibit a time-dependent (approximate zero order) release due to coupling of diffusional and relaxational mechanisms, has been proposed (20). Complex transport mechanisms incorporating the viscoelastic behavior of the polymer and its relaxational behavior during swelling aid in dictating the drug release processes. Swelling-controlled zero-order drug release from thermoresponsive hydrogels has been also described (21,22). In those studies, drug release profiles were significantly changed by alteration of temperature. In the release of indomethacin from poly(*N*-isopropylacrylamide-*co*-butyl methacrylate) (21), zero-order behavior was observed at 20°C. However, when the temperature was reduced to 10°C, the release profile was sigmoidal. Controlled release from pH-dependent glassy hydrogels (23) and ionic polymer drug conjugates (24,25) were also described.

Finally, a variety of geometric approaches for zero-order release of drugs dispersed in polymer matrices were considered. These may include parabolic geometry (26), rodlike poly (lactide-*co*-glycolide) (PLGA) matrix systems (27), polymer microparticles (28), polymeric micelles (29), coaxial biodegradable implants (30), hollow microspheres (31), macroporous polymeric microcarriers (32), etc.

In this study, a novel hydrophilic absorbable copolyester in the form of a film is described that is capable of providing nearly constant delivery of various hydrophilic and hydrophobic drugs *in vitro* with minimal or no burst effect. No special geometric or experimental condition (e.g., pH, temperature, etc.) was required to achieve these zero-order characteristics. Three model nonsteroidal anti-inflammatory drugs (NSAIDs) were tested; however, this system may prove useful for other drug entities.

EXPERIMENTAL

Materials

Synthesis of Hydroxy Terminated Poly(ethylene diglycolate)

A twin-agitated reactor with intermeshing patterned blades was used to prepare a polycondensation product of diglycolic acid and ethylene glycol with dibutyltin oxide as catalyst. After the reactor was charged with 10.0 kg of diglycolic acid, 13.9 kg of ethylene glycol, and 1.86 g of dibutyltin oxide catalyst, the reaction was carried out at 165°C for a couple of hours until approximately all water was distilled and/or first traces of ethylene glycol appeared in the distillate. After the first nitrogen/argon stage was completed, pressure was lowered gradually to full vacuum in steps while the temperature of the batch was maintained at 165°C. A hydroxy end-capped polymer was discharged after sufficient reaction time spent under vacuum. It was a fully amorphous, colorless, viscous liquid with a glass transition temperature (T_g) of about 3°C. Weight average molecular weight was 12,000 g/mol; the resin exhibited an inherent viscosity of 0.35 dL/g, as determined in hexafluoroisopropanol (HFIP) at 25°C at a concentration of 0.1 g/dL.

Copolymerization of an α,ω-Dihydroxy Poly(ethylene diglycolate) Homopolymer with a Lactone Monomer, Glycolide

A portion of the hydroxy terminated poly(ethylene diglycolate) (2.5 kg) was charged to a reactor equipped with a melt tank reservoir allowing glycolide monomer (3.8 kg) to be added later in a liquid state. After the macroinitiator resin was charged, a vacuum of less than 1 Torr was kept overnight. The next day, the resin was heated to about 130°C, at which point the molten glycolide monomer was transferred from the melt tank with agitation. Agitator mixing was continued (20 rpm), and the batch temperature was raised to 150°C until full mixing was achieved. *In situ*, a real-time Fourier transform near-infrared (FTIR) probe was used to confirm complete mixing of components before the addition of the catalyst, stannous octoate (0.412 ml of toluene solution, glycolide to catalyst ratio 240,000:1). Temperature was then increased to 210°C and the reaction was continued for another 2 h. The discharged copolymer was fully amorphous, with a colorless to slightly yellow tint, and a glass transition temperature of 23°C. Weight average molecular weight was 27,000 g/mol. An inherent viscosity of 0.64 dL/g, as determined in HFIP at 25°C at a concentration of 0.1 g/dL, was recorded. Composition was confirmed by NMR to be 40/60 by weight poly(ethylene diglycolate-*co*-glycolide).

Drug Release

In separate experiments, undyed poly(*p*-dioxanone) (PDS), poly(ethylene diglycolate-*co*-glycolide) 40/60 wt.% [PEDG/Gly 40/60], poly(ethylene diglycolate-*co*-glycolide-*co*-ε-caprolactone) 20/80 (80/20) wt.% [PEDG/(Gly/Cap) 20/80(80/20)], and poly(ε-caprolactone-*co*-glycolide) 35/65 wt.% [Cap/Gly 35/65] were each individually dry blended with 15 wt.% ketoprofen and later compounded using a laboratory-scale compounder (Daca, Goleta, CA, USA). After compounding, extruded samples were cut into small pieces, from which several 5-mil (0.13 mm) films were compression molded by use of a hot press (MTP-14 Tetrahedron™ Compression Molding press, San Diego, CA, USA). Some of the film samples were sterilized by γ irradiation from a cobalt (^{60}C) source. The radiation dose was 25 kGy (1 kGy = 0.1 Mrad).

In vitro drug release testing was conducted in a shaker water bath maintained at 37°C and agitated at 30 rpm. Polymer films (1×1 cm) loaded with ketoprofen (or other drugs) were placed in 20-mL glass scintillation vials filled with 20 mL of 0.1 M phosphate buffer solution (pH 7.4) and sealed with a screw cap. Buffer solution aliquots were collected at designated time intervals (3, 6, 9, 12, 24, 36, 48, and 72 h); during these periods, the buffer in each vial was replaced with fresh medium. The drug contents were measured by use of a high-performance liquid chromatography (HPLC) method.

Ketoprofen, or benzeneacetic acid, 3-benzoyl-a-methyl- (9CI) (registry no. 22071-15-4), is an NSAID effective in treating fever, pain, and inflammation in the body. As a group, NSAIDs are nonnarcotic relievers of mild to moderate pain of many causes, including injury, menstrual cramps, arthritis, and other musculoskeletal conditions.

Ketoprofen HPLC Assay

Ketoprofen release is quantified using reverse-phase HPLC with photodiode array detector, Phenomenex Luna Pheny–Hexyl column (Torrance, CA, USA), and mobile phase of 40:60 ratio HPLC-grade acetonitrile and 0.04 M KH_2PO_4 buffer (pH 3.5). The UV absorbance is measured at 233 nm with a flow rate of 0.75 mL/min. The standard solutions were prepared by dissolving about 50 mg of ketoprofen reference standard in approximately 40.0 mL of mobile phase, using sonication if necessary, in a 50-mL volumetric flask and subsequently bringing up to volume. This standard stock solution was diluted with the mobile phase to the desired concentrations.

Diclofenac sodium, or 2-[(2,6-dichlorophenyl)amino]-, monosodium salt (9CI) (registry no. 15307-79-6), is also an NSAID. Diclofenac sodium works by reducing hormones that cause inflammation and pain in the body. It is used to reduce pain, inflammation, and stiffness caused by many conditions, such as osteoarthritis, rheumatoid arthritis, abdominal cramps associated with menstruation, and ankylosing spondylitis.

Diclofenac Sodium HPLC Assay

Diclofenac sodium release is quantified using a reverse-phase HPLC with photodiode array detector, Phenomenex Luna Pheny–Hexyl column, and mobile phase of methanol and phosphate buffer (pH 2.5) in a volumetric ratio of 70:30. The UV absorbance is measured at 254 nm with a flow rate of 1 mL/min. The standard solutions were prepared by dissolving about 50 mg of diclofenac sodium reference standard in approximately 40.0 mL of methanol, using sonication if necessary, in a 50-mL volumetric flask and subsequently bringing up to volume.

Indomethacin, or 1*H*-indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl- (9CI) (registry no. 53-86-1) is an NSAID that reduces fever, pain, and inflammation. It is similar to ibuprofen (Motrin) and naproxen (Naprosyn, Aleve). Indomethacin works by reducing the production of prostaglandins, chemicals that the body uses to cause fever, pain, and inflammation. Indomethacin blocks the enzymes that make prostaglandins (cyclooxygenase 1 and 2) and thereby reduces the levels of prostaglandins.

Indomethacin HPLC Assay

Indomethacin release is quantified using reverse-phase HPLC with photodiode array detector, Phenomenex Luna Pheny–Hexyl column, and two mobile phases (A/B 80:20). The first mobile phase was prepared by mixing an equal volume of phosphate buffer (0.01 M dibasic sodium phosphate and 0.01 M monobasic sodium phosphate) and acetonitrile (A). The second mobile phase was water (B). The UV absorbance is measured at 254 nm with a flow rate of 1 mL/min. The standard solutions were prepared by dissolving about 50 mg of indomethacin reference standard in 40.0 mL of methanol, using sonication if necessary, in a 50-mL volumetric flask. The standard solution was brought to volume with methanol and the standard stock solution was diluted with methanol to the desire concentrations.

Hydrolysis Profiler

In vitro absorption time was measured by an automated titration unit (718 Stat Titrino, Brinkmann, Westbury, NY, USA) at 37 and/or 75°C, under constant pH (7.3) in 70 mL of deionized (DI) water using 0.05N NaOH as a base. The weight of material was about 100 mg.

Dielectric Relaxation Spectroscopy

Instrument

The technique used was broadband dielectric relaxation spectroscopy (DRS). A brief description of our experimental facility for dielectric measurements follows. In this study we used Novocontrol's α Analyzer (3 μHz–10 MHz; Hundsangen, Germany), which is interfaced to computers via IEEE 488.2 and is connected to a heating/cooling unit (modified Novocontrol's Novocool System). Steel parallel plates with diameters of 10 mm were used as sample cells. More details are given elsewhere (33), and several comprehensive reviews of experimental methodology for dielectric measurements were recently published (34,35).

Measurement Procedure

DRS was conducted on gamma-irradiated 15×15-mm squares of the 3-mil (0.076 mm)-thick films. A portion of these squares was immersed as described earlier, whereas a portion was left dry. Dry samples were tested from 30 to −100°C, and then from 30 to 150°C; the frequency range used was from 3×10^6 to 10^{-2} Hz. At temperatures higher than 60°C, the measurement was stopped when the dielectric loss was higher than 100, which is an indication that conductivity prevails. In the wet film tests, the temperature range used was between 20 and −100°C.

Samples were removed from the aging environments after selected times, weighed, and tested. Water and buffer immersion experiments were performed at 37°C. The buffer solution used was prepared with NaH_2PO_4 and Na_2HPO_4 with a concentration of 0.08 M and pH value of 7.4 (one sample mixture is composed of 0.4944 g NaH_2PO_4 and 2.249 g Na_2HPO_4 for 250 ml buffer solution). The buffer solution was renewed every 7 days to keep the pH value consistent.

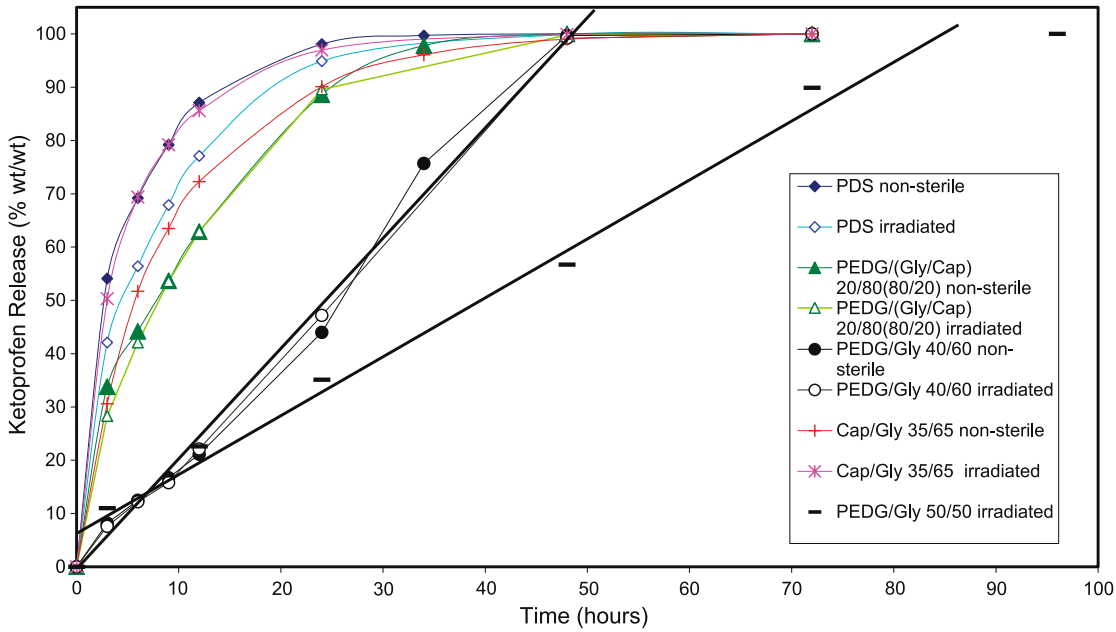

Fig. 1. Ketoprofen release as a function of time from different nonirradiated and gamma-irradiated polymer films (all thicknesses 0.13 mm). [The square of the correlation coefficient, r^2, for the combined observations for 40/60 PEDG/(Cap/Gly) copolymers, nonsterile and irradiated, was 0.991. The corresponding value for the observations made between 10 and 90% drug released from the 50/50 copolymer was 0.993].

Fourier Transform Infrared Spectroscopy

Mid-infrared (MIR) spectra were collected using Nicolet Instrument's Magna 750 Spectrometer (Madison, WI, USA). For MIR experiments, 0.076-mm-thick samples were used to obtain good resolution. Near-infrared (NIR) spectra were collected using an ANTARIS NIR analyzer (Thermo's Nicolet Industrial Solution). For NIR measurements, a sample thickness of 0.13 mm was used to obtain good resolution.

Weight Change Data

The weight change data were recorded as a function of aging time prior to DRS/FTIR measurements. Sample weight was recorded on a Mettler Toledo AX105 balance (Columbus, OH, USA), with a precision range of ±0.005 mg. Samples were prepared as follows: three pieces of 15 × 15-mm film were immersed in 0.08 M (pH 7.4) buffer at 37°C for selected times. Samples were then removed from the bath, rinsed with DI

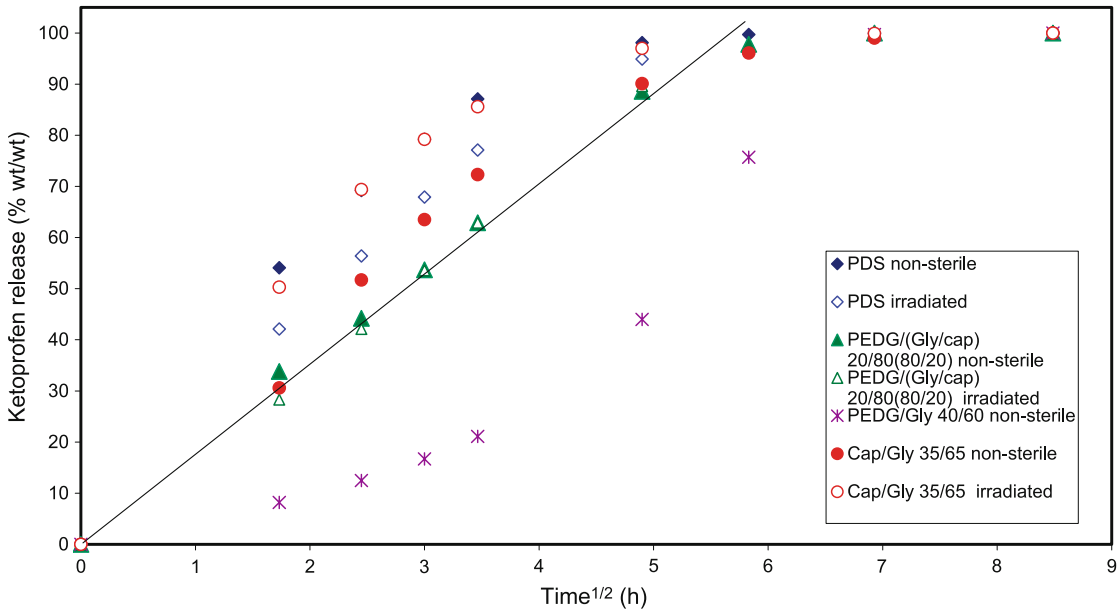

Fig. 2. Ketoprofen release as a function of square root of time using different nonirradiated and γ irradiated polymer films (thickness 0.13 mm). [The square of the correlation coefficient, r^2, for the combined observations for 20/80 PEDG/(Cap/Gly) copolymers, nonsterile and irradiated, was 0.998].

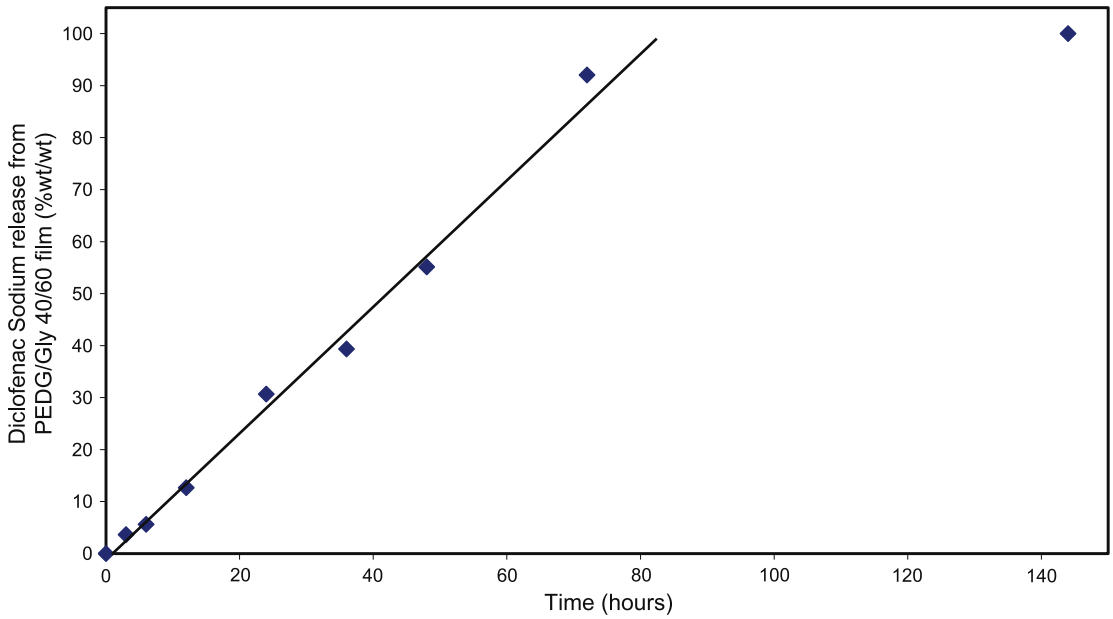

Fig. 3. Diclofenac sodium release from the PEDG/Gly 40/60 film (thickness 0.13 mm) as a function of time. (The square of the correlation coefficient, r^2, for the observations made between 0 and 95% drug released was 0.993).

water, their surfaces carefully dried with paper towels, and film weight recorded.

RESULTS AND DISCUSSION

Films prepared by PEDG/Gly 40/60, either by compression molding or by film extrusion, exhibit outstanding physical properties. These samples appear fully transparent, colorless, soft and slightly elastic, but relatively strong and durable materials so that they can be potentially used as stand-alone devices in various *in vivo* medical applications. These are also fully amorphous, hydrophilic, but not tacky materials, which aid tremendously in processing and easy handling during open surgical procedures, and especially during minimally invasive laparoscopic surgical procedures. Recently, excellent adhesion-prevention performance of this copolymer has been disclosed using a multistudy, rabbit sidewall abdominal hernia model (36). These materials can be sterilized by γ irradiation, exhibiting a long shelf life (greater than 1 year) without losing any of their original physical

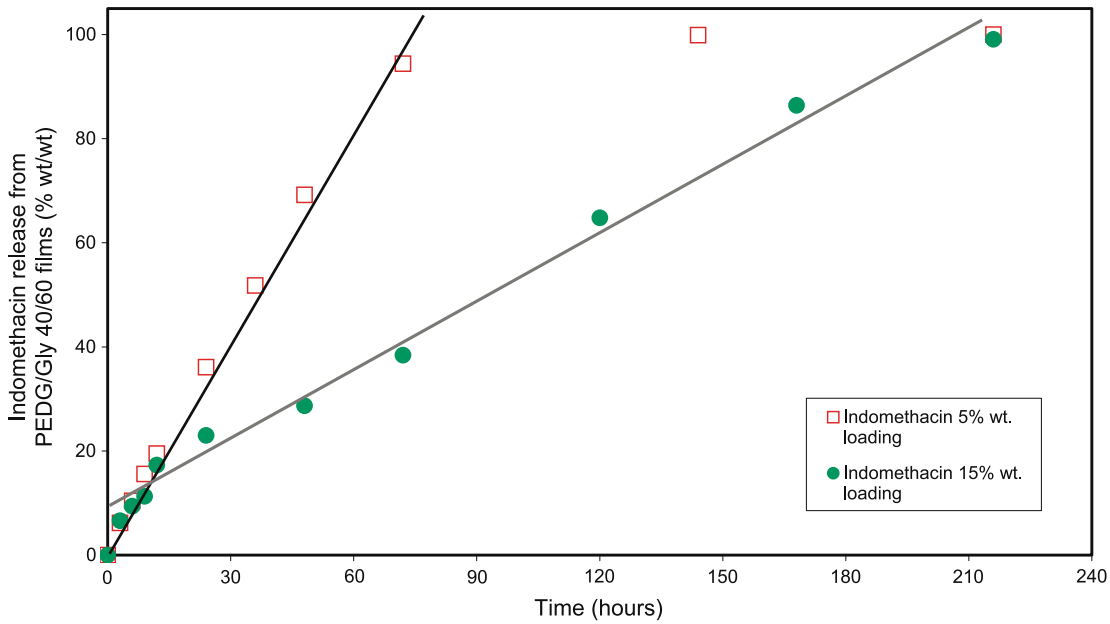

Fig. 4. Indomethacin release from PEDG/Gly 40/60 films (thickness 0.13 mm) having two different loadings. [The square of the correlation coefficient, r^2, for the observations up to 95 wt.% released, for the PEDG/(Cap/Gly) 40/60 copolymer, initially loaded at 5%, was 0.996. For the film initially loaded to at 15%, the value of r^2 for the observations made after 10% of the drug was released was 0.991].

Table I. Weight Change Measurements for the PEDG/Gly 40/60 Film

Time (h)	Weight change in DI water (%)	Weight change in buffer (%)
13	/	+2.6
24	+2.3	+8.3
48	+2.8	+10.6
66	+2.5	+10.1

properties. In addition, these new hydrophilic copolymers have favorable absorption profile, whose significance will be discussed later in the text.

Drug Release Study

A variety of different absorbable polyester films containing 15 wt.% ketoprofen were immersed in buffer solution at 37°C and the release of the drug was detected by an HPLC method. Some of the film samples were sterilized by γ irradiation using a cobalt source with a radiation exposure of 25 kGy. A summary of data is presented in Fig. 1. It is evident that the ketoprofen release from PEDG/Gly 40/60 exhibits zero-order performance without any burst effect detected. Complete release of the drug was observed at 48 h. In addition, an effect of γ irradiation on the release profile for this formulation was found to be negligible, which is very important for sterilization purposes of a medical device potentially made from this polymer/drug combination. Earlier, we found that the film properties of the neat resin, PEDG/Gly 40/60, including molecular weight, inherent viscosity, sub- and supramolecular morphology, mechanical strength, bulk and surface hydrophilicity, and *in vitro* absorption rate, all remained relatively unchanged when the film was subjected to γ irradiation. Films were packed and sealed under dry nitrogen atmosphere and subjected to doses as high as 38 kGy. We also found that these irradiated films showed excellent shelf-life stability (no change in physical properties) for at least 1 year after sterilization.

A slightly different, more hydrophilic PEDG/Gly 50/50 formulation also exhibits zero-order release, but with about 5–6% burst effect. The release rate of this copolymer seems to be slower than that of the PEDG/Gly 40/60 matrix. The ketoprofen release from other formulations exemplified in Fig. 1 follows more typical, first-order, or diffusion control mechanisms. This is evident in Fig. 2, which represents a Fickian diffusion plot of the release kinetics data already presented in Fig. 1. The formulation PEDG/(Gly/cap) 20/80 (80/20) exhibits a classical diffusion control mechanism for the entire time-release period, including both sterilized and nonsterilized samples. Except for the PEDG/Gly 40/60 composition, the formulations studied also showed a significant initial burst of drug followed by the diffusion control mechanism.

To investigate if the PEDG/Gly 40/60 polymer provides zero-order release for other drug combinations, a second study on this polymer was conducted, this time containing 15 wt.% diclofenac sodium. As shown in Fig. 3, the zero-order release behavior was obtained for the entire time-series interval. No burst effect was seen for this formulation, which shows complete release of the drug in about 80 h. A third study-based on the PEDG/Gly 40/60 polymer was conducted. Zero-order with no burst behavior was also found during the release of 5 wt.% indomethacin dispersed in 5-mil (0.13 mm)-thick PEDG/Gly 40/60 film. The results displayed in Fig. 4 suggest that the release of drug for this combination was completed in about 72 h. However, higher concentration of indomethacin (15 wt.%) distributed in this polymer generated zero-order behavior with about 10% burst effect as portrayed in Fig. 4. Also, the overall release from this latter system lasted up to 210 h. The same drug loading (15 wt.%) dispersed in thicker films (7 and 10 mil) produced an almost identical drug release profile (data not shown here).

We also found that relatively small changes in the copolymer's composition affect the morphology and, therefore, drug release characteristics. For instance, a semicrystalline PEDG/Gly 30/70 formulation did not achieve zero-order release kinetics; a faster-absorbing PEDG/Gly 50/50 formu-

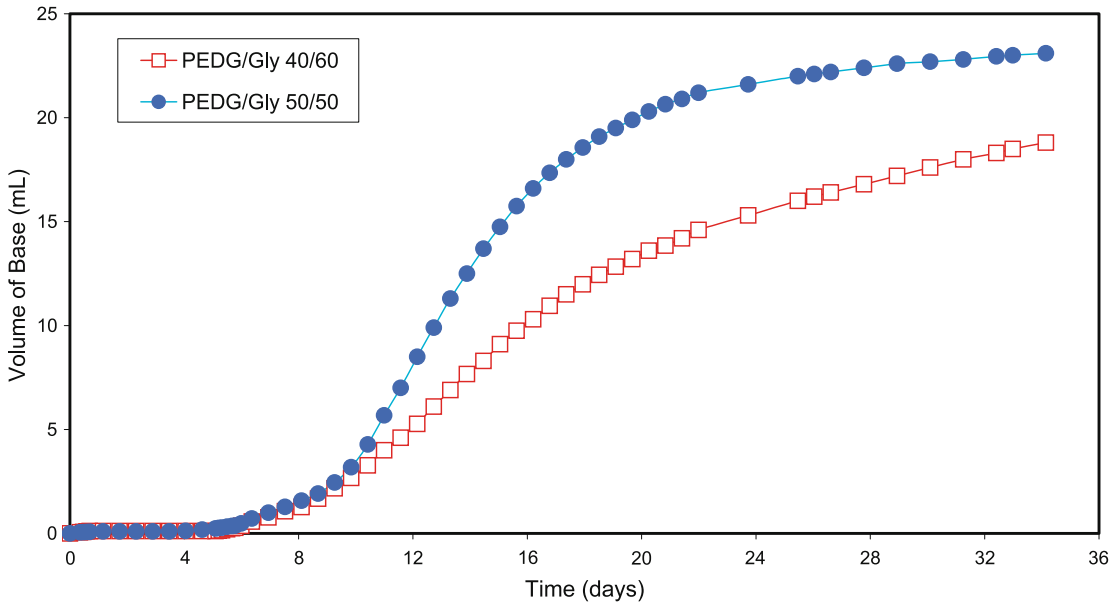

Fig. 5. Hydrolysis profiles at a pH of 7.3 at 37°C of PEDG/Gly 40/60 and PEDG/Gly 50/50 films (thickness 0.13 mm).

lation showed a small burst effect (5–10%) and somewhat longer release of ketoprofen than the 40/60 counterpart. In addition, if L(−)lactide is used instead of glycolide in a variety of combinations with PEDG (maintaining the amorphous morphology), zero-order characteristics are lost, particularly in the later release stages.

Water Uptake and Film Absorption Study

The next set of measurements was performed to investigate the ability of PEDG/Gly film to absorb water and to determine its *in vitro* hydrolysis profile.

Water uptake experiments on 15 × 15-mm, 3-mil (0.076 mm)-thick films were conducted in DI water and in buffer solution at 37°C. Weight changes for neat PEDG/Gly 40/60 film as a function of aging time are summarized in Table I.

Data indicate that the amount of water taken by the polymer in a buffer (pH 7.4) is higher than in experiments conducted in DI water. It seems that in both cases the equilibrium is reached at about 48 h upon immersion. In a separate set of measurements conducted at room temperature, FT near-infrared spectroscopy data revealed that water (moisture) pickup for a vacuum-dried PEDG/Gly film is fastest in the first 30 min of exposure; it seems that the moisture level continues to increase for up to about 20 h and then levels off.

Hydrolysis measurements on neat PEDG/Gly films were conducted for up to 35 days by use of an automatic titration unit at 37°C while maintaining a constant pH level of 7.3. An

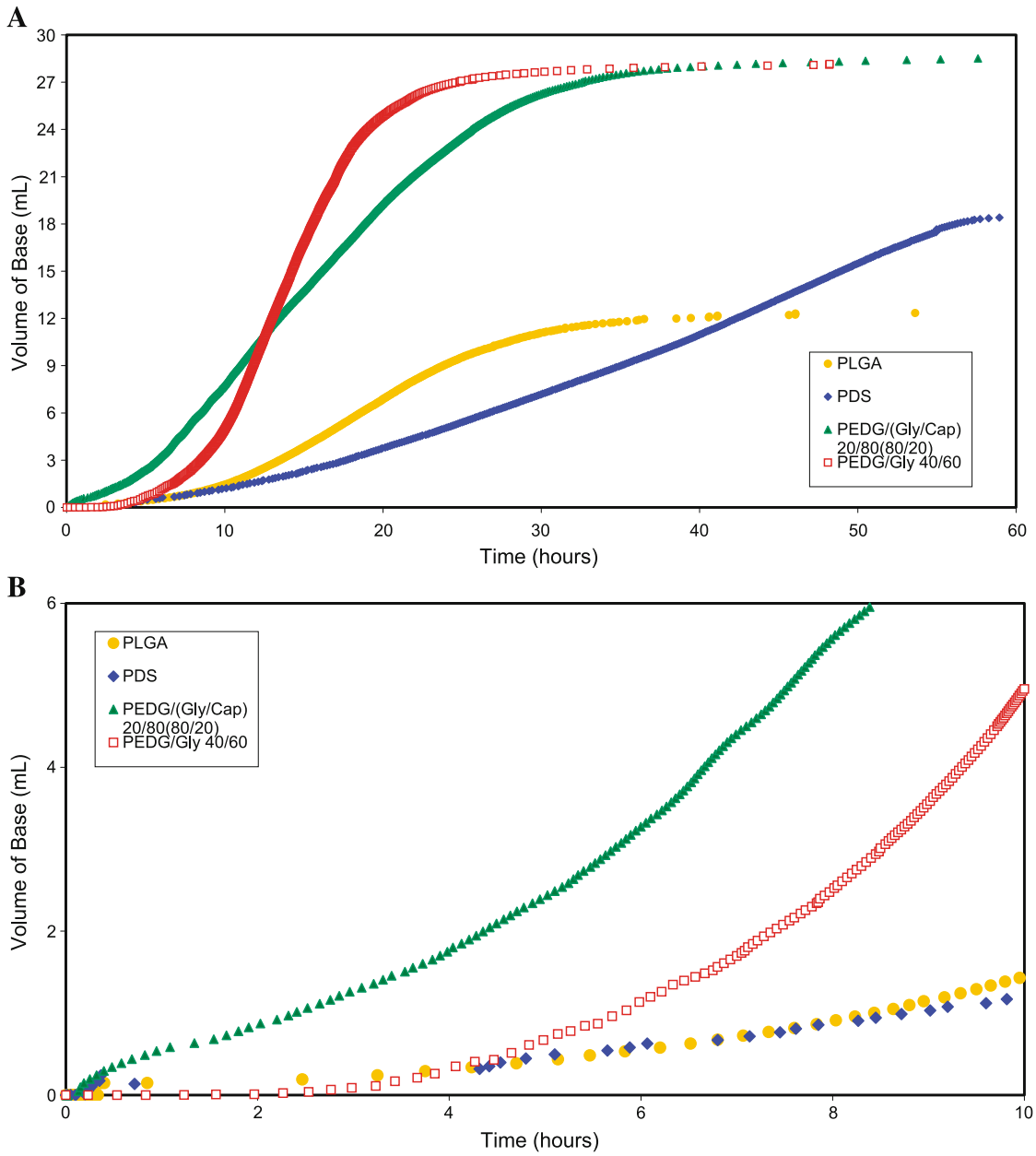

Fig. 6. (A) Hydrolysis profiles at a pH of 7.3 at 75°C of various polymer films (all thicknesses 0.13 mm). (B) Hydrolysis profiles at a pH of 7.3 at 75°C of various polymer films (all thicknesses 0.13 mm)—Enlarged initial hydrolysis region of Fig. 6A.

Table II. GPC Data of Two PEDG/Gly 40/60 Films Subjected to Hydrolysis in a Buffer Solution at 50°C (pH 7.3)

Hydrolysis time	Compression molded 5-mil film			Extruded 3-mil film		
M_w	M_w	M_n	M_w/M_n	M_w	M_n	M_w/M_n
Original film	24,200	3,500	6.9	25,500	3,500	7.2
1 day	13,900	2,700	5.1	15,200	2,600	5.8
2 days	6,300	1,500	4.2	6,300	1,200	5.1
3 days	3,300	1,300	2.5	3,100	900	3.4
4 days	1,700	1,000	1.7	1,800	1,100	1.7
7 days	1,200	680	1.7	1,200	700	1.6
9.5 days	1,050	600	1.8	1,040	670	1.5
14 days	920	530	1.7	1,030	680	1.5
18 days	850	490	1.7	870	500	1.7
23 days	800	450	1.8	820	490	1.7
30.5 days	440	180	2.4	820	500	1.6

example of this study is shown in Fig. 5. We have identified a unique hydrolysis feature for two of the PEDG/Gly compositions (40/60 and 50/50) that is generally not seen in other absorbable copolyesters, that is, a relatively long induction period (no hydrolysis occurred for up to 5–6 days), followed by relatively active hydrolysis period, resulting in an S-shaped profile. Delayed hydrolysis for this copolymer may have great advantages in different medical applications. For instance, during surgery, in cases where this material is implanted on an injured tissue, an initial absence of the acid generated by ester hydrolysis may keep inflammatory reactions low until the healing process has sufficiently progressed.

As indicated in Fig. 5, hydrolysis of the PEDG/Gly 50/50 composition is essentially completed in 35 days, whereas a longer time is needed for the PEDG/Gly 40/60 formulation. Based on experiments conducted at higher temperature (75°C), a hydrolysis time of 40 to 50 days at body temperature is extrapolated for this latter polymer. In addition, several *in vivo* studies involving this polymer seem to confirm our *in vitro* findings (36). Elevated-temperature hydrolysis experiments on several absorbable polymer films conducted at 75°C are shown in Fig. 6A and B. These data emphasize again the unique feature of our PEDG/Gly 40/60 copolymer—a long induction period followed by a rather rapid rate of hydrolysis.

In vitro degradation study of PEDG/Gly 40/60 copolymer performed on two different thicknesses, 3 mil (made by extrusion) and 5 mil (made by compression molding), conducted at 50°C in a buffer solution was used to assess molecular weight changes with time. Gel permeation chromatography (GPC) data obtained from this study are summarized in Table II. Results suggest that degradation profiles of both types of films are essentially identical. Weight average molecular weight decreases more rapidly during the first several days, leading to the narrowing of molecular weight distribution.

To investigate the effect of drug on the absorption rate of the PEDG/Gly 40/60 composition, an *in vitro* hydrolysis study was conducted on this polymer loaded with 10 wt.%

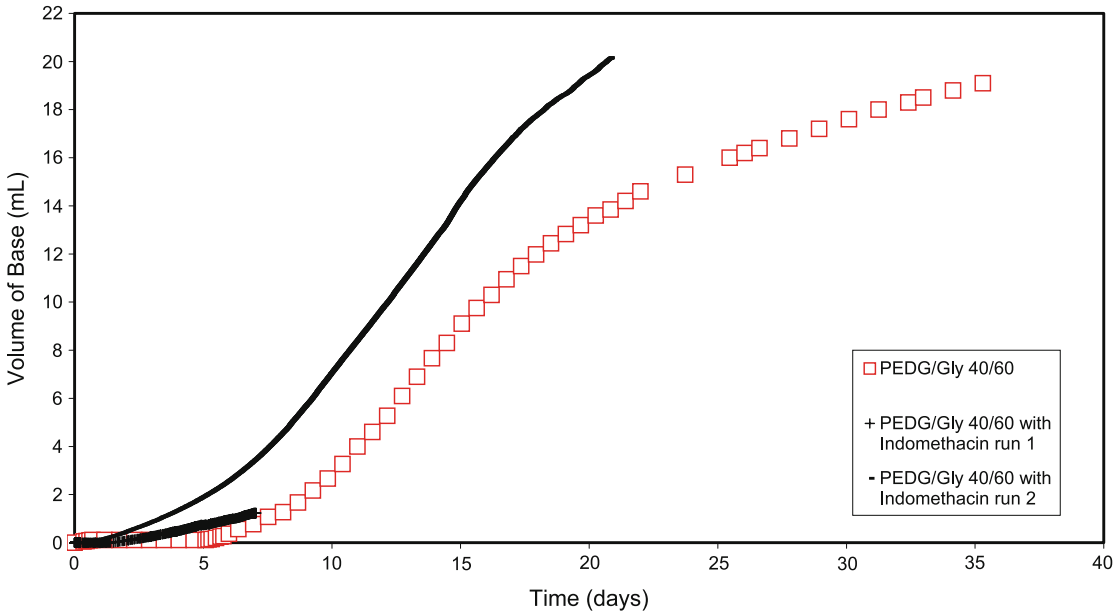

Fig. 7. Hydrolysis profiles at a pH Stat of 7.3 at 37°C of PEDG/Gly 40/60 and PEDG/Gly 40/60 films (thickness 0.13 mm), containing 10% wt. Indomethacin.

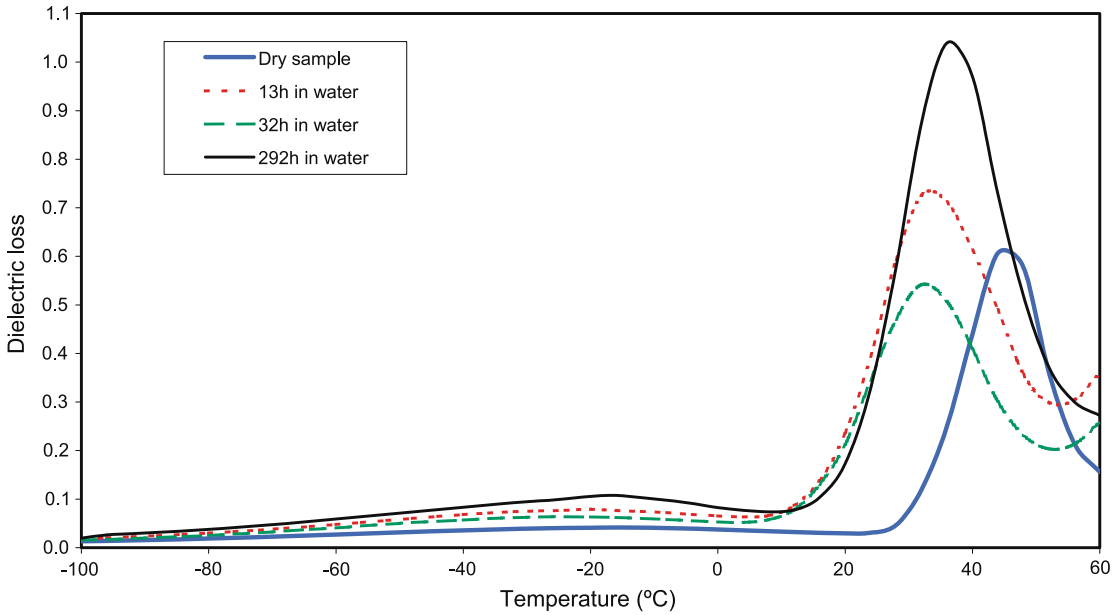

Fig. 8. Dielectric loss as a function of temperature at the constant frequency of 1 kHz of dry PEDG/Gly 40/60 film and for films (all thicknesses 0.076 mm) aged in DI water at 37°C for different amounts of time.

indomethacin at 37°C. As presented in Fig. 7, two separate hydrolysis runs (carried on up to 1 and 3 weeks) suggest that the drug may speed up the hydrolysis of the polymer. Specifically, the induction time for hydrolysis is reduced from 5–6 to1–2 days for the drug-loaded material. Nevertheless, delayed hydrolysis of 1–2 days may still help prevent the burst effect, especially in cases where more hydrophilic drugs are released from the polymer carrier. The basis for faster polymer degradation in the presence of this drug has not yet been determined. A number of reasons come to mind, including increased porosity caused by compounding the crystallizable drug into the polymer matrix.

Dielectric Relaxation Spectroscopy Study

The relatively long induction period associated with the hydrolysis of PEDG/Gly 40/60 films followed by a rather rapid rate of hydrolysis is a unique behavior in synthetic polymers. To further explore this phenomenon, we decided to investigate possible molecular interactions between water molecules and polymer chains at different stages of the aging (degradation) process.

One of the techniques particularly suitable for the investigation of molecular dynamics in polymers is dielectric relaxation spectroscopy (DRS). Dipole characteristics of

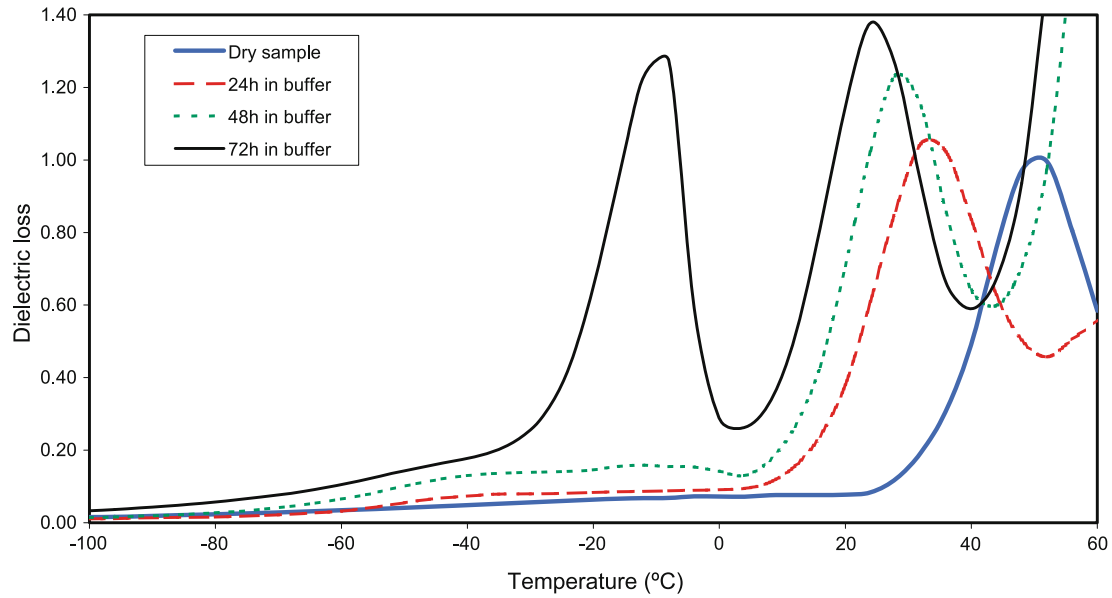

Fig. 9. Dielectric loss as a function of temperature at the constant frequency of 1 kHz of dry PEDG/Gly 40/60 film and for films (all thicknesses 0.076 mm) aged in phosphate buffer at 37°C for different amounts of time.

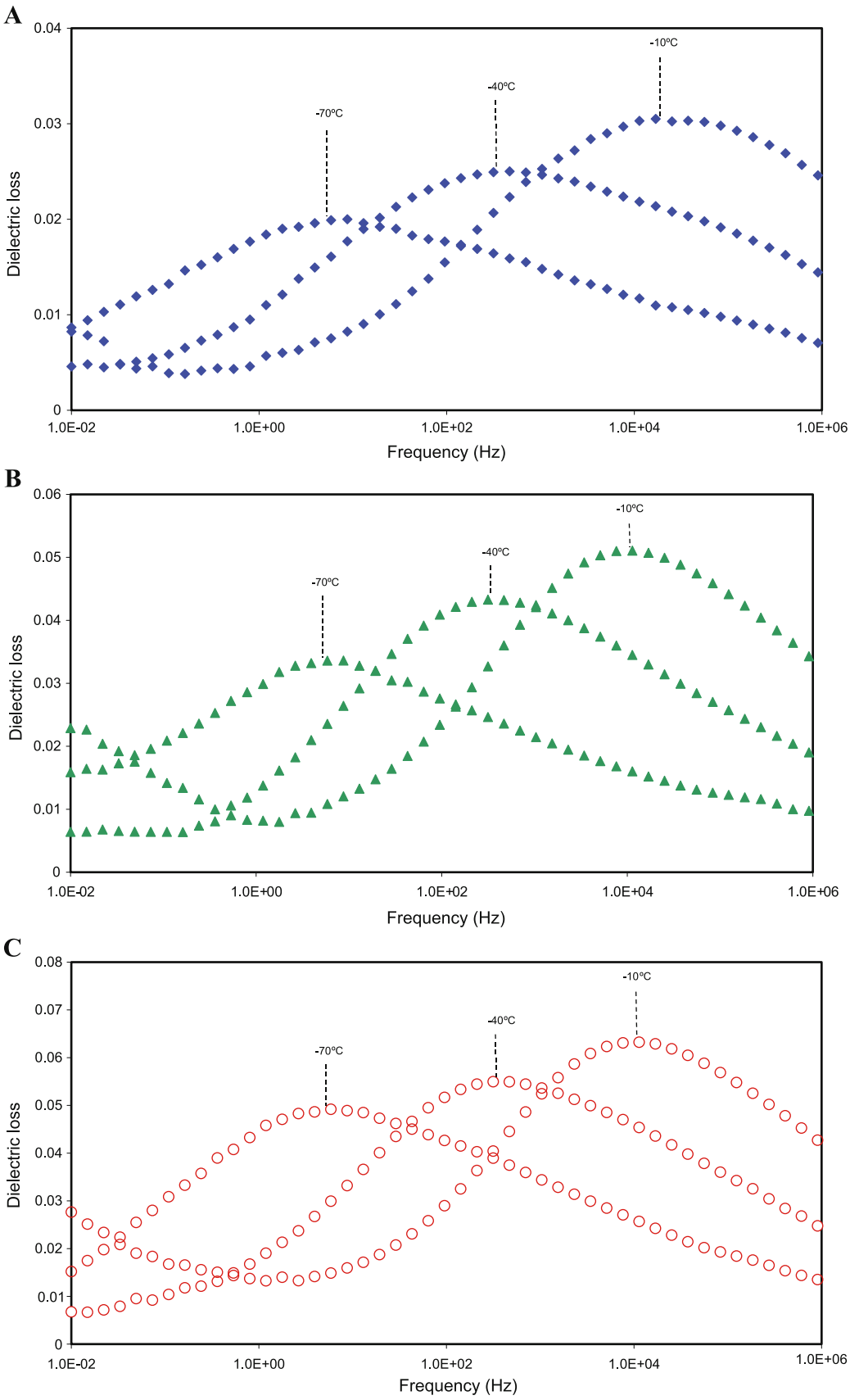

Fig. 10. Dielectric loss, featuring β secondary relaxation, as a function of frequency, obtained at the constant temperatures of −10, −40, and −70°C for dry PEDG/Gly 40/60 film and for the films (all thicknesses 0.076 mm) aged in DI water at 37°C for (A) 0 (dry), (B) 13, and (C) 32 h.

melt-extruded 3-mil (0.076 mm)-thick PEDG/Gly 40/60 films were analyzed in dry form after aging in DI water or buffer solution for selected time intervals. Figure 8 represents the dipole loss of the polymer films at the constant frequency of 1 kHz as a function of measuring temperature (temperature domain presentation) with a heating rate of 1°C/min, after being immersed in DI water at 37°C for various lengths of time. Two relaxation processes related to each dielectric curve are visible in the spectrum displayed in Fig. 8. The main (α dipole) relaxation, which is connected with the onset of large-scale motions of the chain segments in the glass transition temperature (T_g) region, is located at about 40°C in dry samples under the given experimental conditions. Because absorbed water strongly influences the T_g of the polymer and acts as a plasticizer, the location of the α relaxation is shifted to the lower temperatures for water-aged samples (to approximately 30°C). The secondary (β dipole) relaxation is connected with localized motions of short CH_2 sequences with involvement of the ester groups and ether groups typical for this polymer. This low-intensity peak in Fig. 8 is located at temperatures around −20°C for all samples studied in DI water (up to 292 h).

Dipole relaxation spectra of PEDG/Gly 40/60 films immersed in buffer solution at 37°C produced remarkably different results. Dipole loss spectra of buffer-aged samples in the temperature domain (heating rate 1°C/min, frequency 1 kHz), shown in Fig. 9, indicate the birth and continued growth of a new secondary relaxation peak located at about −10°C. This peak was first detected in the sample aged after 48 h, and then was observed to grow in intensity with aging time. At the same time, the α relaxation peak associated with segmental motions showed the expected shift to lower temperatures caused by the water plasticizing effect. The effects described were reproducible.

Analysis of secondary dipole relaxations peaks identified in Figs. 8 and 9 was performed next in the frequency domain settings, scanning the samples at constant temperature using frequency sweeps between 100 Hz and 1 MHz. Examples of such measurements are plotted in Fig. 10A–C, where dielectric loss in frequency domain for PEDG/Gly 40/60 films is presented as a function of both aging time and testing temperature. This type of analysis can help us obtain the apparent activation energy of the secondary relaxation process, which in a sense is a measurement of how easily dipole segments relax in the dielectric field. From frequency sweep measurements exemplified in Fig. 10A–C, we selected the frequency at the maximum dielectric loss for each sample scanned at the particular temperature and later use these data to compose the Arrhenius plot.

The summary of these calculations are presented in Fig. 11, where the natural logarithm of the frequency at the maximum loss is plotted as a function of reciprocal temperature for the secondary dipole relaxations observed for PEDG/Gly 40/60 films aged in both DI water and in buffer solution. First, we found that the original β dipole relaxation found in dry samples and in films aged in DI water have identical Arrhenius-type activation energy (56.4 kJ/mol). Second, our analysis revealed that this β relaxation is also present in films aged in the buffer solution with the same relaxation dynamics, as shown in Fig. 11. However, the new secondary relaxation (Fig. 11, open triangles), found in samples aged in buffer solution for about 48 h, is a faster process that is located at higher frequency than the original β relaxation measured at any given testing temperature. In addition, data connected to new relaxation peak produce a lower slope value in the Arrhenius plot, suggesting that lower activation energy is associated with this process (49.0 kJ/mol).

One of the possible explanations for the origin of this effect is that water molecules in the presence of ions (buffered solution, after all) do not cluster as well, and thus their distribution throughout the polymer matrix after 48

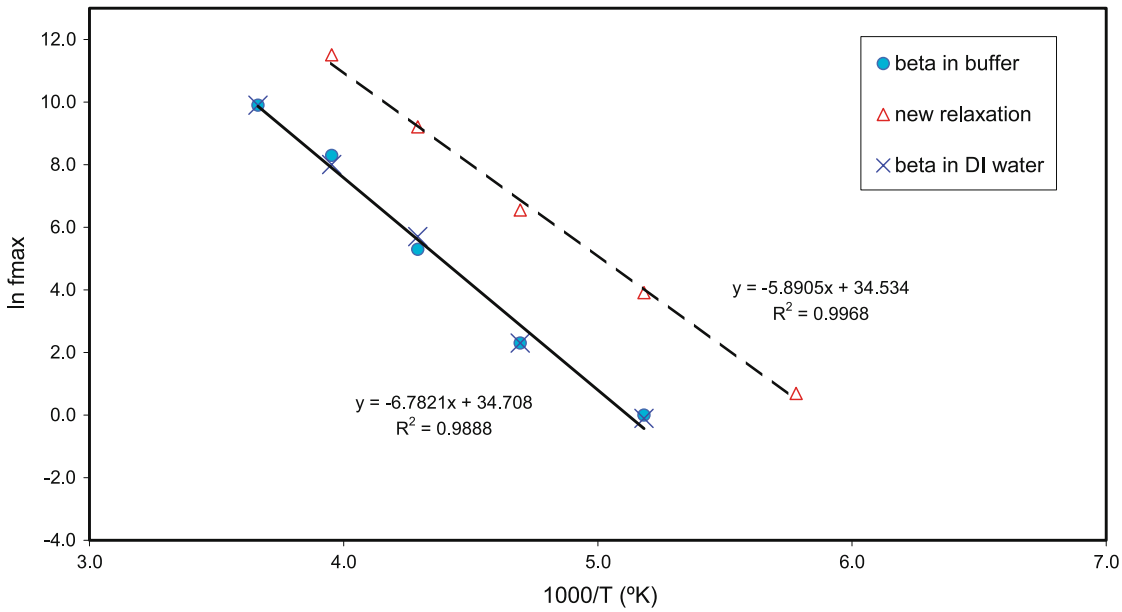

Fig. 11. An Arrhenius plot of natural logarithm of the frequency at the maximum loss *vs.* reciprocal temperature for β secondary relaxation of the PEDG/Gly 40/60 film (thickness 0.076 mm) obtained from the frequency domain after the films were aged in DI water or in buffer solution at 37°C.

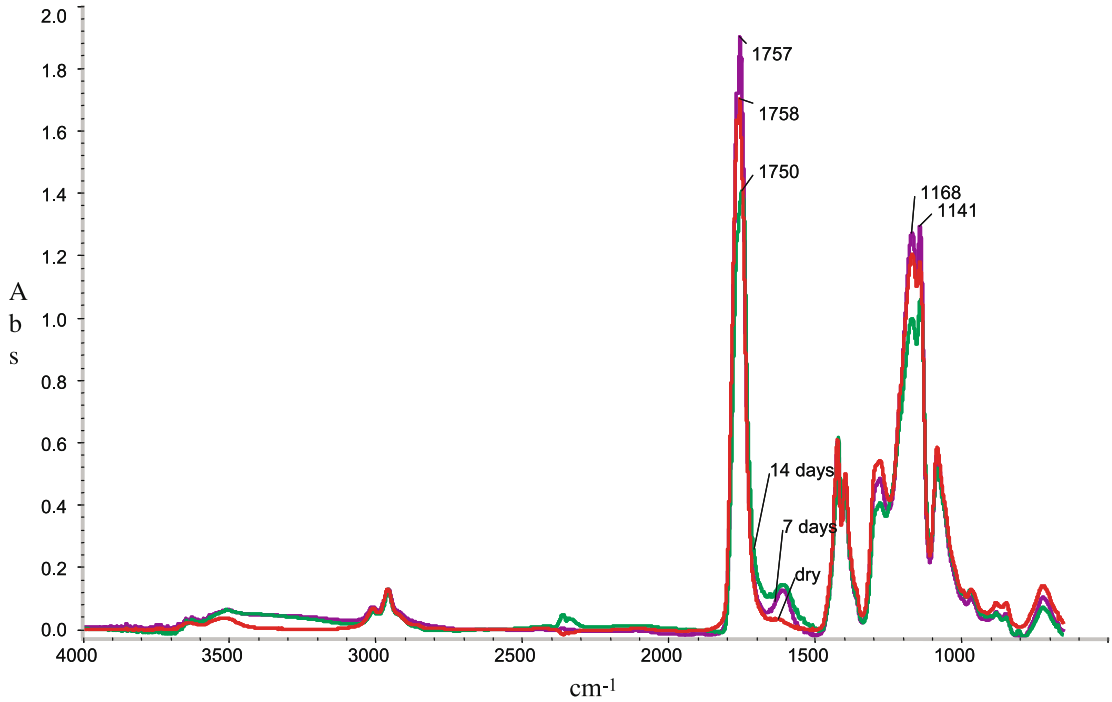

Fig. 12. MIR spectra of dry PEDG/Gly 40/60 film and the films (all thicknesses 0.076 mm) aged in buffer solution at 37°C for different amounts of time.

h was significantly enhanced. With this, internal mobility of the chain segments increase. Such lubricated motions of the short localized segments produce a new secondary relaxation that is considerably faster and proceeds with fewer difficulties (lower activation energy) than the original β process. The fact that the intensity of the new secondary relaxation increases with the aging time at the expense of the peak belonging to the standard β process may aid in supporting this hypothesis. It is worth mentioning that similar behavior is described in the literature. For instance, lowering the

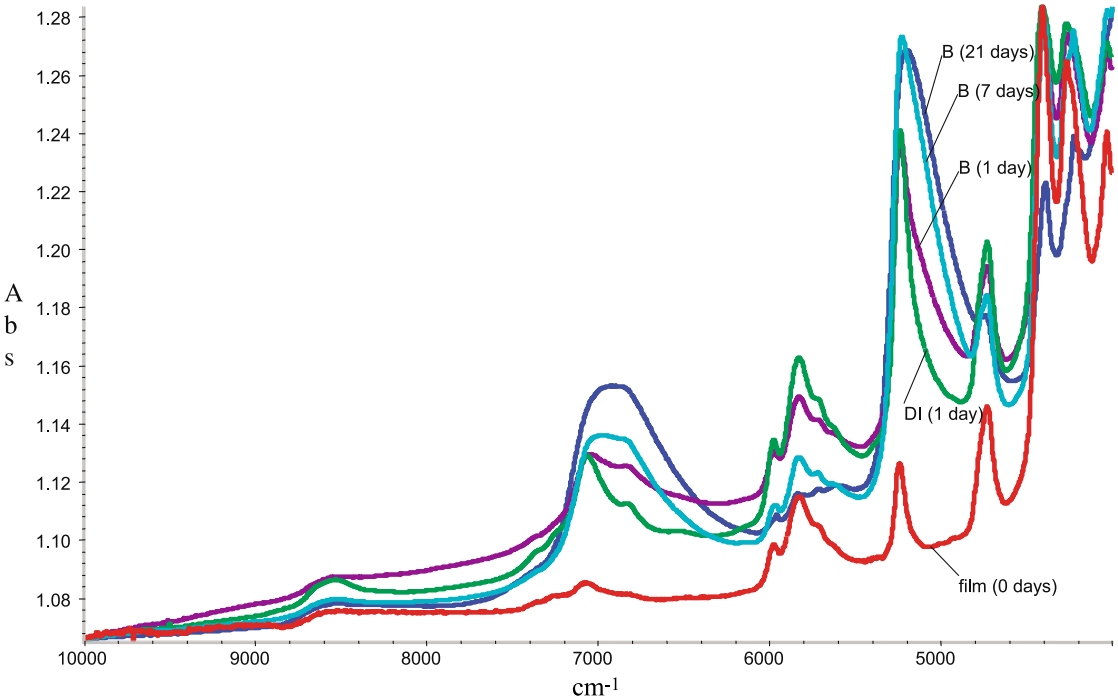

Fig. 13. NIR spectra of dry PEDG/Gly 40/60 film and the films (all thicknesses 0.13 mm) aged in DI water and buffer solution at 37°C for different amounts of time.

activation energy of the secondary relaxation in nylon 6,6 and amorphous cellulose with the addition of water was observed by dielectric spectroscopy (37) and dynamic mechanical analysis (38), respectively. In addition, an increase of the dielectric strength of one secondary relaxation process at the expense of the other secondary relaxation process with higher water content was reported earlier on nylon-6 utilizing thermally stimulated depolarization currents (TSDC) (39).

Vibrational Spectroscopy Studies

We have shown in our DRS study that water molecules affect the dynamics of the short segmental motion (approximately 3–5 carbon units) in the film samples aged in buffer solution after about 48 h. Our next goal was to determine the moment when the water molecules situate close enough to the atoms and functional groups to be able to initiate the hydrolysis. To explore molecular interactions in this domain, we decided to investigate the vibrational spectra of PEDG/Gly 40/60 films aged in both water and buffer media.

Specifically, MIR spectroscopy was used to investigate changes in carbonyl (1758 cm^{-1}) and ether group (1168 and 1141 cm^{-1}) vibrations as a function of aging time in water and buffer solution. Interestingly, MIR spectra of films immersed in DI water do not show any qualitative change even after 12 days at 37°C. However, spectroscopic analysis of vibration motions of films immersed in buffer solution revealed the onset of carbonyl hydrogen bonding processes between 7 and 14 days, as indicated in Fig. 12. This shift (from 1758 to 1750 cm^{-1}) can be associated with hydrogen bonding interaction between the carbonyl group and a proton donor, most likely hydrogen in a water molecule.

NIR spectroscopy, on the other hand, is particularly suitable for monitoring changes in water concentration and water molecular interactions as a function of aging time. Due to its relatively high hydrophilicity, the vacuum-dried PEDG/Gly 40/60 film quickly absorbs moisture from the air, producing the pronounced water combination peak located at 5240 cm^{-1}. This is shown in Fig. 13. The other water peak associated with a first overtone of stretching vibrations is located around 7000 cm^{-1}. Although this peak may also aid analysis, it is less reliable because it overlaps with other –OH group vibrations. After immersing the film in DI water and in a buffer solution for 24 h, the combination water peak grew in intensity in both media. However, the film aged in buffer shows a large, lower-frequency tail, indicating some type of hydrogen bonding interactions, probably intramolecular in nature, that are present at this time. After 7 days' aging in buffer, the water peak continuously grew in intensity with a more pronounced, lower-frequency tail, but the peak maximum location remained invariant. Finally, in the sample aged for 14 days in buffer, an increase in the peak's intensity was accompanied by a significant shift of the water peak to lower frequencies; this indicates the presence of intermolecular hydrogen bonding, most likely with the carbonyl group, as seen earlier by MIR spectroscopy.

Based on data from our multiple aging studies, we propose that water molecules, while being absorbed relatively quickly through the polymer matrix, do not produce a structured association with the PEDG/Gly 40/60 chains for an unusually long period. One should note that TDSC has already been used to examine the association of water with an absorbable polyester amide. Suarez *et al.* (40) described a lack of water association with the backbone phenyl ester group in the degradable poly(DTH succinate). They found that water seemed to be more tightly bound to the amide carbonyl group, but more loosely bound to the ester carbonyl group in the pendent chain. Although poly(DTH succinate) is a much more hydrophobic material than the one used in this study, this finding can serve to explain the unexpectedly high stability of that polymer toward hydrolysis. Dipole relaxation data observed from our system indicate that after about 48 h of aging in buffer medium, the water molecules start to affect the localized motions of polymer chains, but they are still not in proximity of the carbonyl moieties to initiate hydrolysis. After about a week's aging in buffer, vibrational spectra revealed the presence of the hydrogen bonding interaction between water and the carbonyl group, which coincides with the onset of hydrolysis reactions detected by the hydrolysis profiler. The question remains as to whether this delayed degradation mechanism may play a role in avoiding the burst effect in drug delivery applications, contributing to the experimentally observed zero-order release associated with our PEDG/Gly 40/60 copolymer. We are not yet in a position to definitively state the mechanisms or pinpoint the reasons responsible for this unusual behavior. We think that multiple factors are at work.

CONCLUSION

A novel amorphous synthetic absorbable polyester, 40/60 poly(ethylene diglycolate-*co*-glycolide), was found to provide zero-order release of a variety of NSAIDs with minimal or, in most cases, no burst effect. *In vitro* hydrolysis conducted at 37°C on this hydrophilic copolyester revealed an unusually long induction period (no hydrolysis for up to 6 days), followed by the relatively rapid hydrolysis. Data from dipole relaxation spectroscopy indicate that the water molecules do not structurally associate with the polymer chains in phosphate buffer for at least 48 h. After this period, a new secondary dipole relaxation peak having lower activation energy is formed, suggesting that water molecules begin to affect a short-chain segmental motion of the polymer. The presence of the hydrogen bonding interaction between carbonyl groups and water was detected by MIR and NIR spectra in films aged between 7 and 14 days in buffer. At this time point, water molecules seem to structurally associate near hydrolyzable groups in the polymer chain, setting the conditions to initiate the hydrolysis. We believe that the molecular interactions associated with this new synthetic absorbable material may find a critical utility in important medical applications, including drug delivery, adhesion prevention, medicated dressings, and others.

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