Drug Release from Poly(ortho esters)–Poly(ethylene glycol) Polyblend

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ABSTRACT: A polyblend of poly(ortho esters)–poly(ethylene glycol) (POE–PEG) was prepared. The release behavior of the acetanilide-loaded film of the POE–PEG polyblend was studied. Blending POE with water-soluble PEG can promote the release of drug in pH 7.4 PBS buffer at 37°C, while POE has plasticizing effect on PEG. Infrared and X-ray diffraction studies reveal that there is some interaction between POE and acetanilide. The SEM micrographs disclose that the porosity of the drug-loaded film enhances with an increase immersing time. © 1999 John Wiley & Sons, Inc. J Appl Polym Sci 71: 303–309, 1999

Key words: poly(ortho esters); poly(ethylene glycol); polyblend; acetanilide; drug release

INTRODUCTION

Biodegradable or bioerodible polymer matrices have been investigated and used for drug release since the last decade because of their major advantage to eliminate surgical removal of an implanted delivery device after the release system is exhausted.[1] All these kinds of polymers cover poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(LA-*co*-GA),[2] poly(ortho esters) (POE),[3] and polyanhydrides.[4] Among these, poly(ortho esters) (POE) are hydrophobic, surface-erodible polymers and have fine biocompatibility.[5,6] There are a few families of POE, one of which was prepared by the reaction of dikene and diols and has recently been used to control release of drugs.[7,8] But the degradation rate of this kind of POE is very slow under the physiological conditions of pH 7.4 and 37°C.[9,10] Its hydrolysis rate can be accelerated by using acidic excipients or copolymerization with hydrophilic monomers.[11,12]

As we know, poly(ethylene glycol) (PEG) is a biocompatible, nontoxic, nonimmunogenic, water-soluble polymer of much use in biomaterials, biotechnology, and medicine.[13] In considering solubilization and hydrophilicity of PEG, a novel drug delivery system based on a poly(ortho esters)–poly(ethylene glycol) (POE–PEG) polyblend was developed to enhance drug release from POE. In this study, we used cosolvent tetrahydrofuran (THF) evaporating to prepare drug-loaded film of the POE–PEG polyblend. The main function of PEG is to accelerate drug releasing. The POE–PEG polyblend film and acetanilide-loaded film were characterized via Fourier transform infrared (FTIR) analysis X-ray diffraction (XRD) and scanning electron microscopy (SEM). Drug release behavior and weight loss performance were investigated as well.

EXPERIMENTAL

Materials

POE (provided by Advance Polymer System, California) with average molecular weight of 4.8

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$\times 10^4$ were prepared by the condensation of equimolar amounts of 3,9–bis(methylene) 2,4,8-tetraoxaspiro[5,5]undecane, and diols. The diols are *trans*-cyclohexane dimethanol (*t*-CDM) and 1,6-hexanediol (1,6-HD); *t*-CDM to 1,6-HD equal to 6 : 4 PEG (Tianjin Chemical Co., China) with average molecular weight of 4000 was used as received.

Acetanilide (Chemical Experimental Factory, China) was of chemical grade. Tetrahydrofuran (THF) and other reagents were of analytical grade.

Preparation of the Drug-Loaded POE–PEG Polyblend Film

2.5 g of POE and 0.24 g of acetanilide were dissolved in 30 mL of THF, and then PEG 4000 was added at approximately 50°C under agitating. After PEG was dissolved completely, the mixture was poured into a Teflon model, and the solvent was evaporated in a vacuum oven at 20°C overnight and dried at 40°C for 1 day.

FTIR Spectra

The solution of polymers and drug, which was prepared at approximately 50°C, was sealed and kept at approximately 20°C for 2 days. After filtering solid precipitate, original solution and filtrate were dried vacuum at 40°C. The FTIR spectra of them, POE, PEG, drug, the blend of two polymers, and drug-loaded film, were obtained on a Bio-Rad 135 FTIR spectrometer.

X-ray Diffraction

The XRD of POE, PEG, acetanilide, the POE–PEG blend, and drug-loaded film were carried out with a Rigaku Model 2038 diffractometer. The X-ray source was Ni-filtered CuKα radiation (25 KV, 10 mA). The specimens were mounted on aluminum frames and scanned from 5 to 40°, 2θ at speed of 4°, 2θ/min and a chart speed of 2 cm/min.

Differential Scanning Calorimetry (DSC) Analysis

The glass transition temperature (T_g) of POE, melting temperature (T_m) of PEG, and the same characteristics of the POE–PEG polyblend films were measured with a Perkin–Elmer DSC-2B differential scanning calorimeter. The measurements were carried out in the range of 240–380 K at a heating rate of 20 K/min.

Scanning Electron Microscopy Observation

The fracture section morphology of the POE–PEG polyblend films was examined by using a scanning electron microscope (Hitachi Model 1650). Samples were broken in liquid nitrogen, mounted on metal stubs, coated with the gold film under vacuum, and then observed.

In Vitro Release

The release experiments were performed in a rotating shaker (100 rpm) containing 500 mL of pH 7.4 PBS buffer at 37°C. The drug-loaded specimens with a surface area of 2.5 $\times$ 2.5 cm^2 were immersed into the shakers. A 10-mL aliquot of medium was withdrawn at different time intervals, and the same volume of fresh buffer was added. The loss of medium taken into account,

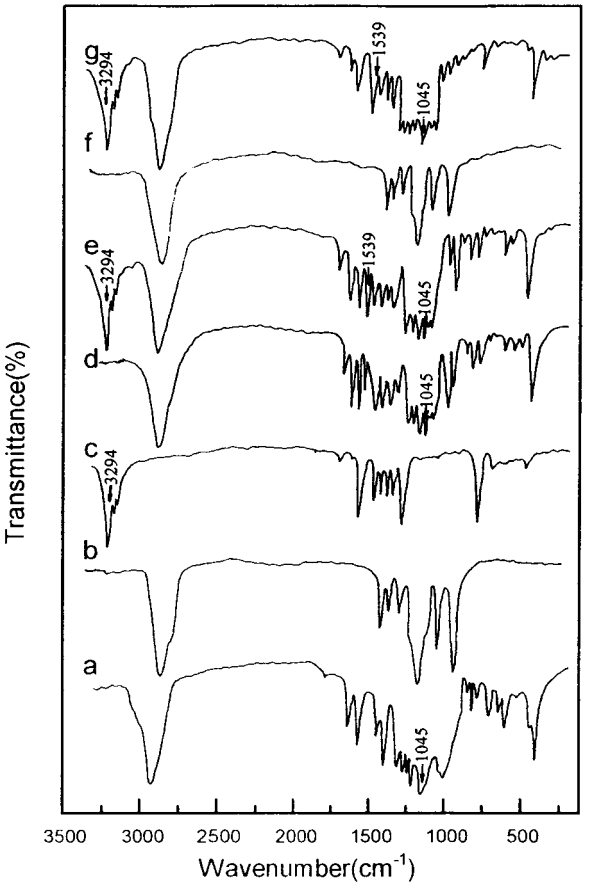

Figure 1 FTIR spectra of (a) POE, (b) PEG, (c) acetanilide, (d) the blend of POE–PEG (POE : PEG equals 2.5 : 1), (e) the drug-loaded polyblend film (POE : PEG : acetanilide equals 2.5 : 1 : 0.24), (f) the solid precipitated form of solution, and (g) the film made from filtrate evaporation.

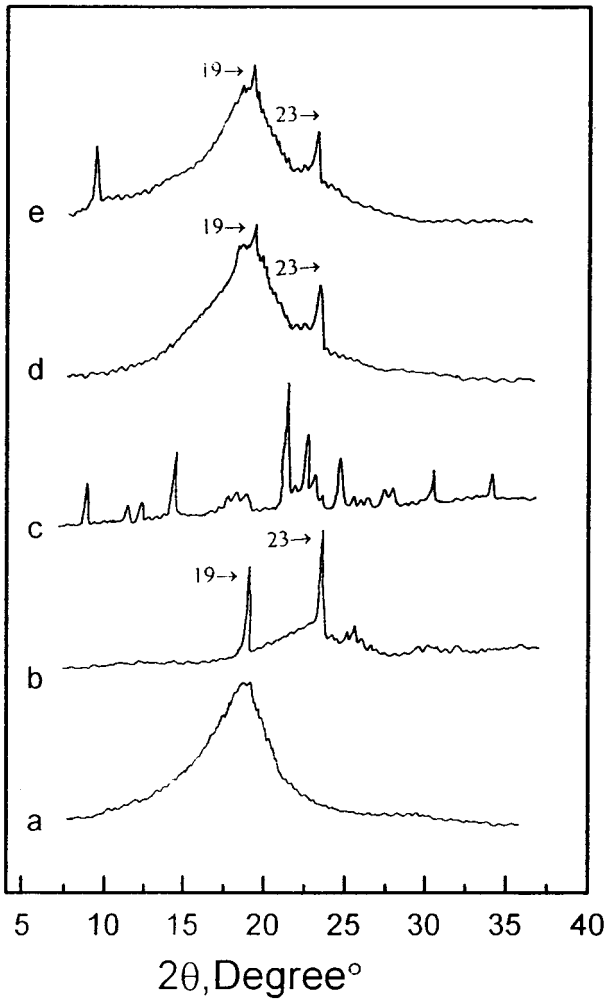

Figure 2 X-ray diffraction patterns of (a) POE, (b) PEG, (c) acetanilide, (d) the polyblend of POE–PEG (POE : PEG equals 2.5 : 1), and (e) the drug-loaded polyblend film (POE : PEG : acetanilide equals 2.5 : 1 : 0.24).

acetanilide content was assayed at 210 nm spectrophotometrically.

In Vitro Weight Loss

Dry films were equilibrated in pH 7.4 PBS buffer and incubated at 37°C. Weight loss was monitored at various intervals of time gravimetrically.

Solubility of the Drug in PEG Aqueous Solution

Different amount of PEG were dissolved in 100 mL of distilled water to produce a solution in which an excess of acetanilide was added. After stirring at 25°C for 3 h, aliquots of mixture were removed and filtered through 0.3 μm of mixed cellulose esters micropore filters. Diluted and blanked filtrates were measured for absorbance to calculate solubility.

Water Sorption

POE, PEG, and the polyblend films were put into beakers, respectively. The beakers were placed into a big jar containing distilled water. The jar was sealed and then kept at 37°C. Weight gain of samples were measured with a microbalance until the weight was kept constant.

RESULTS AND DISCUSSION

IR Spectra Analysis

Figure 1 shows the FTIR spectra of (a) POE, (b) PEG, (c) acetanilide, (d) the blend of POE–PEG, (e) the drug-loaded polyblend film, (f) the solid precipitated from the solution, and (g) the film made from filtrate evaporation. In the spectrum of the solid precipitate, the peaks at 1045 cm^{-1} (C—O, stretching vibration of POE) and 3294 cm^{-1} (—NH— stretching vibration of acetanilide) disappear. It implies that the solid precipitate is PEG, in which there is little distributed drug. So, most drug partitions are in the POE phase, while drug release is controlled mainly by POE erosion.

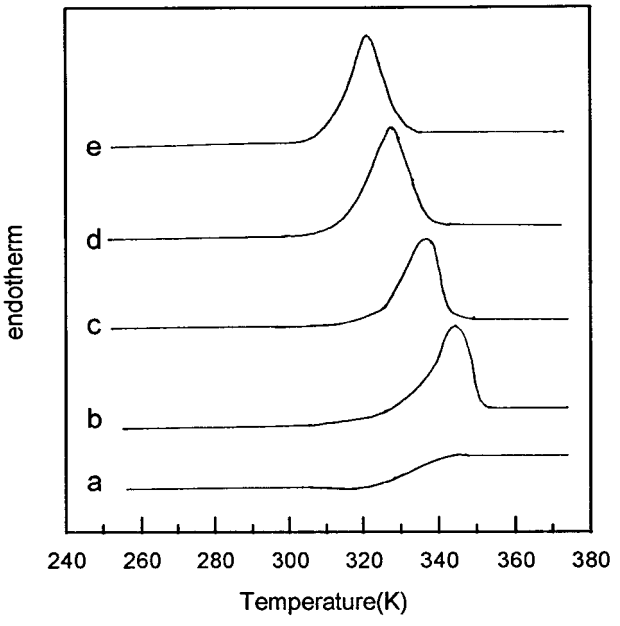

Figure 3 DSC scans of (a) POE and (b) PEG4000, with the ratio of POE to (POE + PEG) by weight of (c) 0.63, (d) 0.71, and (e) 0.83, respectively.

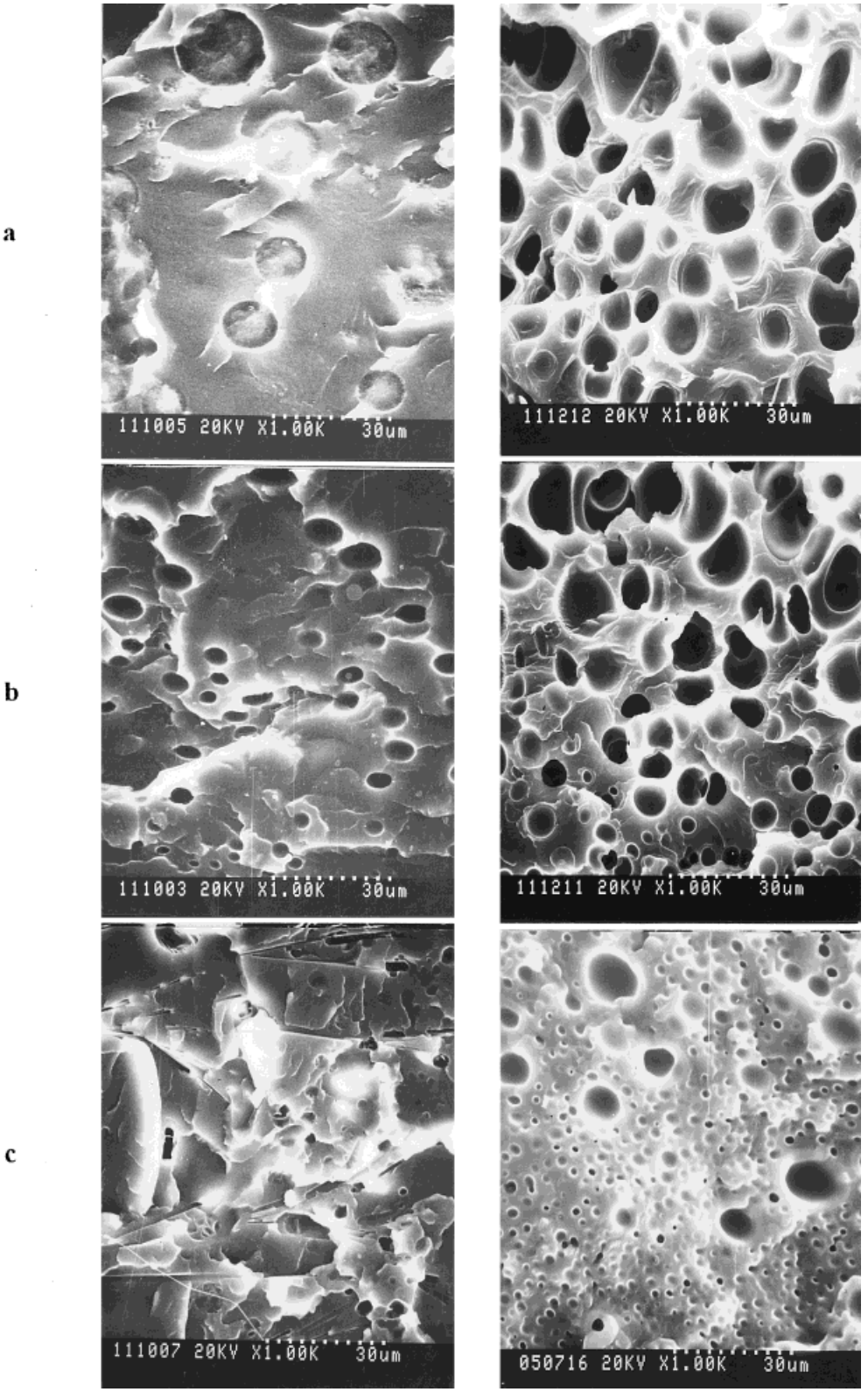

Figure 4 SEM micrographs of the POE–PEG polyblend film fracture section before and after 10 days of immersing in water. POE : PEG : acetanilide is equal to (a) 2.5 : 1.5 : 0.24, (b) 2.5 : 1 : 0.24, and (c) 2.5 : 0.5 : 0.24 (the right is after release).

Besides, a new absorption band was seen at 1539 cm^{-1} (—CO—NH— bending vibration) in spectra (e) and (g). That reveals that some interaction may exist between POE and acetanilide.

X-ray Patterns

X-ray diffraction patterns (compare Fig. 2) disclose that amorphous POE and crystalline PEG are maintained, respectively, in the blend. There may be no interaction between POE and PEG. But, the crystal form of acetanilide in the polyblend film is different from that in the original state. Some peaks of acetanilide disappear for its loaded polyblend film. This result coincides with the variation in IR spectra, which implies some interaction between POE and acetanilide.

DSC Analysis

DSC scans of POE–PEG films with different composition are displayed in Figure 3. The glass transition temperature (T_g) of POE, being 55°C approximately, with the melting temperature (T_m) of PEG being approximately 65°C, are observed in their scans [Fig. 3(a,b)], respectively. Adding amorphous POE into crystalline PEG leads the T_m of PEG in the POE–PEG polyblends to shift to lower ones along with an increase in POE content. The result may be attributed to the plasticizing effect of POE on PEG.

Morphology of Film Fracture Section

Figure 4 displays SEM micrographs of POE–PEG films with different compositions before and after 10 days of immersing in water. It can be seen from these micrographs that the less the PEG weight fraction in film, the smaller the sphere-like microdomains. The porosity of films obviously enhances after 10 days of immersing. The pores may be formed by the dissolution of PEG in water,[14] which results in expansion of the interface between POE and water. This induces enhancement of drug release from surface-erodible POE.

Release Study

Release of acetanilide from the POE–PEG polyblend films against the weight fraction of PEG is demonstrated in Figure 5. Each curve has an initial burst effect followed by a slow release of drug. These results illuminate that *in vitro,* a near-zero-order delivery of acetanilide is observed for the POE–PEG polyblend matrix. Data reveals that the initial release is improved, and the time to the constant rate decreases with an increase of the PEG weight fraction. Because it has the greatest drug-loaded ratio (w/w), the sample of POE : PEG : acetanilide = 2.5 : 0.5 : 0.24 has the highest drug release. Besides, the initial burst also tends to be gentle. Results indicate that PEG has a promoting function for drugs release from

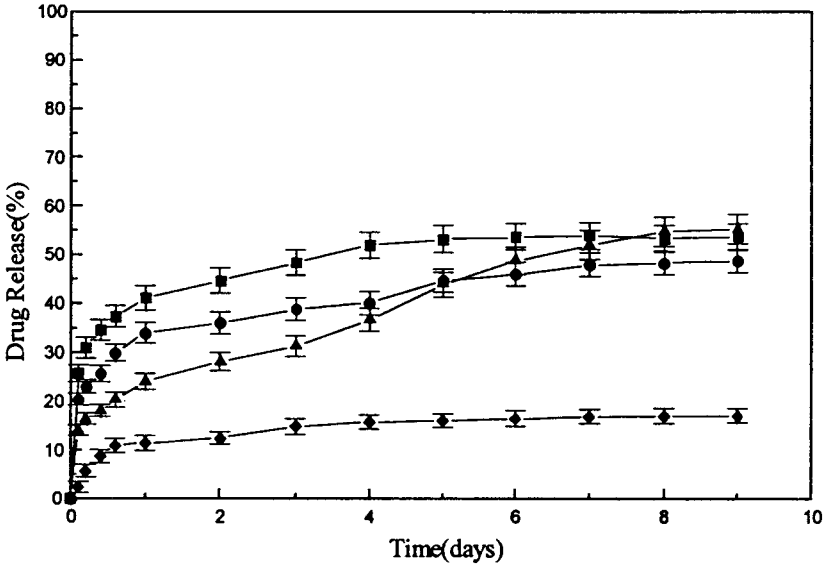

Figure 5 Release acetanilide from the POE–PEG polyblend film with different PEG weight fractions of POE : PEG : acetanilide equal to (■) 2.5 : 1.5 : 0.24, (●) 2.5 : 1 : 0.24, (▲) 2.5 : 0.5 : 0.24, and (◆) 2.5 : 0 : 0.24. Each point represents the mean ± SD of at least three experiments.

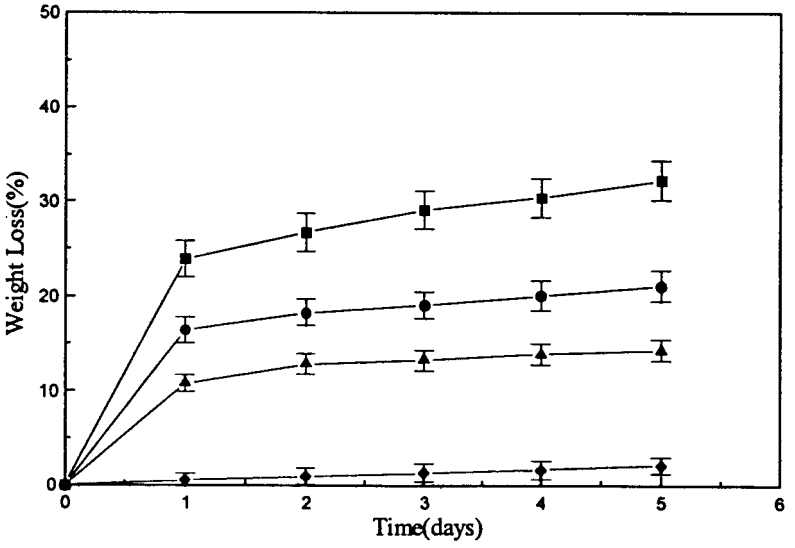

Figure 6 Weight loss profiles for different POE–PEG polyblend films by the following weight ratios: POE : PEG equals (■) 2.5 : 1.5, (●) 2.5 : 1, (▲) 2.5 : 0.5, and (◆) 2.5 : 0. Each point represents the mean ± SD of at least three experiments.

POE; that is, the release rate can be controlled by varying the composition of the POE–PEG matrix.

Weight Loss Behavior

Figure 6 shows the weight loss of the POE–PEG film with different weight fractions of PEG against incubation time. It exhibits that the film containing more PEG has a faster weight loss. According to *in vitro* release, these curves also have a initial burst and then become slower. Compared with uniform rate of POE, weight loss of the polyblend goes up drastically at the initial stage, which is due to part of the PEG dissolving in water. From the slower parts of the curves, one can see a faster weight loss rate in the polyblend containing more PEG.

Solubilization of Drug with PEG

Figure 7 illustrates the amount of acetanilide dissolving in PEG solution with different concentrations. The curve is approximately linear. It can be observed that drug solubility is raised with an increase in the concentration of PEG. This way, the

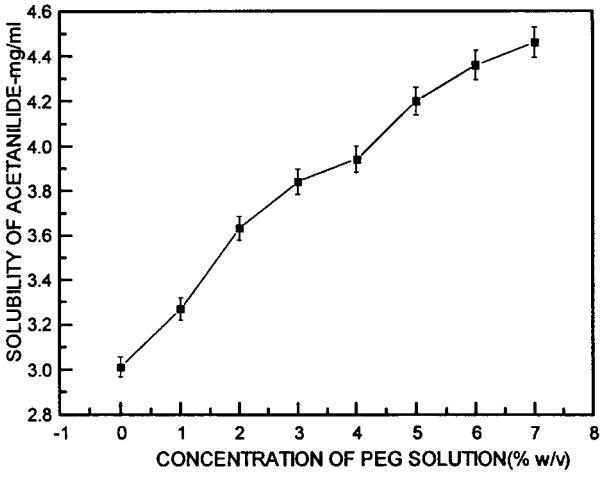

Figure 7 Solubility of acetanilide in different concentrations of PEG aqueous solution. Each point represents the mean ± SD of at least three experiments.

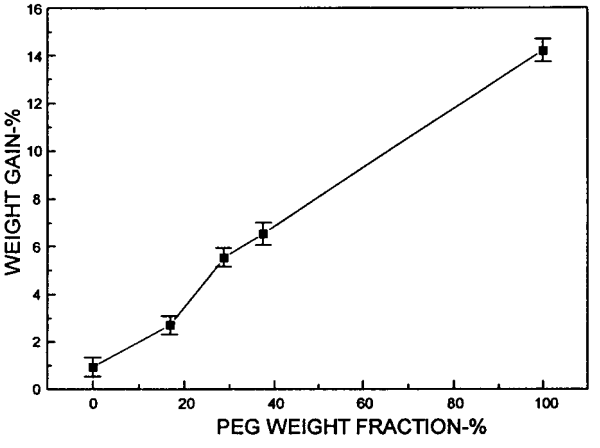

Figure 8 Water sorption against the PEG weight fraction in the POE–PEG polyblend film. Each point represents the mean ± SD of at least three experiments.

"concentration difference" can be enlarged between the drug-loaded system and the medium. Thus, the drug release rate is speeded up. This is a reason that PEG enhances drug releasing from POE.

Water Uptake Study

Water sorption also has an effect on erosion of POE via hydrolysis of the orthoester bond because hydrolysis relates to the water content. The more the water content is, the higher hydrolysis will be seen.[15] As for the POE–PEG release system, PEG also can promote absorbing water into the drug-loaded polyblend before PEG dissolving in water completely. So, the drug release rate will be enhanced. Figure 8 shows water sorption of the POE–PEG polyblend films versus PEG content by weight at 37°C under saturated vapor pressure. The curve indicates that more water is absorbed by the film with more PEG weight fraction.

CONCLUSION

PEG can enhance the drug release rate from POE while the drug release rate can be controlled by changing the ratio of poly(ortho esters) to poly(ethylene glycol). It is expected to get a suitable release rate by optimizing the composition of the polyblend. Furthermore, PEG may render POE more fit to be implanted in a body with good biocompatibility.

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