Biodegradable Poly(glycerin citrate) and Its Application to Controlled Release of Theophylline

Shixin Liu,[1] Man Jiang,[2] Sai Ye,[1] Xiaohong Xu,[1] Ping Lu,[1] Jian Dong[1,3]

[1]*Department of Chemistry, Shaoxing University, Shaoxing 312000, China*
[2]*Faculty of Materials Science & Chemical Engineering, Ningbo University, Ningbo 315211, China*
[3]*State Key Laboratory of Coordination Chemistry, Nanjing University, Nanjing 210093, China*

Received 28 January 2011; accepted 6 May 2011
DOI 10.1002/app.34886
Published online 22 November 2011 in Wiley Online Library (wileyonlinelibrary.com).

ABSTRACT: This study reports properties of a class of biodegradable polyesters based on citric acid and glycerin, both of which are safe ingredients in food, and their usefulness for drug control release applications. Transparent thin films of poly(glycerin citrate) (PGC) prepared by condensation polymerization were characterized by dynamic mechanical analysis, tensile testing, and FTIR spectroscopy. Depending on the acid-to-glycerin molar ratios, the crosslinked films could have glass transition temperatures varying from 30 to 81°C as shown by dynamic mechanical analysis. The ductile PGC films were more prone to hydrolytic degradation than poly(lactic acid). The controlled release properties of the PGC films were evaluated by a permeation study of an exemplary drug theophylline. The diffusion of theophylline in PGC film follows a Super Case II mechanism, but in PGC film modified with PEG4000, the diffusion follows approximately a Case II mechanism (near zero-order release mechanism). © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 124: 3633–3640, 2012

Key words: polyester; citric acid; glycerin; biodegradable; controlled release

INTRODUCTION

Synthetic biodegradable polyesters, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymers, are valuable bioresorbable materials in the field of surgery (suture materials and orthopedic devices) and sustained release drug delivery systems. PLA and PGA belong to the linear polyester materials. PLA itself is a hard and brittle plastic with high modulus, high strength, but low elongation at break (about 5%).[1–3] Because many of the body tissues have high elasticity, network polyester elastomers are gradually replacing the traditional linear materials.[4–7] For drug delivery purpose, the presence of crosslinks not only leads to excellent physical properties, but also increases degradation tendencies by eliminating (or minimizing) crystalline structure. The extent of crosslinking may result in ductile to glassy materials, or precisely engineered resilient gels with controlled rates of drug delivery. At present, several kinds of network-type biodegradable polyesters have been studied[8–12]; however, some require complicated procedures of preparation, or involve monomer sources which have limited availability.

In this study, we investigate a type of crosslinked polyesters by using citric acid (CA) and glycerin (G) as main monomer raw materials, both of which are FDA approved safe ingredients for food (generally recognized as safe, GRAS).[13] The reaction product is a polymeric network, capable of forming biodegradable hydrogels when exposed to aqueous solutions, and their hydrolytic degradation intermediates/products, glycerin citrate esters are also categorized by FDA as GRAS.[13] CA is a renewable resource-based substance, mainly manufactured by fermentation of starch or glucose. CA also participates in a fundamental metabolic cycle ("Krebs cycle") in all living cells that use oxygen as part of cellular respiration. In aerobic organisms, the Krebs cycle is part of a metabolic pathway involved in the chemical conversion of carbohydrates, fats, and proteins into CO_2 and H_2O to generate a form of usable energy. Upon forming polyesters, the unused (or unreacted) hydroxyl group in CA can act as bonding sites for drugs and yield hydrophilicity to the polymers. A recent study concerning polycondensation of CA with gluconolactone, a type of polyol, showed that the network polyester formed is a brittle material with an elongation at break of only 4%.[14] Since the value of polycitrate materials for drug control

Correspondence to: J. Dong (jiandong@usx.ed.cn).
Contract grant sponsor: National Natural Science Foundation of China; contract grant number: 20974063.
Contract grant sponsor: Department of Science and Technology of Zhejiang Province; contract grant number: 2009R10040.
Contract grant sponsor: Natural Science Foundation of Zhejiang Province; contract grant number: Y4090504.

applications has not been recognized or explored, we present here the fundamental properties of the polyesters [poly(glycerin citrate); PGC] formed from CA and G, and those of the copolyesters formed in the presence of several types of polyols. The diffusion kinetics of PGC films is evaluated by using theophylline as an example for sustained release. This compound is commonly used to treat chronic asthma by opening the air passages to the lungs, making it easier to breathe. Theophylline is well known to have a narrow therapeutic index which requires constant monitoring of serum theophylline concentrations to minimize toxicity. It is crucial to have slow release forms of theophylline to prevent adverse effects and promote efficient use.[15] Therefore, despite its efficiency to treat chronic obstructive pulmonary disease, theophylline has to be administered in controlled release forms.[16,17] The crosslinked polycitrates are found to be highly useful for controlled release applications.

TABLE I
Samples with Various Molar Ratios of Citric Acid (CA), Glycerin (G), and a Diol or Polyol Modifier Used in This Study[a]

Sample name	CA	G	Diol or polyol modifier
PGC B1	125	100	–
PGC B2	115	100	–
PGC B3	110	100	–
PGC B4	100	100	–
PGC B5	95	100	–
PGC B6	90	100	–
PGC B7	85	100	–
PGC B8	75	100	
PGC T1	100	90	10 (ethylene glycol)
PGC T2	100	90	10 (PEG400)
PGC T3	100	90	10 (PEG1000)
PGC T4	100	90	10 (PEG4000)
PGC T5	10	100	0.0024 (PEG4000)
PGC T6	100	90	10 (gluconolactone)

[a] The values are molar ratios of [-COOH] in CA, [-OH] in polyol, and [-OH] in G.

EXPERIMENTAL

Materials

Anhydrous CA, G, ethylene glycol, poly(ethylene glycol) (PEG) 400, PEG1000, and PEG4000 were all purchased in analytical grade from Sinopharm (Shanghai, China). δ-Gluconolactone was acquired in analytical grade from Shanghai Aladdin Reagent Co.

Polymerization

CA and G were first mixed in different molar ratios of the COOH groups in CA to the OH groups in G, ranging from 100/75 to 100/125, and then 0.50 mL of sulfuric acid (with a concentration of 40% by weight) was added to the mixture. The colorless solution was heated for 0.5 h at 80°C in a water bath, cast uniformly on clean aluminum foil surfaces, and heated at 110°C in an oven for 12 h, resulting in bubble-free ductile polymeric films (see Table I for compositions of sample series PGC B1–B8). To further modify the films, the acid–glycerin mixture solutions were added with an additional diol or polyol (denoted as samples PGC T1–T6 in Table I), and solutions were reacted in the same condition. The resulting films were transparent and could be removed easily from the metal surfaces. All the samples were sealed in air-tight bags and analyzed immediately after they were made.

Characterization

Infrared spectra were recorded after adding at least 32 scans at a resolution of 4 cm^{-1} by using a Nicolet Nexus FTIR spectrometer (Thermo Electron, Madison, WI). Dynamic mechanical analysis was carried out on DMA8000 system (Perkin–Elmer, Co. Waltham, MA) in tension mode at a frequency of 1.0 Hz, at a temperature ramp rate of 3 °C/min. The samples were cut in a size of 10 mm × 3 mm ×0.5 mm. Differential scanning calorimetric analysis was conducted on Diamond DSC instrument (Perkin–Elmer, Co., Waltham, MA) at a temperature scanning rate of 10 °C/min. During the DSC test, a temperature program was set in four steps: (1) heating from −50 to 120°C, (2) an isotemp step at 120°C for 5 min, (3) cooling from 120°C to −50°C, and (4) reheating from −50 to 150°C. The data were recorded in the final step. Tensile test of the films were prepared by cutting samples (approximately 5.00 mm wide and 0.50 mm thick) with a standard dumbbell-shaped mold and measured at a stretching rate of 50 mm/min according to ASTM D638-10, by using a universal tensile test machine (model CMT 6104, SANS Testing Machine Co., Shenzhen, China). The strain defined as elongation percentages was measured by the computerized (integrated) tensile testing machine which can automatically record the elongated lengths while the samples are stretched and the initial lengths between sample grips. Three to four parallel samples were made in the tensile test and the data were averaged. For degradation test, square film samples were cut in a size of 10 mm × 10 mm × 0.5 mm and immersed in pH = 7.4 phosphate buffer saline solutions (PBS) at 37°C (physiological condition) under gentle stirring. The sample weight loss averaged from three parallel tests was measured at a time interval of every 12 h.

Drug permeation test was performed by using a horizontal Valia-Chien cell assembly held on a

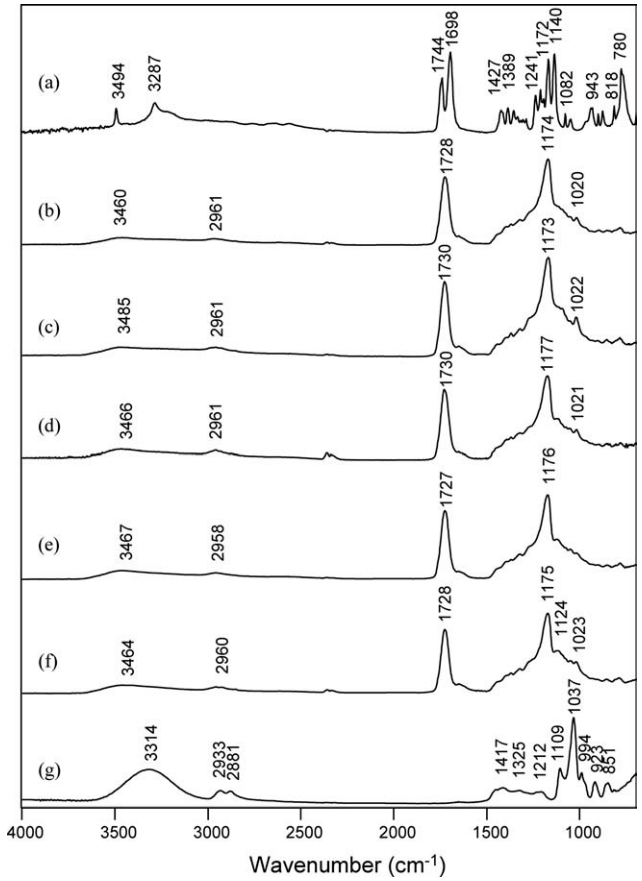

Figure 1 FTIR spectra of raw materials and PGC films (with different molar ratios of the materials): (a) pure CA material; (b) PGC B1 film (CA/G = 125/100); (c) PGC B3 film (CA/G = 110/100); (d) PGC B4 film (CA/G = 100/100); (e) PGC B6 film (CA/G = 90/100); (f) PGC B8 film (CA/G = 75/100); (g) pure G material.

magnetic stirrer, according to our previous study.[18] Briefly, a PGC film was sandwiched between two circular windows, each on a half-cell positioned side-by-side. Three hundred milliliters of phosphate buffer (50 m*M*, pH 7.0) solution were added to fill the receptor half-cell. The donor half-cell was filled with 300 mL of a theophylline solution (0.0005 g/mL, in 50 m*M* phosphate buffer, pH 7.0). Ten milliliters of the permeated solution were withdrawn from the receptor cell at a time interval of every 1 h and 10 mL of buffer solution was added immediately to compensate the receptor solution. To determine the concentration of theophylline, a series of 10 mL of theophylline solutions were prepared in phosphate buffer (50 m*M*, pH 7.0) solution at different concentrations (c, in 10^{-5} g/mL), and the absorbance values (Abs) at 272 nm were measured on a HP8453 UV–VIS spectrophotometer (Hewlett–Packard Co., Santa Clara, CA) to obtain a standard calibration line c ($\times 10^{-5}$ g/mL) = 0.0622 Abs + 0.0006, with a linear regression coefficient of $R^2 = 0.9999$.

RESULTS AND DISCUSSION

Structure, mechanical, and viscoelastic properties of PGC films

PGC films were characterized by FTIR spectroscopy and the spectra are shown in Figure 1 (see Table I for the nomenclature and compositions of the films). For comparison, FTIR spectra of the raw materials CA and G are shown in Figure 1(a,g), respectively. Prominent peaks near 1727–1731 cm^{-1} and 1174 cm^{-1} in Figure 1(b–f) are due to the absorption of the citryl ester groups formed, because of the C═O stretching and C─O stretching, respectively. In addition, the appearance of broad peaks at 3469 cm^{-1} in Figure 1(b–f) indicates the presence of hydrogen-bonding structures, which may improve the hydrophilicity of the polymers. The absence of the COOH doublet peaks from the CA raw materials near 1744 and 1698 cm^{-1} in the films indicates that the esterification proceeded almost completely with ease.

The stress–strain mechanical tests on the PGC films showed that the elongation-at-break can reach above 40% (Fig. 2). Table II also lists the averaged tensile strengths and elongation-at-break of the films. The data indicate that the PGC films are ductile, and may show plastic deformation instead of brittle failure for samples in Figure 2(a–c). Although the PGC films have tensile strengths very close to the crosslinked polyester films prepared by polycondensation between citrate acid and gluconolactone (a type of polyol) reported recently, the latter are very brittle materials with elongation-at-break of less than 4%.[14] For the monomer molar ratios of citric acid to glycerin used here, the moderate variations of the tensile strengths and elongation-at-break indicate their modest dependence on the degree of

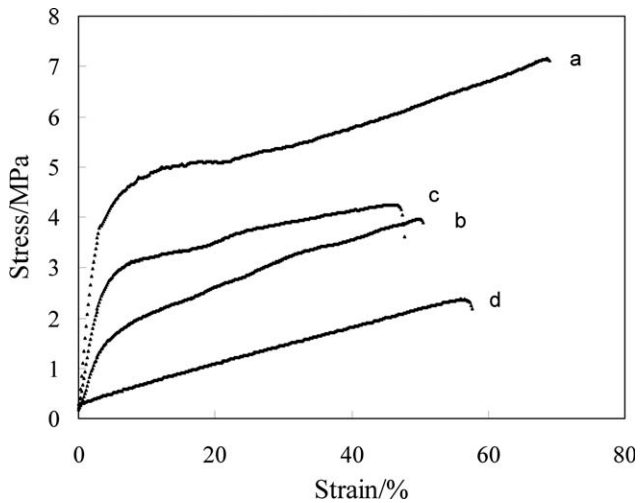

Figure 2 Stress–strain curves of PGC films (with different molar ratios of CA to G): (a) PGC B5 film (CA/G = 95/100); (b) PGC B7 film (CA/G = 85/100); (c) PGC B4 film (CA/G = 100/100); (d) PGC B2 film (CA/G = 115/100).

TABLE II
Tensile Testing and Dynamic Mechanical Analysis Results of PGC Films

Sample name	PGC B2	PGC B4	PGC B5	PGC B7
Molar ratio of CA/G	115/100	100/100	95/100	85/100
Elongation-at-break (%)	50.6 ± 5.7	42.3 ± 9.4	69.2 ± 8.4	52.3 ± 2.8
Tensile strength (MPa)	2.6 ± 0.9	5.7 ± 1.5	6.5 ± 5.4	5.5 ± 3.1
T_g (°C)	60	81	30–60	n.m.
Storage modulus at 20 °C/MPa	145	1247	2120	n.m.

crosslinking. On the other hand, the glass transition temperatures described below are more sensitive to the monomer molar ratios. The good ductility of the PGC polymers is essential for formation of films and valuable for thin film drug delivery systems. For such delivery applications, a dissolving film or oral drug strip to administer drugs via absorption in the mouth (buccally or sublingually) requires the strips to be relatively flexible and devoid of the brittleness.

Figure 3 displays dynamic mechanical analysis results of three PGC films. In the loss factor (tan δ) versus temperature curves (top panel of Fig. 3), the sample with CA/G = 100/100 underwent a glass transition at a temperature near 81°C, higher than the other two samples. A small change in the molar ratio of the acid to glycerin used affects the crosslinking density. The broad and asymmetric peaks of the glass transitions in the tan δ curves reflect the presence of asymmetric distribution of the chain lengths between the crosslinks and/or local-scale heterogeneity in the polymer (i.e., broad distributions of polymer α-relaxation times).[19] The changes in the tan δ peak heights indicate changes in the elastic resistance with the polymer formulation. Since the T_g positions of such crosslinked polyesters are just moderately above the room temperature, it is possible to reduce their T_g to near or below room temperature by copolymerization with a polyol comonomer, as described below.

The storage modulus versus temperature curves of the PGC films are illustrated in the bottom panel of Figure 3 (their modulus values at 20°C are listed in Table II). The DMA test shows that the storage modulus is sensitive to the acid-to-glycerin ratio used. For the sample with CA/G = 95/100, the storage modulus (2.12 GPa) is very close to that of common polyesters, including poly(L-lactic acid).[20]

Modification of PGC films by polyols

The effect of a small amount of polyols as comonomers on the polyesters formed was studied. The selected polyols were gluconolactone, ethylene glycol, PEG400, PEG1000, and PEG4000. Each was mixed with glycerin according to the molar ratios of [polyol-OH]/[glycerin-OH] as listed in Table I, and the polyester films formed from the mixed polyols were first examined by FTIR. As shown in Figure 4, it is evident that the key infrared peaks of these films are quite similar. Again, the broad strong peak at 3475–3482 cm^{-1} indicates the presence of the hydroxyl groups in hydrogen bonded state, which is critical for the hydrophilicity and mechanical properties. The citryl ester peaks are observed at 1727–1731 cm^{-1} for C=O stretching while the intense peaks near 1173–1174 cm^{-1} are due to C—O

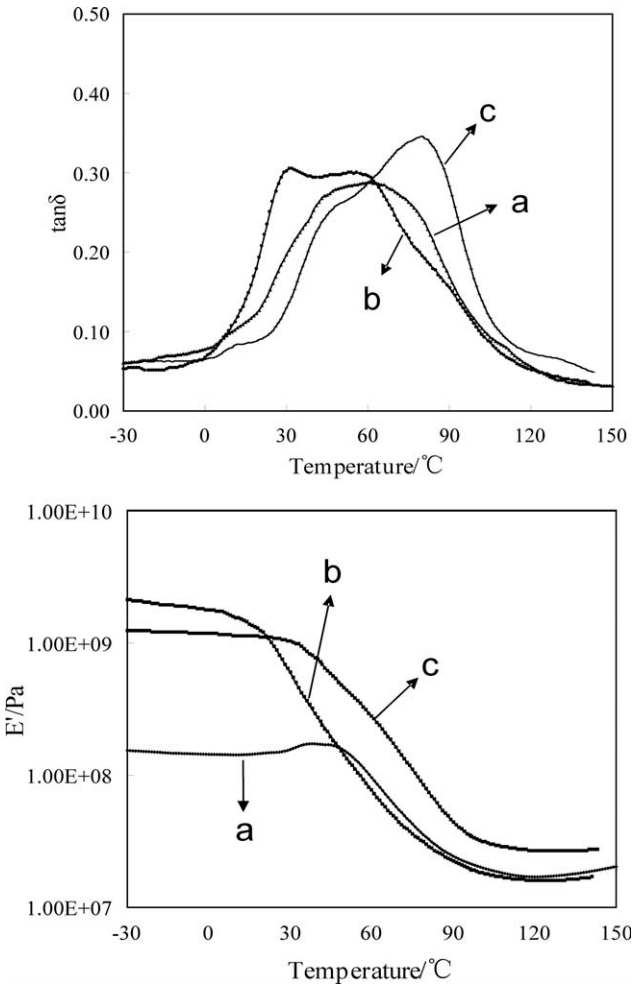

Figure 3 DMA curves of PGC films prepared in different molar ratios of CA to G: (a) PGC B2 film (CA/G = 115/100); (b) PGC B5 film (CA/G = 95/100); (c) PGC B4 film (CA/G = 100/100). Top: tan δ versus temperature; Bottom: storage moduli E' in logarithmic scale versus temperature.

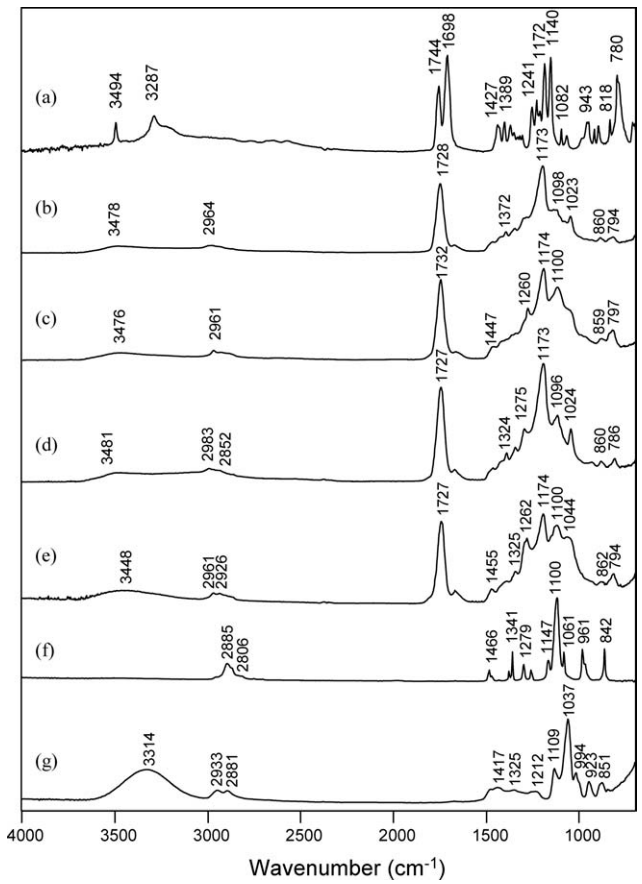

Figure 4 FTIR spectra of PGC films copolymerized with CA and polyol mixtures : (a) pure CA material; (b) PGC T1 film (CA/ethylene glycol/G = 100/10/90); (c) PGC T3 film (CA/PEG1000/G = 100/10/90); (d) PGC T6 film (CA/gluconolactone/G = 100/10/90); (e) PGC T4 film (CA/G/PEG4000 = 10/100/0.0025); (f) pure PEG4000 material; (g) pure G material.

stretching of the ester group. The weak peaks between 800 cm^{-1} and 1500 cm^{-1} can be mainly attributed to vibrations from the glycerin moiety. The intense bands at 1100 cm^{-1} in the films containing PEG [Fig. 4(c,e)] can be assigned to the PEG chains which has an intense band at 1100 cm^{-1} [Fig. 4(f)].

Results of differential scanning calorimetric analysis of these films are shown in Figure 5. As can be seen in Figure 5, the T_g positions move to lower temperature side with the increase of the molecular weight of PEG used. This can be understood from the flexible nature of the PEG chains. The significant lowering of the T_g by using PEG comonomers is valuable for adjustment of the drug release profiles, as described below. The product formed from a mixture of ethylene glycol and glycerin has a relatively high T_g (approximately 25°C) in this series. DSC analysis shows that the PGC films formed from neat glycerin has a T_g near 32°C which is reasonable since T_g measured from DSC may be 20–30°C lower than that obtained from the DMA analysis.

Hydrolytic degradation and water absorption of the PGC films

The degradation occurring in pH = 7.4 buffer solutions at 37°C was followed by weight loss measurement of the films and the results are shown in Figure 6. After 96 h, the PGC films prepared from CA and G only were completely degraded, while the degradation was completed in 72 h for the film prepared with the addition of comonomer PEG1000. This phenomenon can be interpreted by their different water absorptivities described below.

Network polyesters prepared by glycerin and sebacic acid monomers (PGS polymers) could be

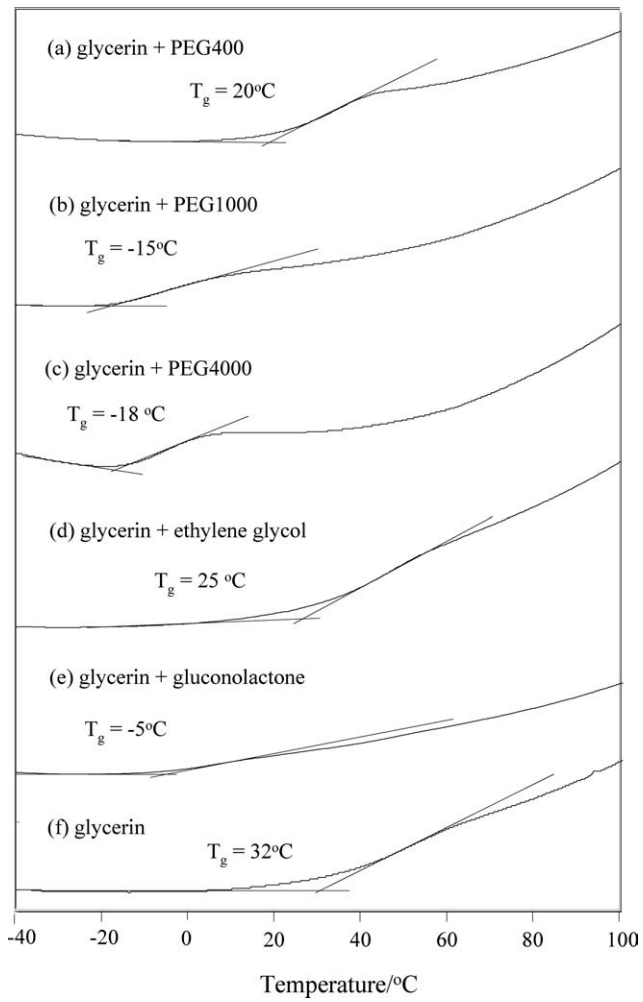

Figure 5 DSC curves of PGC films formed with CA and different polyol mixtures: (a) PGC T2 (CA/PEG400/G = 100/10/90); (b) PGC T3 (CA/PEG1000/G = 100/10/90); (c) PGC T4 (CA/PEG4000/G = 100/10/90); (d) PGC T1 (CA/ethylene glycol/G = 100/10/90); (e) PGC T6 (CA/gluconolactone/G = 100/10/90); (f) PGC B4 (CA/G = 100/100). All ratios are molar ratios of [-COOH] in CA to the [-OH] in polyol (or diol) to the [-OH] in glycerin.

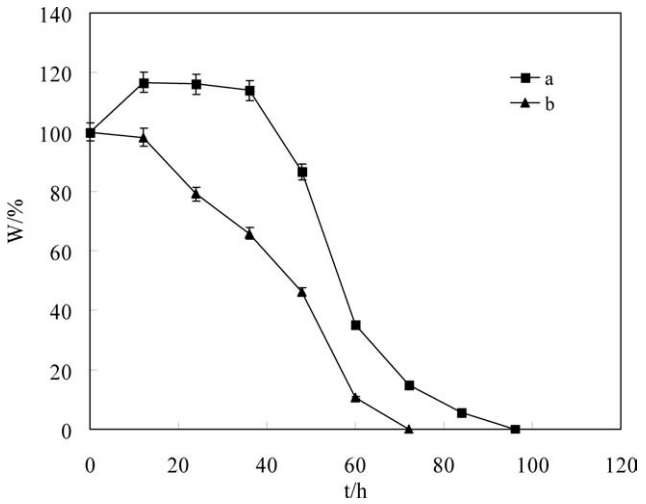

Figure 6 Degradation of PGC films in phosphate buffer saline (pH = 7.4, 37°C): (a) PGC B4 film (CA/G = 100/100) (solid squares); (b) PGC T3 film (CA/PEG1000/G = 100/10/90) (solid triangles). The ratios are molar ratios of [-COOH] in CA to the [-OH] in PEG1000 to the [-OH] in G.

degraded within 60 days in pH = 7.4 buffer solutions (37°C),[4] while polyesters synthesized from CA and octamethylenediol (POC polymers) could be degraded in 180 days under similar conditions.[5] Hence, the PGC films are more degradable than these polyesters. Poly(DL-lactide) (PLA_{50}) could be degraded in 37°C pH 3.7 solutions in 20 weeks,[21] however, it had very little weight loss (only 3%) in the first 70 days because of its partial crystallinity. Between 70 and 84 days, a weight loss burst up to 87% was observed for PLA_{50}, corresponding to the release of internal oligomers. Thereafter, weight loss increased only slightly to reach 93% at the end of 126 days. The smooth degradation of PGC network polymers under physiological conditions provides us with a good chance to use them for drug controlled release applications before they are cleared *in vivo*.

Table III lists the water absorption levels of PGC films prepared with different kinds of polyols mixed with glycerin after soaking for 24 h. The weight increase (in percentages) of the films becomes the most obvious for the polyester with PEG1000. This reflects its higher swelling ratio and lower crosslinking density in the network polymer formed, most likely due to the large size of the hydrophilic PEG chain.

Drug permeation test

PGC films with a monomer feed molar ratio of CA/G = 95/100 and that of CA/G/PEG4000 = 10/100/0.0024, respectively, were evaluated for drug permeation test. In the latter film, the total weight of PEG4000 added was only about 0.5% relative to the CA used, creating a smaller crosslinking density than the former film. Theophylline, with a planar geometry and a molecular dimension of 0.35 nm × 0.35 nm, was used as a drug example in this study due to the reasons described in the Introduction section. The diffusion kinetics was measured in an approach similar to our recent study of drug diffusion in hydrogels.[18] *In vitro* release profiles of theophylline in the two types of PGC films are shown in Figure 7. The data reflect the early release kinetics of the drug solute. Linear regression of the theophylline concentration (C_t, in 10^{-5} g/mL) in the acceptor half-cell versus time (t, in h) gives the relationships for release in the PGC films, shown in Figure 7. Evidently, permeation of theophylline through the polyester films was almost linear, but the film without PEG4000 (open squares in Fig. 7) underwent a retarded diffusion, showing essentially no drug permeation in the first 4 h, after which the permeation occurred smoothly. The retardation is possibly due to plasticization by the buffer solution to lower the intrinsic T_g of the film, from above the room temperature to near the room temperature.

Permeability coefficients (P) were calculated by using the following equation[22,23]:

$$-\ln\left(1-\frac{2C_t}{C_0}\right)=\frac{2A}{V}Pt \qquad (1)$$

where C_t is the concentration of theophylline in the receptor half-cell at time t, C_0 is the initial concentration of theophylline in the donor half-cell (0.0005 g/mL), V is the volume of the each half-cell (300 mL), and A is the effective area of the permeation window (0.9499 cm^2). A plot of $-(V/2A)\ln[1-2(C_t/C_0)]$ versus t gave the slope P (shown in Fig. 8). The calculated permeability coefficient P for theophylline in the film with CA/G = 95/100 is 0.4713 cm/h and

TABLE III
Water Absorption of PGC Copolymerized with Different Polyols After 24 h

Sample name	PGC B4	PGC T3	PGC T1	PGC T6
Polyol used	neat glycerin	PEG1000/ glycerin = 10/90	ethylene glycol/ glycerin = 10/90	gluconolactone/ glycerin =10/90
Water absorption/ % wt	17.7 ± 0.3	53.4 ± 0.4	20.5 ± 0.2	17.7 ± 0.2

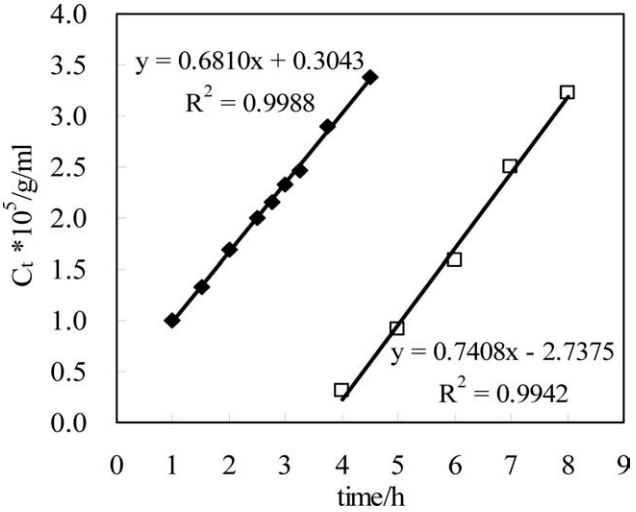

Figure 7 Release profiles of theophylline in PGC B5 film (CA/G = 95/100) (open squares) and PGC T5 film (CA/G/PEG4000 = 10/100/0.0024) (solid diamonds).

that in the film with CA/G/PEG4000 = 10/100/0.0024 is 0.4339 cm/h. This indicates a small decrease of the drug's ability to penetrate the film after modification of the PGC by the PEG.

The following equation is used to estimate the cumulative amount of theophylline released

$$M_t = \frac{V\rho_n + \sum_{i=1}^{n-1} \rho_i V_i}{A} \quad (2)$$

where M_t is cumulative release amount (in grams), V and A are the same as in eq. (1), ρ_n and ρ_i are the receptor half-cell's concentration at the nth sampling and at the ith sampling, respectively, V_i is the sampling volume (10 mL).[18]

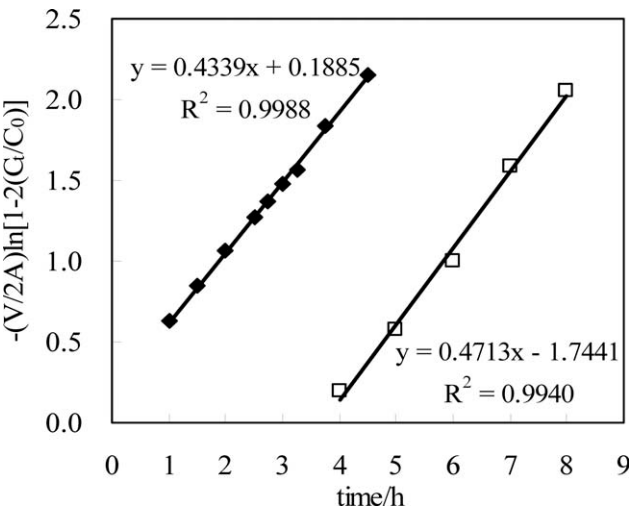

Figure 8 Determination of the permeability coefficients for theophylline through PGC B5 film (CA/G = 95/100) (open squares) and PGC T5 film (CA/G/PEG4000 = 10/100/0.0024) (solid diamonds).

The log value of cumulative amount (ln M_t) of theophylline released at time t is plotted against ln t, to obtain the release exponent value (n) from the Peppas eq. (3):

$$\ln M_t = n \ln t + C \quad (3)$$

In general, if the diffusional exponent $n < 0.45$, the diffusion is Fickian; when $0.45 < n < 0.89$, the drug diffusion follows non-Fickian transport mechanism, corresponding to coupled effect of diffusion and polymer relaxation/erosion; $n > 0.89$, the diffusion is mainly aided by polymer relaxation. $n = 1$ indicates ideal zero-order release mechanism (Case II transport mechanism). Values of $n > 1$ indicate Super Case II transport mechanism, implying swelling and relaxation of hydrophilic polymer chains help to transport.[24,25]

We find that the cumulative release of theophylline (shown in Fig. 9) can be fitted by the above Peppas equation very well (see fitting results shown in Fig. 9). The release exponent value (n) of the PGC film with CA/G = 95/100 is 3.4031 (with a regression coefficient $R^2 = 0.9780$), while that for the film with CA/G/PEG4000 = 10/100/0.0024 is found to be 0.9213 (with a regression coefficient $R^2 = 0.9959$). Therefore, the release exponent of the PGC film without PEG4000 corresponds to a Super Case II transport mechanism, implying that the transport is driven by swelling and relaxation of the hydrophilic polymer chains, instead of the drug's chemical potential gradient. It is fascinating that in the PEG modified film the diffusion is mainly assisted by

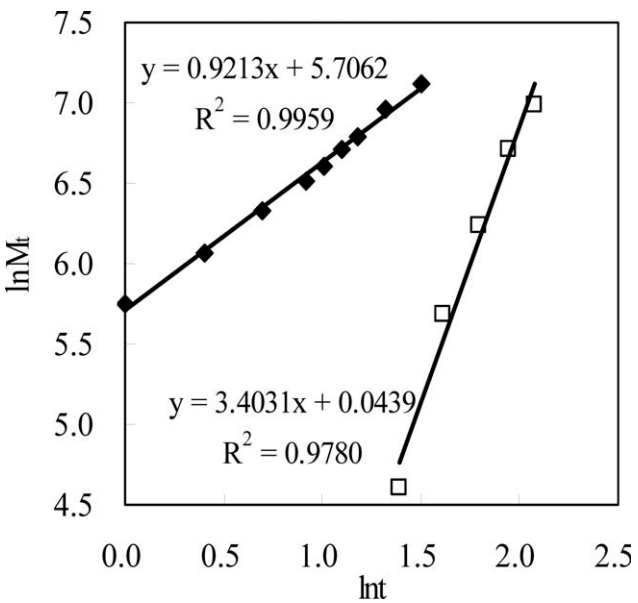

Figure 9 Cumulative release of theophylline through PGC B5 film (CA/G = 95/100) (open squares) and PGC T5 film (CA/G/PEG4000 = 10/100/0.0024) (solid diamonds) analyzed by Peppas equation.

polymer relaxation, and very close to a zero-order release mechanism (Case II transport mechanism) ($n \approx$) This means that the release rate becomes nearly constant and independent of the theophylline concentration used, which is the target for drug delivery. Thus, the PGC films can effectively control the release rate by their structures, yielding well-defined kinetics. Because several factors can influence the transport of drug molecules through polymers, including the specific interaction of the drug with the polymer, the internal structure and viscoelastic properties of the polymer, the swelling forces by the solvent and restriction forces exerted by the crosslinks, and exact analysis of such factors have been a very complex process and beyond our current understanding.[26]

CONCLUSIONS

In this study, crosslinked biodegradable polycitrates were developed and applied for controlled release of theophylline. Transparent and ductile polyester films can be conveniently formed by polycondensation from citric acid and glycerin. The T_g of the hydrophilic network polymers are in a range of 30–81°C as determined by DMA method. Modification of the polyesters by certain polyol comonomers shows that participation of PEG can lower the polymer T_g significantly. The PGC films are susceptible to hydrolytic degradation, and more ductile than poly(DL-lactide) or polyesters formed by citric acid and gluconolactone. They are degraded to nontoxic products in 4 days in neutral pH buffer solution at 37°C. The controlled release performance of the PGC films has been examined by a permeation study of theophylline through the films. The release of theophylline in PGC film follows a Super Case II mechanism, while in PGC film modified with 0.5% PEG4000 the release kinetics can be described by a near Case II mechanism mainly aided by polymer relaxation, namely, near zero-order release kinetics.

References

1. Lemmouchi, Y.; Murariu, M.; Dos Santos, A. M.; Amass, A. J.; Schacht, E.; Dubois, P. Eur Polym J 2009, 45, 2839.
2. Bhardwaj, R.; Mohanty, A. K. Biomacromolecules 2007, 8, 2476.
3. Jiang, L.; Wolcott, M. P.; Zhang, J. Biomacromolecules 2006, 7, 199.
4. Wang, Y.; Ameer, G. A.; Sheppard, B. J.; Langer, R. Nat Biotechnol 2002, 20, 602.
5. Yang, J.; Webb, A. R.; Ameer, G. A. Adv Mater 2004, 16, 511.
6. Yang, J.; Webb, A. R.; Pickerill, S. J.; Hageman, G.; Ameer, G. A. Biomaterials 2006, 27, 1889.
7. Venkitachalam, R.; Mark, J. E.; Noda, I. J Appl Polym Sci 2005, 95, 1519.
8. Djordjevic, I.; Choudhury, N. R.; Dutta, N. K.; Kumar, S. Polymer 2009, 50, 1682.
9. Lei, L.; Ding, T.; Shi, R.; Liu, Q.; Zhang, L.; Chen, D.; Tian, W. Polym Degrad Stab 2007, 92, 389.
10. Gyawali, D.; Tran, R. T.; Guleserian, K. J.; Tang, L.; Yang, J. J Biomater Sci Polym Ed 2010, 21, 1761.
11. Peracchia, M. T.; Gref, R.; Minamitake, Y.; Domb, A.; Lotan, N.; Langer, R. J Controlled Release 1997, 46, 223.
12. Aroguz, A. Z.; Baysal, K.; Tasdelen, B.; Baysal, B. M. J Appl Polym Sci 2011, 119, 2885.
13. http://www.fda.gov/Food/FoodIngredientsPackaging/default.htm
14. Tsutsumi, N.; Oya, M.; Sakai, W. Macromolecules 2004, 37, 5971.
15. Woodcock, A. A.; Johnson, M. A.; Geddes, D. M. Lancet 1983, 322, 610.
16. Weinberger, M.; Hendeles, L.; Bighley, L.; Munson, J. S. N Engl J Med 1978, 299, 852.
17. Hendeles, L.; Weinberger, M.; Johnson, G. Clin Pharmacokinet 1978, 3, 294.
18. Jin, L.; Lu, P.; You, H.; Chen, Q.; Dong, J. Int J Pharm 2009, 371, 82.
19. Deppe, D. D.; Dhinojwala, A.; Torkelson, J. M. Macromolecules 1996, 29, 3898.
20. Ljungberg, N.; Wesslen, B. Polymer 2003, 44, 7679.
21. Li, S.; McCarthy, S. Biomaterials 1999, 20, 44.
22. Peppas, N. A.; Wright, S. L. Macromolecules 1996, 29, 8798.
23. Peppas, N. A.; Wright, S. L. Eur J Pharm Biopharm 1998, 46, 15.
24. Ritger, P. L.; Peppas, N. A. J Controlled Release 1987, 5, 37.
25. Lowman, A. M.; Peppas, N. A. In Encyclopedia of Controlled Drug Delivery; Mathiowitz, E., Ed.; Wiley: New York, 1999; pp 397.
26. De Kee, D.; Liu, Q.; Hinestroza, J. Can J Chem Eng 2005, 83, 913.