

## Research Article

# Paclitaxel Release from Polyether-Anhydrides Prepared with UV-Curing Process

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Received 8 April 2013; Revised 23 July 2013; Accepted 2 August 2013

Academic Editor: Jan-Chan Huang

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Polyanhydrides have been used as drug delivery systems to achieve a long-term delivery due to its hydrophobicity and surface erosion degradation behavior. In order to develop a simple, economical, and rapid approach to synthesize polyanhydrides, we prepared a series of polyether-anhydride membranes composed of different mass fractions of sebacic acid, polyethylene glycol dimethacrylate, and poly(tetramethylene oxide) dimethacrylate by ultraviolet curing process. The chemical structure and thermal properties of target polyanhydrides were characterized, while the paclitaxel releases from the polymer matrix were evaluated by HPLC. The results demonstrated that the UV-curing process is a good method to synthesize the target polymers in a short time, and the paclitaxel release procedure can be controlled by changing the component in the copolymers.

## 1. Introduction

A large number of degradable polymers have been introduced into drug delivery systems in recent years [1], and it was found that the degradation procedure could be classified as surface erosion and bulk erosions [2]. For those polymers degraded following the bulk erosion mechanism, for example, poly(lactic-glycolic acid) tends to present the nonlinear drug release and moisture-induced drug metamorphism [3]. While for those surface erosion polymers, for example, the polyanhydrides can achieve predictable near-zero order release [4–6]. Because of the special character, polyanhydrides have been explored widely for long-term release of drugs [7–9].

Polyanhydrides can be synthesized by various techniques, such as melt polycondensation, ring opening polymerization, and interfacial condensation [4, 10]. Under a high vacuum and high temperature condition, the high-molecular-weight polyanhydride can be achieved [11], but the reaction condition is difficult to implement and the molecular weight also badly depends on the purity quotients of the reactants [12].

On the other hand, light-initiated polymerization, widely known as UV-curing technique with remarkable advantages

such as slow energy consuming, low solvent emission, high productivity, and excellent surface quality [13], has attracted much attention and is being widely applied in the preparations of various polymers, especially the crosslinked coating and adhesions, and so forth, even on the synthesis of polyanhydrides for bone augmentation applications, protein release, and DNA delivery [3, 14, 15]. One of the most typical UV curing techniques is the polymerization of the acrylate monomers. In this system, the reactive prepolymers, photo initiator, and various additives were reacted under the UV radiation [16] without rigorous conditions. For the UV-curing polyanhydrides, a monomer containing anhydride bonds and unsaturated terminal groups, for example, vinyl or 2-propenyl, is often used with various unsaturated monomers, while the diversified monomer composition proposed opportunities to control the properties of the target products.

In this study, sebacic acid capped with methacrylate functionalities was synthesized and selected as the prepolymer to construct the primary chemical structure of the UV-curable polyanhydrides. Methacrylate polyethers, including polyethylene glycol, and polytetramethylene oxide were introduced into the polyanhydride system, and a series of the polyether-anhydride copolymers were synthesized by

UV curing process. After being characterized, the paclitaxel release properties and degradation behaviors were investigated.

The target products were hoped to be applied on the drug-controlled release coating for medical devices such as the drug eluting stents (DES). In the application of DES, it was found that the drug release rates should match the proliferation of vascular endothelial cells and smooth muscle cells which determined the restenosis rates, one of the most important indicators of the safety and effectiveness of DES. With a biodegradable drug carrier coating, for example, the polyanhydride and a relative faster drug eluting rate, a DES was expected to cause lesser late thrombosis and lower restenosis rates. Moreover, by introducing UV-curing process into the synthesis of polyanhydride copolymers, the drug carrier polymeric coating is expected to be directly polymerized during the preparation of the coating, which will avoid the difficulties of dissolving polyanhydrides.

## 2. Experimental

**2.1. Materials.** Polyethylene glycol dimethacrylate (DMAPEG, molecular weight 600 Dalton) and trimethylolpropane triacrylate (TMPTA) were obtained from Sartomer Company and used as received. Paclitaxel (PTX) was purchased from Zhongshuo Pharmaceutical Technology Development Co. (Beijing, China) and used as received. Sebacic acid (SA), polytetramethylene oxide (PTMO) with molecule weight of 1000 Dalton, triethylamine (TEA), and methacryloyl chloride were all purchased from Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China). Methylene dichloride, purchased from Sinopharm Chemical Reagent Co. (Shanghai, China), was purified by vacuum-distillation before use. The complex ultraviolet photoinitiator system compounded with benzophenone (BP) and N,N-dimethyl ethanolamine (DMEA) were obtained from Shanghai Jingchun Industry Co. (Shanghai, China) and used without further treatment.

**2.2. Instrumentations.** Fourier transform infrared spectroscopy (FTIR) was performed on a Nicolet Nexus 870 FTIR spectrometer (Thermo Nicolet, USA) from 4000 to 400  $\text{cm}^{-1}$  with a resolution of 4  $\text{cm}^{-1}$  at room temperature. Nuclear magnetic resonance (NMR) was performed on a 500 MHz Nuclear Magnetic Resonance (AVANCE DRX-500 NMR, Bruker, Switzerland). The thermal properties of polymers were determined by Differential Scanning Calorimeter (Pyris 1 DSC, PerkinElmer, USA). The X-ray diffraction, which characterizes the degree of crystallinity, scanned from 10 to 40° at the scanning speed of 2° per minute. The paclitaxel release of samples was recorded with a Waters 2695 High-Performance Liquid Chromatography (HPLC) (Milford, MA, USA) equipped with a 4.6250 mm Discovery HS F5 HPLC column (Supelco, Bellefonte, PA, USA) and a UV detector (Waters 2487). The determination was proceeded with mobile phase composed of  $\text{CH}_3\text{OH}:\text{H}_2\text{O}:\text{CH}_3\text{CN} = 23:41:36$  (volume ratio) at flow rate of 1.0 mL/min at 37°C with sample injection volume 10  $\mu\text{L}$ .

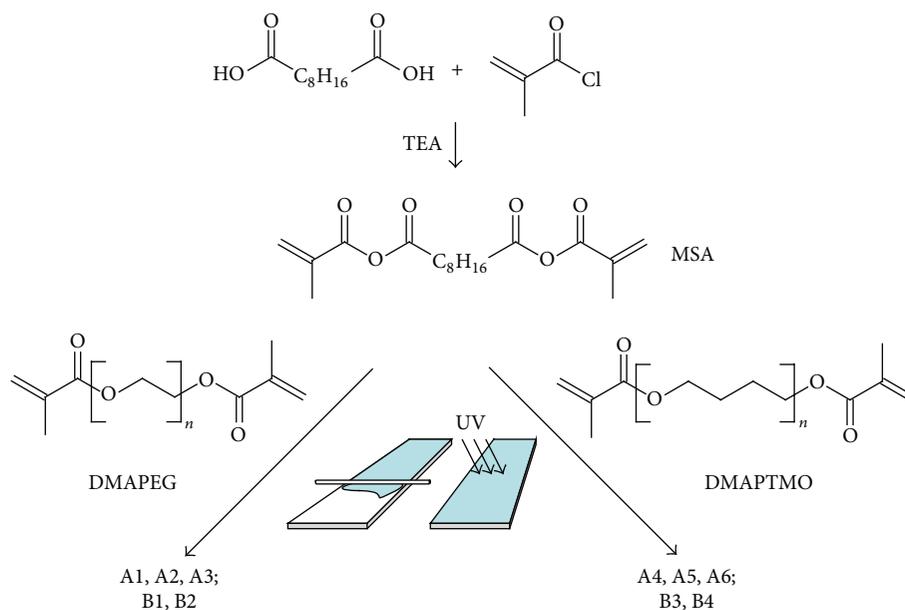
### 2.3. Preparation of the Samples

**2.3.1. Synthesis of Dimethacrylated SA and PTMO.** Sebacic acid dimethacrylate (MSA) was synthesized from sebacic acid and methacryloyl chloride [17]. In detail, 6.0 g SA and 4.1 g triethylamine were dissolved in 200 mL methylene chloride; the mixture was stirred at 0°C for 30 min. Then 6.4 g methacryloyl chloride was slowly dropped into and kept stirred for another 3 h at 0°C. The precipitated triethylamine hydrochloride was filtered out by vacuum filtration and the crude solution was washed sequentially with saturated  $\text{NaHCO}_3$  and distilled  $\text{H}_2\text{O}$  till neutral. After being dried over  $\text{Na}_2\text{SO}_4$ , methylene chloride was then removed in vacuum drying at 0°C and 9.2 g MSA was obtained (FTIR 945, 1040, 1450, 1630, 1840, and 3100  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{C}^2\text{HCl}_3$ ) 6.24, 5.83, 2.45, 2.01, 1.66, and 1.33 ppm). Similar as the synthesis process of MSA, poly(tetramethylene oxide) dimethacrylate (DMAPTMO) was synthesized from PTMO and methacryloyl chloride.

**2.3.2. Preparation of Polyanhydride Membrane Samples.** UV-curing crosslinked polyanhydrides were composed of MSA, DMAPTMO, and DMAPEG with different mass fractions and cured under ultraviolet. The preparation route was shown in Scheme 1.

In order to prepare the membrane samples, MSA, DMAPEG, and DMAPTMO with different mass fractions as listed in Table 1 were mixed at 50°C and shaken in the test tubes till obtained the homogeneous reactive fluid. In the mixture, BP, DMEA were charged and kept shaken for more 10 min. The mixtures were coated evenly on a clean glass microslide with a blade coating method and then irradiated under a 200 W UV lamp (365 nm) to complete the UV-curing process. The obtained membranes with the thickness of about 0.5 mm were extracted in anhydrous ethanol for 24 h to eliminate the unreacted monomers and additives and then dried over vacuum at 50°C. The described membrane samples are used for characterization while the mass loss experimental samples are prepared by cutting the membrane into 8 × 8 mm slices. The membrane samples (8 × 8 mm) containing 5 wt% paclitaxel are also prepared for drug release measurements as described above by additional charging paclitaxel into the reaction mixtures.

**2.4. Paclitaxel Release Determination and Polymer Degradation.** The paclitaxel loaded membranes (88 mm) were immersed into each sealable tube containing 5 mL phosphate buffer solution (PBS, 0.1 mol/L, pH 7.4), respectively, and kept in a water-bathing constant temperature vibrator at 37 ± 1°C. At every scheduled time, PBS was drawn out and diluted, and the paclitaxel contents were determined with HPLC. The results were normalized by the amount of accumulative paclitaxel released. The release experiments were done independently in quadruplicate. The degradation of the copolymer is recorded by the mass loss test. The dry mass of the membrane samples ( $M_0$ ) was measured before the degradation experiment in PBS. The membrane samples were removed at each scheduled time, rinsed with PBS, dried by vacuum at 50°C for 48 h, and then weighed to obtain the dry



SCHEME 1: Synthesis and preparation of samples.

TABLE 1: The exact constituents\* (in wt%) of UV-curing cross-linked polyether-anhydride membrane.

Sample no.	Dimethacrylate polyether		MSA	TMPTA	Paclitaxel
	DMAPEG	DMAPTMO			
MSA	/	/	100	/	5
A1	10	/	90	/	
A2	30	/	70	/	5
A3	50	/	50	/	
A4	/	10	90	/	
A5	/	30	70	/	5
A6	/	50	50	/	
B1	10	/	85	5	
B2	10	/	80	10	5
B3	/	10	85	5	5
B4	/	10	80	10	

\*In every sample, there are also 3% wt BP and 3% wt DMEA as a complex photo initiator system.

mass after degradation ( $M_D$ ). The mass loss (ML) was calculated as  $ML (\%) = [(M_0 - M_D)/M_0] \times 100$ .

### 3. Results and Discussion

**3.1. XRD and DSC Characterization of Polyether-Anhydrides.** Two series of polyether-anhydrides were synthesized in this paper, one was the linear polyether-anhydride composed of DMAPEG or DMAPTMO with MSA, and the other one was the additional crosslinked polyether-anhydrides with TMPTA. Figure 1 shows the XRD and DSC spectra of the linear products. Obviously, with the increasing of polyether segments, the crystallinity of the products decreased which

should be attributed to the flexibility of the polyether segments. It was well known that the low-molecular-weight polyether, PEG and PTMO used in this study are all amorphous polymers, even they are introduced into the copolymers with sebacic acid segment, they still cannot crystallize. Moreover, the introduction of the polyether segments destroyed the chemical regularity of the sebacic acid segment, which caused the decrease of the crystallinity.

The introduction of the soft polyether segments also led to the reduction of melting point of the polymers. The DSC curves in Figure 1 obviously expressed the trend: with the increasing of the soft polyether segments, the melting points of the copolymers decreased from more than  $100^\circ\text{C}$  to about  $85^\circ\text{C}$ . The results from DSC were according to the XRD; the decreasing of the crystallinity also leads to the decrease of the melting points.

As for the crosslinked polyether-anhydrides, the trifunctionality monomer TMPTA further reduced the crystallinity of the copolymers and the XRD curves showed that the completely amorphous polyether-anhydrides were synthesized.

**3.2. Paclitaxel Release and Mass Loss of Linear Polyether-Anhydrides.** Figure 2(a) shows the paclitaxel release for 5 wt% paclitaxel loaded linear polyether-anhydride composed of PEG segment and MSA. Along with the content of PEG segment increased from 10% to 50%, the percent paclitaxel release in 24 hours was 12%, 35%, and 69%, respectively. Almost all of the paclitaxel encapsulated in sample A3 (composed of 50 wt% DMAPEG and 50 wt% MSA) was released after 48 h, while for the sample A1 (composed of 10 wt% DMAPEG and 90 wt% MSA); the paclitaxel release continued for about 7 days. The differences are obviously caused by the different PEG contents which probably induced the different water uptake in the polymer matrix.

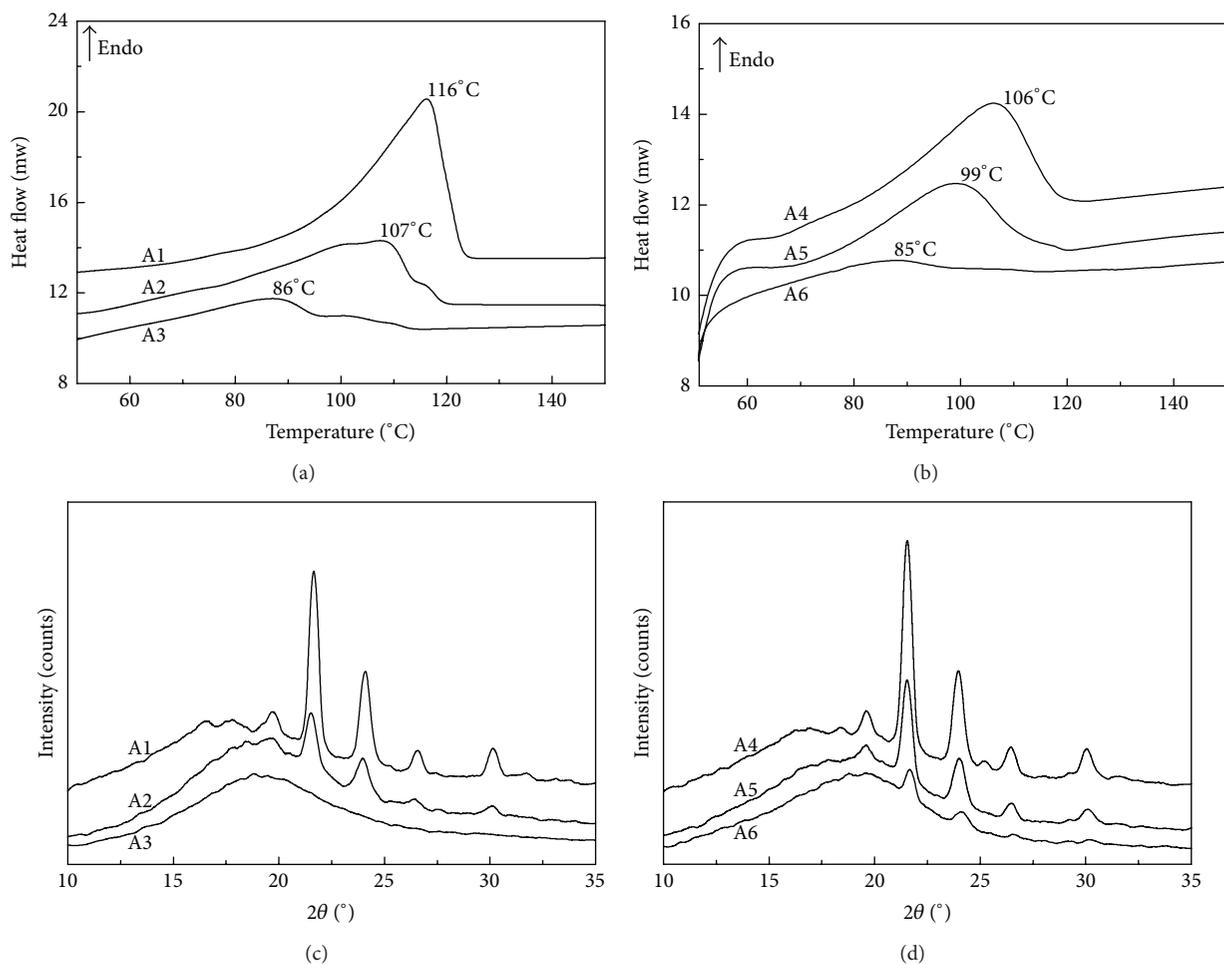


FIGURE 1: DSC (a, b) and XRD (c, d) spectra of linear DMAPEG-MSA and DMAPTMO-MSA polyether-anhydrides.

When the polyether-anhydride samples were immersed into PBS, the anhydride bonds degraded following the hydrolysis mechanism which led to the mass loss. From Figure 2(b), the sample weights lost about  $30 \pm 10\%$  after being contacted with water in 100 hours. Moreover, the more the PEG segments contained, the less the mass loss showed. This phenomenon is in agreement with the content of the anhydride bonds in the polymers because there are only anhydride bond which could degrade in the polymer chains.

Comparing the paclitaxel release curves and the mass loss curves, it could be found that the paclitaxel release rate is faster than that of the mass loss. The phenomenon indicated that the paclitaxel release is not only controlled by the degradation of anhydride bonds but also influenced by the dissolve and penetration procedure of drugs. It was well known that the polyanhydride is a hydrophobic polymer, and the drug release from polyanhydride matrix is a typical degradation-controlled surface erosion process. However, when the PEG segments were introduced into the main chain, the hydrophobicity of poly(sebacic anhydride) reduced and led to the infiltration of water, which accelerated the degradation of anhydride bond and also promoted the dissolve of paclitaxel.

In order to study the influence of the different polyether segments, PEG was replaced by PTMO and the paclitaxel

release, and mass loss curves from polyether-anhydride composed of DMAPTMO and MSA were shown in Figures 2(c) and 2(d). In this series of polyether-anhydrides, PTMO segment is more hydrophobic than PEG segment and the difference should be observed in the water uptake and degradation rate of polymer matrix. From Figure 2(d), after being immersed into water for about 100 hours, the polyether-anhydride composed with DMAPTMO and MSA lost their weight for about  $20 \pm 10\%$ , which is less than that of DMAPEG-composed polymers and is according to the differences of PEG and PTMO. It looks like that the contents of anhydride bonds presented the influence on the degrade rate: the more the PTMO segments contained, the less the mass loss showed. But when the Student's *t*-test analysis was applied on the data, we found that the *P* values are 0.04 and 0.08, respectively, among the B series samples at the 100th hours. Thus, it should be concluded that the degradation trended to be different, but no significantly differences were found till 100-hour's degradation.

However, the paclitaxel release from variety DMAPTMO contents composed polyether-anhydride was indistinguishable as shown in Figure 2(c): in about 100 hours, almost all of the paclitaxel released from polymer matrix and the release procedure were also mainly controlled by dissolve

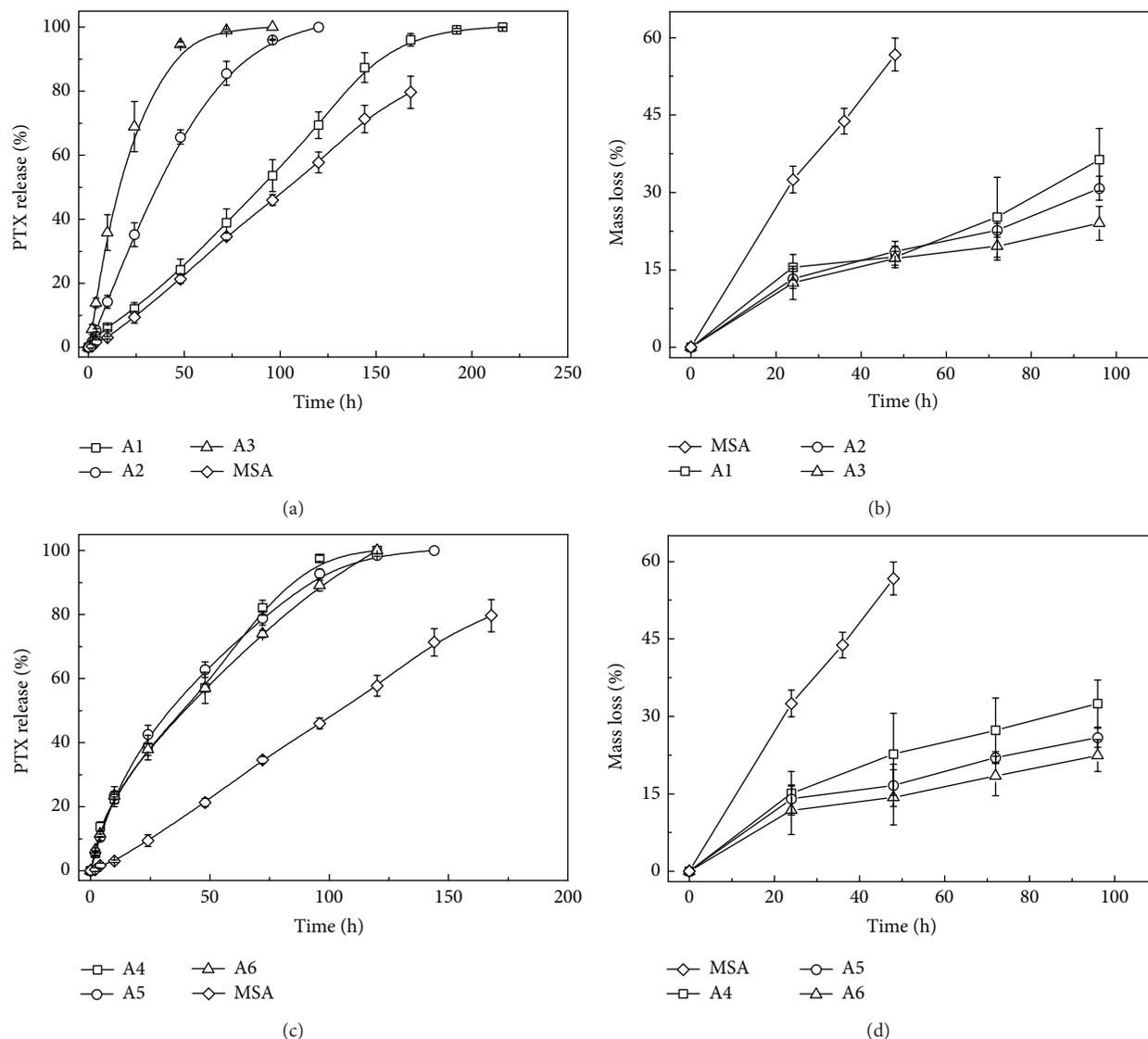


FIGURE 2: Paclitaxel release (a, c) and mass loss (b, d) of linear DMAPEG-MSA and DMAPTMO-MSA polyether-anhydrides.

mechanism. Moreover, regardless of the PTMO contents in polymer chain, the paclitaxel released at a similar rate. This result indicated that even the hydrophobic polyether influenced the crystalline of copolymer as shown in XRD and DSC curves, but it takes fewer effects on the water infiltration and crystallinity of copolymer matrix and almost performed no influence on the release of paclitaxel.

### 3.3. Paclitaxel Release from Crosslinked Polyether-Anhydrides.

Besides the linear polyether-anhydride, the crosslinked polyether-anhydrides were also synthesized by simply introducing trifunctional monomer TMPTA. Into the two groups of linear polymer, 5 wt% and 10 wt% TMPTA were incorporated, respectively, to control the crosslinked density. Figure 3 shows the paclitaxel release from the crosslinked matrix. From the curves, it could be found that the paclitaxel released faster from PEG-composed polyether-anhydride than from

PTMO-composed ones, and the results were obviously related to the different hydrophilicity of the two polyether segments. However, the crosslinked density affected a little the drug release rates while it is probably that the paclitaxel release was controlled by the degradation of composed anhydride bonds [18, 19].

## 4. Conclusions

By UV-curing technique, a series of linear and crosslinked polyether-anhydrides composed of sebacic acid and various amounts of polyether were synthesized conveniently. The incorporation of the polyether changed the crystallization property of polyanhydride and decreased its melting point. By choosing different type and different amount of polyether segments, the drug release properties of the matrix could be adjusted to satisfy the target applications.

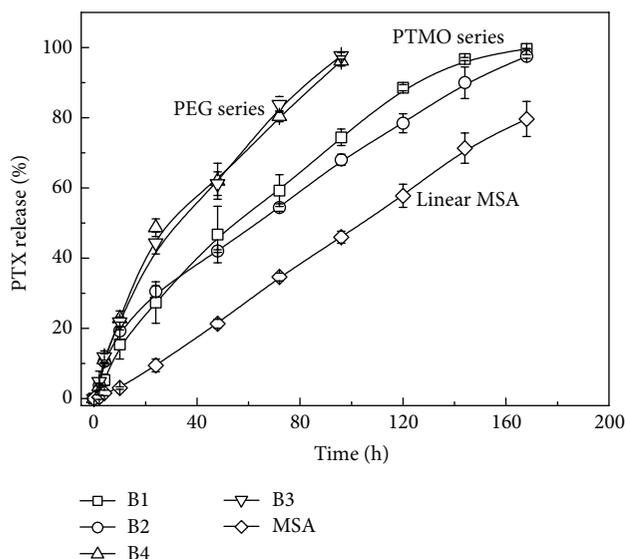


FIGURE 3: The paclitaxel release from crosslinked polyether-anhydrides.

## Acknowledgments

The authors acknowledge the support of the National Natural Science Foundation of China (NSFC nos. 20874043 and 21176111), the Key Project of Chinese Ministry of Education (no. 109070), the National Basic Research Program of China (no. 2011CB933400), Science and Technology Support Program (Society Development) of Jiangsu Province (no. BE2012735). This work is also a part of the project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD).

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