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Preparation and Characterization of Biodegradable Poly(sebacic anhydride) Chain Extended by Glycol as Drug Carrier

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ABSTRACT: Glycol modified poly(sebacic anhydride) (PSA), a biodegradable poly(ester anhydride) copolymer, was prepared by melt bulk reaction of PSA and glycol. The structure of PSAG was characterized by FTIR, ^{1}H NMR, and GPC. The results indicate the formation of ester bonds along the polyanhydride backbone. The thermal properties and crystallinity changes of the polyanhydrides were investigated using DSC and XRD. *In vitro* degradation experiments show that the degradation rate of PSAG is slower than that of PSA because of the introduction of the glycol. Using dexamethasone as a model drug, the *in vitro* release rate of a drug from PSAG discs was shown to be slower than that from PSA discs, and no initial burst releases were observed for 13 days. PSAG is therefore a promising candidate, which control the release of an incorporated drug over a sustained period of time. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

KEYWORDS: polyanhydride; biodegradation; poly(sebacic anhydride); glycol; drug delivery

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INTRODUCTION

Synthetic biodegradable polymers are attractive candidate materials for biomedical applications like sutures, drug delivery devices, orthopedic fixation devices, wound dressings, temporary vascular grafts, different types of tissue engineered grafts, etc.[1–3] The extensively investigated biodegradable polymers for drug controlled release systems include polyesters,[4,5] polyanhydrides,[6] poly(amino acid),[7,8] poly(ortho ester),[9,10] polyphosphazenes, polycarbonate etc.[11–13]

Polyanhydrides are a particularly promising class of biodegradable polymers for drug delivery systems, because of their chemical properties, good tissue biocompatibility *in vivo*. Surface-eroding property of polyanhydrides in aqueous medium makes them desirable for drug controlled release and functional soft tissue substitutes.[14–16] The first application of polyanhydrides as a bioerodible matrix for drug controlled delivery systems was reported by Rosen et al. in 1983.[17] By variation of the kind of monomer or the ratio of monomer to comonomer, desirable release profiles can be realized and erosion durations can last from weeks to months.[18]

Hundreds of polyanhydrides such as aliphatic polyanhydrides, aromatic polyanhydrides, crosslinked polyanhydrides,[19,20] poly(ester anhydride),[21–23] poly(ether anhydride),[24–26] and poly(amide anhydride)[27,28] have been synthesized in the last 20 years. However, only poly(sebacic anhydride) (PSA) and its derivatives have been widely studied and applied in controlled release system.[29–36] For example, poly(1,3-*bis*-*p*-carboxyphenoxy propane-*co*-sebacic acid) (20 : 80 CPP : SA) has been approved by the FDA to deliver carmustine for the treatment of brain cancer.[37]

The poly(ester anhydride) behaves both the bulk degradation and surface erosion properties, which belong to polyesters and polyanhydrides, respectively. Thus, this kind of materials may provide extended advantages as compared to other polymer alone. By modulating the ratio of different segments of polyanhydride, we can prepare materials more suitable for controlled drug delivery systems. Poly(sebacic anhydride-*co*-ethylene glycol) was synthesized by introducing poly(ethylene glycol) (PEG) into a polyanhydride system has been reported.[38] However, this is the first case that the small molecule glycol as chain extender is introduced into polyanhydride system.

In this article, a family of functional poly(ester anhydride) copolymers, PSA modified by the small molecule glycol (PSAG), was synthesized based on sebacic acid and glycol. PSAG showed lower melt temperature (T_m) and lower

crystallinity, which was more conducive for its application in controlled release system. The influences of introduction of glycol and ester bonds in the *in vitro* degradation and release of PSAG were mainly investigated with dexamethasone as model drug at 37°C.

EXPERIMENTAL

Materials

Glycol was provided by Baishi (Tianjin, China). Sebacic acid (SA) was obtained from Damao Chemical Reagent Manufactory (Tianjin, China) and recrystallized twice in ethanol before further operation. Dexamethasone was provided by Yilong Co (Guangzhou, China). Acetic anhydride (99.5%), toluene (anhydrous), ethyl ether (anhydrous), petroleum ether (anhydrous), and chloroform (anhydrous) were all analytical grade and purchased from Kewei (Tianjin, China).

Preparation of PSAG

Prepolyanhydride (PPSA) was prepared from the purified diacid monomer (10 g) by refluxing in the presence of excess acetic anhydride (100 mL) under nitrogen protection at 140°C for 40 min. Acetic acid and excess acetic anhydride were removed under vacuum at 50–60°C. The hot clear viscous residue was dissolved in dry toluene, and then cooled to 0°C overnight. The precipitate was separated by filtration and washed thoroughly with a 1 : 1 mixture (v/v) of anhydrous ethyl ether and petroleum ether for three times. The white purified prepolymer was dried under vacuum at room temperature for 48 h, and stored at −20°C until being used.

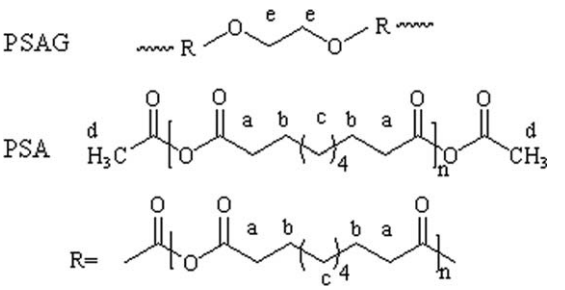
Melt polycondensation of PPSA (10 g) was carried out at 180°C under vacuum for 90 min.[22,37] The product was dissolved into dry chloroform, and precipitated in cooled and anhydrous ethyl ether. The white precipitate was collected by a low speed desk centrifuge (LD5-2A, Beijing Medical Centrifuge Factory, China), dried under vacuum at room temperature for 48 h, and stored at −20°C before usage.

PSA (10 g) and glycol (56.4 mg) were dissolved in excess dry chloroform in a 100 mL round-bottom flask equipped with a mechanical stirrer. Chloroform was distilled at 140°C for 20 min, and the melt-polycondensation continued at 180°C under vacuum and nitrogen protection for 60 min. The raw product was dissolved into dry chloroform, and precipitated in cooled and anhydrous ethyl ether. The precipitate was separated by filtration and washed with anhydrous ethyl ether for three times. Finally, PSAG was dried under vacuum at room temperature for 48 h and stored at −20°C. The structure of PSAG is shown in Scheme 1.

Characterization of PSAG

FTIR spectroscopy (Nicolet MAGNA-IR 560, Bio-Rad, US) was used to confirm the structures of PSAG and their degradation products.[39,40] The polymer samples were pressed into KBr pellets (1 : 100 copolymer/KBr ratio) and analyzed with IR data manager software.

^{1}H NMR spectrum was recorded with a Bruker 500 MHz (INOVA, Varian, US), and the chemical shifts were reported in ppm units with tetramethylsilane (TMS) as internal standard. The 1 wt % polymer solutions in $CDCl_3$ were used for ^{1}H NMR measurement.



Scheme 1. Structure of PSAG.

The gel permeation chromatography system (GPC, Agilent 1100) was used to measure the molecular weight distributions of PSAG at the flow rate of 1.0 mL/min, using tetrahydrofuran as eluting solvent and polystyrene as the standards. Amounts of the samples were about 5 mg/mL.

DSC thermograms of PSAG and drug-loaded PSAG were recorded using DSC (Model-204F1, Netzsch, Germany). DSC measurements were carried out at 10°C/min heating rate using a second scan under dry nitrogen atmosphere and ranged from −25°C to 200°C. Rescans were performed immediately after each scan, in order to erase the thermal history.

XRD spectra of PSAG and drug-loaded PSAG were carried out using an X-ray diffraction (Rigaku D/max 2500 v/pc, Rigaku, Japan) and the scanning was done over a range of 2θ angles from 6° to 60°.

In Vitro Hydrolytic Degradation of PSAG

The PSAG discs (200 mg in weight, 13 mm in diameter, and 1 mm in thickness) were prepared by compression molding from PSAG powder with a press (769YP-24B, Tianjin KeQi New Technology, China) of 40 MPa at room temperature for 5 min. The surface morphologies of degradable products of PSA and PSAG discs were visualized by environmental scanning electron microscopy (XL30ESEM, Phlilps, Holland).

The degradation of PSAG discs was performed in 100 mL phosphate buffer saline (PBS, pH 7.4) in an incubator shaker (SHZ-88, Jintan Medical Treatment Instruments manufactory, China) at 75 rpm and 37°C. A 100-mL aliquot of PBS was replaced by fresh PBS at appropriate time intervals. The erosion rate of PSAG was measured by the change of dry weight of the polymer samples as shown in Formula (1).

$$wt\% = \frac{W_0 - W}{W_0} \times 100\% \quad (1)$$

In eq. (1), W_0 is the initial weight of PSAG discs and W is the weight of PSAG discs after degradation.

In Vitro Release of Drug-Loaded Discs

The drug-loaded PSA and PSAG discs (200 mg in weight, 13 mm in diameter, and 1 mm in thickness) containing dexamethasone were prepared by compression molding from drug and PSAG mixed powder with a press (769YP-24B, Tianjin KeQi New Technology, China) of 40 MPa at room temperature for 5 min. The drug-loaded discs were immersed in a conical flask containing 60 mL PBS (pH 7.4). *In vitro* release was preformed

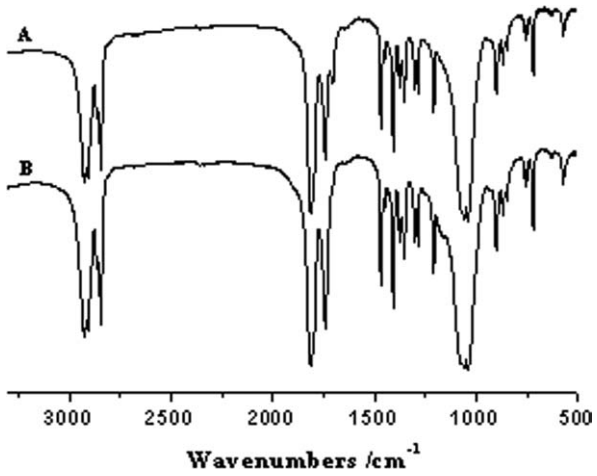


Figure 1. FTIR spectra of (A) PSA and (B) PSAG.

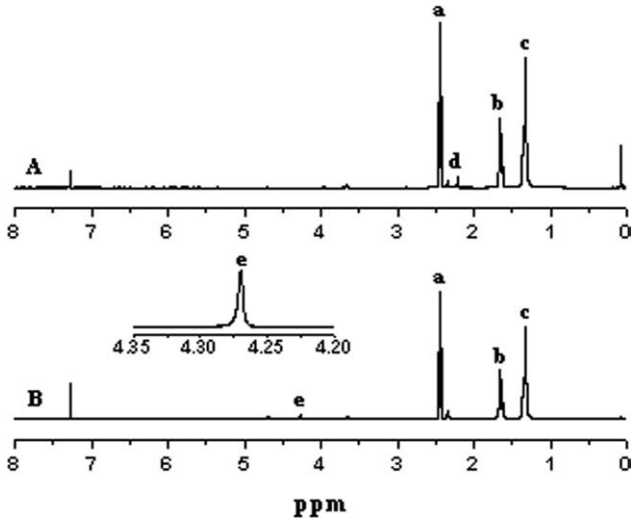


Figure 2. [1]H NMR of (A) PSA and (B) PSAG.

in an incubator shaker (37°C, 130 rpm) during the duration of the study (13 days). Aliquots (50 mL) were collected from the conical flask at predetermined intervals and replaced with equal volume of fresh PBS to maintain sink conditions throughout the study. The concentration of dexamethasone in the release medium was determined using HPLC at a wavelength of 249 nm in this article. The release medium was injected into a HPLC (Agilent 1100, US) with a GEM ODS-2 (250 × 4.6 mm^2) C18 column. The mobile phase, composed of acetonitrile and water (62 : 38, v/v), was performed at a temperature of 30°C and a flow rate of 1.0 mL/min. Before this analysis, the standard curve of dexamethasone was calibrated by HPLC. The accumulated release was calculated as follows:

$$E_r = \frac{V_e \sum_{1}^{n-1} C_i + V_0 C_n}{m_{drug}} \quad (2)$$

where E_r is the accumulated release amount (%), V_e is the volume of replaced fresh PBS (50 mL), V_0 is the initial volume (60 mL), C_i is the drug concentration (μg/mL) at i time, n is the number of replacement, and m_{drug} is the mass of drug in the drug-loaded copolyanhydride discs (μg).

RESULTS AND DISCUSSION

Characterization of PSA and PSAG

The FTIR spectrum of PSAG is illustrated in Figure 1. The peaks at 2935–2915 cm^{-1} and 2854–2840 cm^{-1} correspond to the methyl and methylene vibrations. The peaks at 1816 and 1740 cm^{-1} are the characteristic peaks of anhydride bonds. The C—O—C stretching band appears at 1100 cm^{-1}. Disappearance of carboxylic carbonyl band at 1704 cm^{-1} shows that all of carboxylic groups change into anhydride linkages. The dramatic differences between the spectra of PSAG and PSA lie on that the relative intensity of peak at 1740 cm^{-1} of PSAG becomes stronger, and the peak at 1100 cm^{-1} (C—O—C stretching band) becomes broader, which indicate that ester linkages are contained in PSAG.

The [1]H NMR spectrum of PSAG is displayed in Figure 2. In this figure, distinct chemical shifts at δ = 1.32, 1.63, 2.2, and 2.43 ppm are all well resolved, and belong to the hydrogen atoms of individual functional groups on PSA. However, introducing glycol into the polymer causes another chemical shift for methylene protons of glycol next to the ester bond of PSAG at δ = 4.27 ppm. The chemical shift are disappeared for methyl protons of PSA at δ = 2.2 ppm. These phenomena can confirm the reaction between PSA and glycol. The molecular weight (M_n) and polydispersity index (PDI) of PSA were 4800 and 1.09, and the M_n and PDI of PSAG were 15,300 and 1.24.

DSC analysis was performed on polyanhydride and drug-loaded polyanhydride are presented in Figure 3. Introduction of glycol destroyed the regularity of PSA, and thus made the degree of crystallinity and the melt temperature of polyanhydride that decreased lightly. The melt temperature of PSA and PSAG appeared around 75 and 71°C, respectively. However, the melt temperature of drug-loaded PSA and PSAG segment were shifted to 77 and 75°C, respectively. Melting temperatures of polyanhydride increased when incorporated with 1%

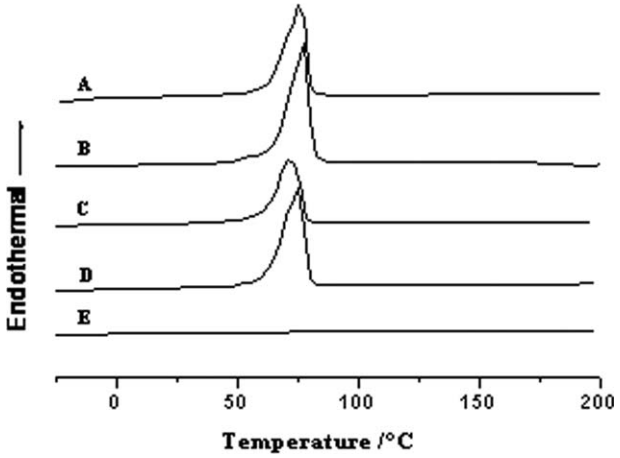


Figure 3. DSC thermograms of (A) PSA, (B) dexamethasone-loaded PSA, (C) PSAG, (D) dexamethasone-loaded PSAG, (E) dexamethasone. The dexamethasone-loaded amount was 1 wt %.

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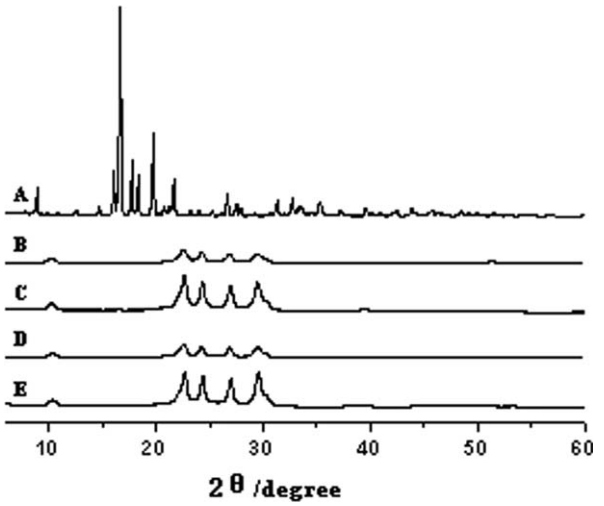

Figure 4. XRD of (A) dexamethasone, (B) PSA, (C) dexamethasone-loaded PSA, (D) PSAG, (E) dexamethasone-loaded PSAG. The dexamethasone-loaded amount was 1 wt %.

dexamethasone, but there is no melting peak of drug in the thermogram. Since, the compatibility of drug and matrix is very good, dexamethasone was dispersed uniformly in polyanhydride matrix and promoted crystallization of matrix.

XRD spectra suggest that the ester linkages forming after the introduction of glycol make the degree of crystallinity of polyanhydride that decrease lightly. In Figure 4, the degree of crystallinity of PSA and PSAG were around 62.2% and 60.9%, respectively. However, there is an increase in crystallinity when drug is loaded into PSA and PSAG. The degree of crystallinity of drug-loaded PSA and PSAG were around 63.6 and 61.8%, respectively. These results are consistent with DSC analysis reports.

In Vitro Degradation of PSA and PSAG

Degradation is an important character for biomaterials. In this article, *in vitro* degradation of PSA and PSAG at pH 7.4 in PBS at 37°C was evaluated. The hydrolytic degradations of PSA and PSAG were performed in 100 mL PBS and the degradation media was replaced with 100 mL fresh PBS every day.

"Anhydride loss" is the diminution of anhydride characteristic peaks and intensification of the acid characteristic peaks in FTIR during degradation of the polymer.[25] FTIR spectra of PSAG before and after degradation are shown in Figure 5(a). After degradation, the wavenumbers of the characteristic bands of PSAG, such as the methylene-characteristic bands, the anhydride bond-characteristic bands, and the C—O—C stretching band, are almost changeless. However, the strong carboxylic hydroxyl band appears between 3300 and 2500 cm^{-1} and the strong carboxylic carbonyl band appears at 1704 cm^{-1} and their intensities become stronger with increasing the degradation time. The intensities of the anhydride bond-characteristic bands at 1816 and 1740 cm^{-1} and the C—O—C stretching band at 1100 cm^{-1} obviously become weaker. The above phenomena illuminate that the content of carboxylic groups in PSAG sample gradually increases and the number of anhydride bonds in PSAG sample gradually decreases in the degradation process.

On day 5 following degradation, the ESEM images of the degradation by-products of PSA and PSAG discs [Figure 5(b–i)] show that the discs have many holes, the areas of serious erosion have continuous groove. The rate of degradation of PSAG discs is slower than that of PSA discs.

The degradation rate was determined by weight loss of the polymers. As expected, the degradation rate of polyanhydride

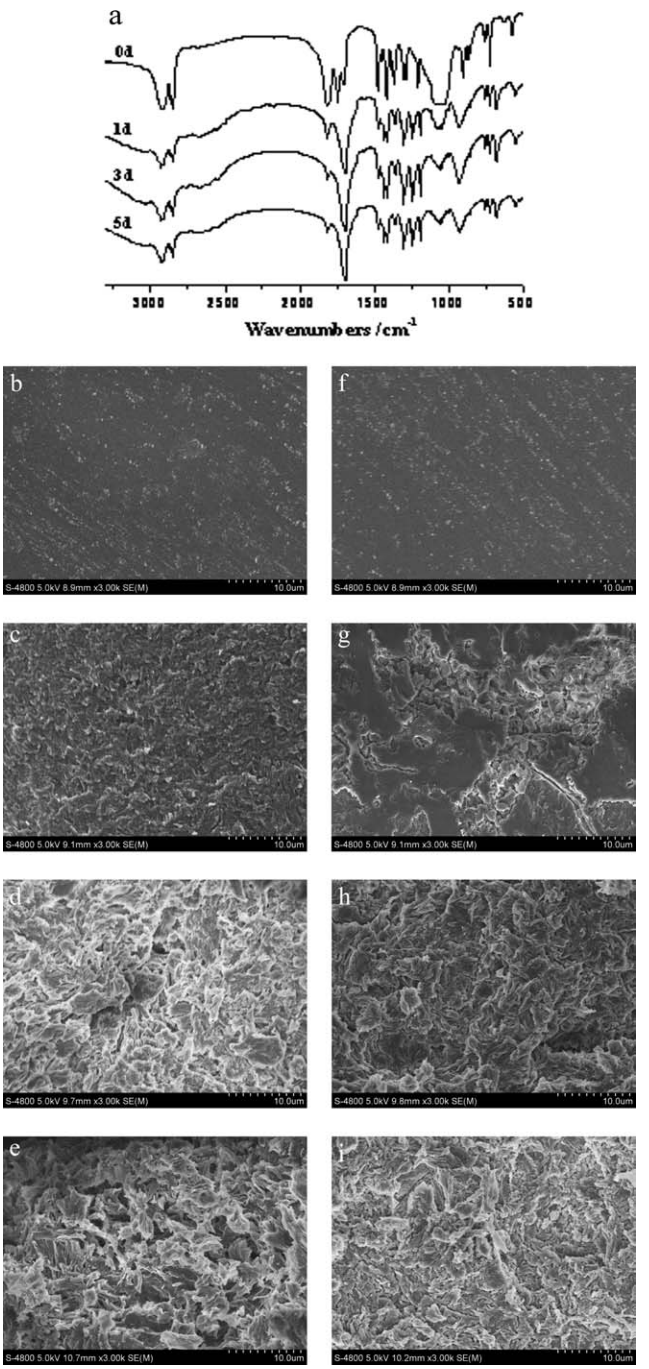

Figure 5. (A) FTIR spectra of degradation by-products of PSAG at different time points. (B–E) Surface morphology of PSA discs after degradation for 0, 1, 3, 5 days, respectively (3000×); (F–I) Surface morphology of PSAG discs after degradation for 0, 1, 3, 5 days, respectively (3000×).

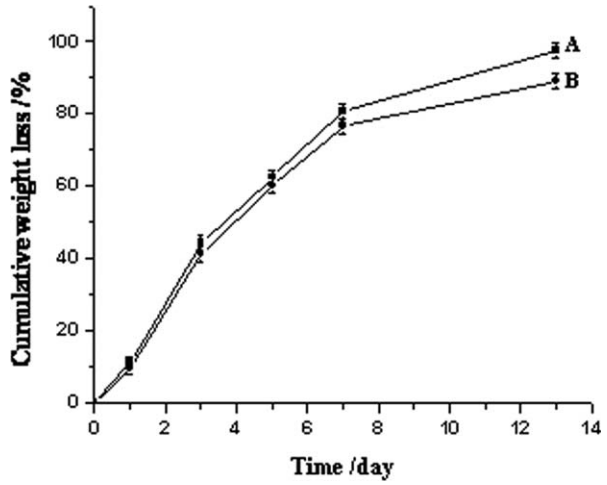

Figure 6. *In vitro* degradation profiles of (A) PSA and (B) PSAG. The degradation data were given as mean ± standard deviation (SD) based on three independent measurements.

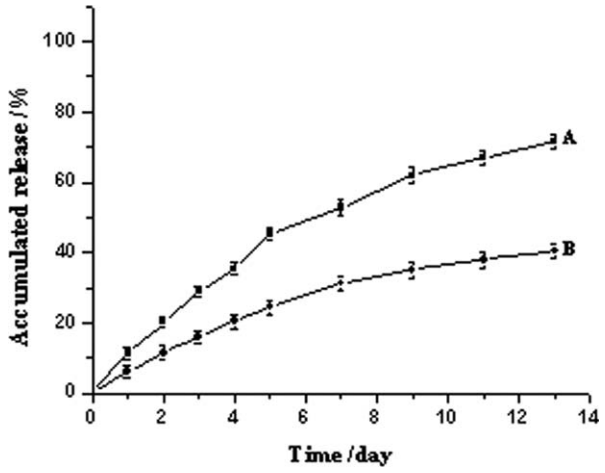

Figure 7. *In vitro* release profiles of drug from (A) PSA and (B) PSAG discs. The drug-loaded amount was 1 wt %. The release data were given as mean ± standard deviation (SD) based on three independent measurements.

becomes slower as the glycol was introduced. As shown in Figure 6, 13 days after degradation, the weight loss of PSAG and PSA was 89% and 98%, respectively, probably because of the introduction of the glycol into PSA may not only form ester linkages but also enlarge the molecular weight of PSA, thus reducing the degradation.

In Vitro Drug Release

In vitro release was carried out with discs of polyanhydride containing 1% dexamethasone in PBS at 37°C. The results are shown in Figure 7. It can be seen that dexamethasone was released from the polymer matrix at the early stage (0–5 days) with a nearly constant release rate, and then the release rate was observed with a decrease on endgame. The whole stage showed a sustainable release, and no abrupt release was observed.

The release of drug from polymer matrix depends on the degradation rate of polyanhydride and the soluble property of the incorporated drug, and they frequently play a significant role on the rate of drug release from bioerodible systems.[22–24] In addition, surface erosion of polyanhydride may influence the release rate of drug. As shown in Figure 7, the release rate of dexamethasone from PSAG is obviously slower than that from PSA. The main reason is that the ester linkages forming after the introduction of the glycol make the hydrophobicity of polyanhydride increases. And then, the compatibility between hydrophobicity drug and matrix becomes better. The other reason may be that the degradation rate of PSAG is slower than PSA.

The influences of the drug-loaded amount on *in vitro* release of dexamethasone from the discs of PSAG were investigated and the results are displayed in Figure 8. The accumulated release amount after 13 days release was 40.5, 67.1, and 100%, respectively. Accumulated release increased with increasing the drug-loaded amount on the same time point. This is because the drug release depends mainly on the degradation rate of polyanhydride and drug diffusion, but not surface dissolution of polyanhydride. If surface dissolution is one of critical factors, the release rate of drug should be almost equal and independent of drug-loaded amount. With increasing the drug-loaded amount, the diffusion channel is more easily formed, and the influence of diffusion release is increased. The release of drug is easier along the existing release channel, and so the release rate increases gradually with the increase of dexamethasone fraction.

CONCLUSIONS

PSAG were successfully prepared by introducing the glycol as chain extender in PSA, and the structure of PSAG is the same as the designed copolymer. The degradation rate of PSAG is lower than that of PSA. DSC analysis confirms the incorporation of glycol into polyanhydride, while XRD shows that there is an increase in crystallinity when dexamethasone is loaded into PSAG. PSAG shows lower melt temperature (T_m) and lower crystallinity, which is more conducive to its application in controlled

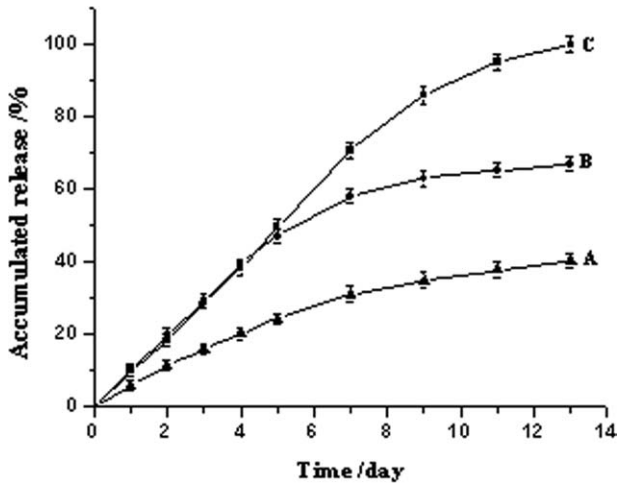

Figure 8. *In vitro* release profiles of drug from PSAG discs. The drug-loaded amount was (A) 1 wt %, (B) 2 wt %, and (C) 3 wt %, respectively. The release data were given as mean ± standard deviation (SD) based on three independent measurements.

release system. Using dexamethasone as a hydrophobic model drug, the *in vitro* release property was studied. The release rate of dexamethasone in PSAG system is lower than that in PSA. To be specific, when the drug-loaded amount was 1%, the accumulated release of PSA is 71.7%; however, that of PSAG is only 40.5% after 13 days. With increasing the drug-loaded amount, the release rate is increased. Conclusively, PSAG as a new degradable copolymer has potential application in biomedicine.

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