Arch. Pharm. Res. Vol. 18, No. 1 pp. 18-21, 1995

Drug Release from Bioerodible Hydrogels Composed of Poly-ε-caprolactone/poly(ethylene glycol) Macromer Semiinterpenetrating Polymer Networks

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(Received October 5, 1994)

Poly(ethylene glycol)(PEG) macromers terminated with acrylate groups and semi-interpenetrating polymer networks (IPNs) composed of poly-ε-caprolactone(PCL) and PEG macromer were synthesized with the aim of obtaining a bioerodible hydrogel that could be used to release drugs for implantable delivery system. Polymerization of PEG macromer resulted in the formation of cross-linked gels due to the multifunctionality of macromer. Non-crosslinked PCL chains were interpenetrated into the cross-linked three-dimensions networks of PEG. The release of 5-fluorouracil(5-FU) from the IPNs increased with increasing PEG contents in the IPNs, large drug loading, lower concentration of PEG macromer in the IPNs concentration and the higher molecular weight of PEG macromer. Also, 5-FU was more fast released than hydrocortisone to the increased water solubility.

Key words: PEG macromer, IPNs, PCL, Bioerodible, Hydrogel

INTRODUCTION

Drug release from biodegradable or bioerodile polymer matrices has been intensively investigated for the last decade (Chasin and Langer, 1990). One major advantage of a biodegradable system is to eliminate surgical removal of an implanted delivery device after the delivery system is exhausted (Heller, 1984). The most thoroughly investigated and used bioerodible polymers are the poly(α-hydroxy ester), such as poly (lactic acid)(PLA), poly(glycolic acid)(PGA) and poly(LA-co-GA) that would degrade into naturally occurring substances (Kulkarni *et al.*, 1971). Polyanhydrides (Domb *et al.*, 1988), poly(ortho esters) (Heller *et al.*, 1983) and poly(α-amino acids) (Negishi *et al.*, 1987) have also been developed. Recently, poly-ε-caprolactone(PCL) as the aliphatic polyester has been considerable interest in the drug delivery systems due to the good biocompatibility and non-toxicity (Pitt *et al.*, 1981). But, the homopolymer itself is degraded very slowly when compared with PGA, PLA and poly(LA-co-GA). The biodegradability can be enhanced by copolymerization (Pitt *et al.*, 1981), or blends with a variety of other polymers (Pitt *et al.*, 1987).

In this study, we aimed to report drug release from bioerodible hydrogel based on semi-interpenetrating polymer networks (IPNs) composed of PCL and poly (ethylene glycol)(PEG) macromer for implantable delivery system. The loading and release behaviors of model drugs with varying aqueous solubilities were investigated. Also, the morphology of IPNs was examined by scanning electron microscopy (SEM) to observe the release behavior. It may be expected that the biodegradability of PCL can be enhanced with incorporation of PEG and the compatability between PCL and PEG can be increased than PCL/PEG blend (Sperling, 1981).

MATERIALS AND METHODS

Materials

PEGs with molecular weights 1,500 and 7,500 were obtained from Wako Pure Chem. Inc.. PEGs with molecular weight 20,000, 5-fluorouracil(5-FU), hydrocortisone(HC), tetracycline HCl(TC) were purchased from Sigma Chem. Co. All PEGs were α,ω-dihydroxy, and purified by azeotropic distillation from benzene solution. PCL(MW=40,000) was obtained from Aldrich Chem. Co. 2-Hydroxy isobutyl phenol was kindly supplied by Kansai Paint Co. LTD. Acryloyl chloride was purchased from Jassen of reagent chimica. All other

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Correspondence to: Chong-Su Cho, Department of Polymer Engineering, Chonnam National University, Kwangju 500-757, Korea chemicals were of reagent grade and used without further purification.

Synthesis of PEG macromer

The method of the PEG macromer synthesis was previously reported (Cho *et al.*, 1994). Briefly, the PEG macromer was obtained by acrylation of PEG benzene solution with acryloyl chloride and triethylamine for 3 h at 80℃.

Synthesis of semi-PCL/PEG IPNs

The semi-IPNs were prepared by simultaneous IPNs method. Ten μl of 2-hydroxy isobutyl phenol as the photoinitiator was added to the methylene chloride solution of PCL and PEG macromer. The solution was irradiated using a low-density LWUV lamp (Toshiba Chemical Lamp FL 20LB: wavelength 300-400 nm, maximum intensity 360 nm) for 5 min, and the solvent was then evaporated to dryness at 4℃. The solid was further dried at 40℃ under vacuum. The prepared semi-IPNs were repeatedly washed to remove unreacted PEG macromer with cold water for 1 day.

Water content

Dry IPNs films without drug were incubated in distilled water at 37℃. At preset time intervals, hydrated samples were weighed after blotting the surface water with filter paper. Water contents were calculated as Ws-Wd/Ws×100%, where Ws and Wd are wet weight and dry weight of the IPNs, respectively.

Drug loading

The desired amount of drug was dispersed in a methylene chloride solution of PCL and PEG macromer. The dispersed solution was then exposed to the UV lamp for 5 min and the solution was then evaporated to dryness at 4℃. The solid residue was further dried at room temperature under vacuum for 1 day.

In vitro release

Cutted disks(diameter: 7.4 mm and thickness: 1.1 mm) of the drug loaded polymer were introduced into a vial with 5 cm^3 of phosphate buffer solution (PBS) (0.1 M, pH=7.4). The mixture was allowed to stir in a shaker whose temperature was maintained at 37℃. At predetermined time intervals, aliquots of 5 cm^3 of the aqueous solution were withdrawn and another 5 cm^3 of PBS was put into the vial. The concentration of 5-FU, HC, and TC released was monitored using a UV-spectrometer at 306, 242, and 365 nm, respectively.

Scanning electron microscope (SEM) observation

Polymeric films were fixed on an adhesive tape and coated with gold/palladium before observation by SEM (JSM-35 CK JEOL microscope).

RESULTS AND DISCUSSION

Water content of PCL/PEG IPNs against an incubation time in distilled water at 37℃ is shown in Fig. 1. These results showed that water contents were dependent on the weight fraction of PEG and the water contents increase with increasing PEG weight fraction due to the hydrophilicity of PEG. Semi-IPNs composed of PCL and PEG macromer are expected to produce different degree of matrix hydration depending on the nature, cross-link density and amount of PEG.

Fig. 2 shows total release of 5-FU from the PCL/PEG IPNs against fraction of PEG. These results indicated that the release of 5-FU from the IPNs rapidly increased with incorporation of PEG in the IPNs. As shown in Fig. 2, the larger the amounts of PEG, the faster

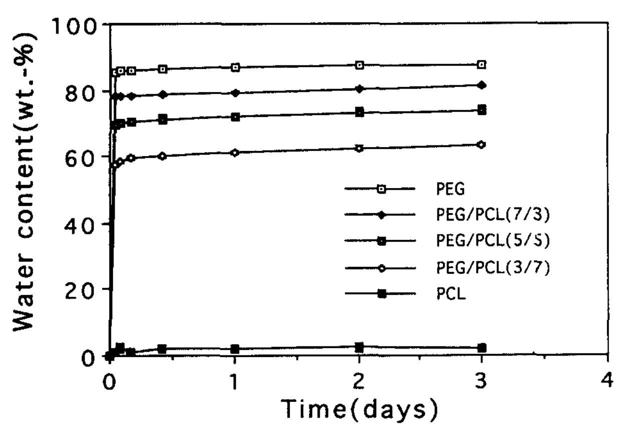

Fig. 1. Water content of PEG/PCL IPNs against weight fraction of PCL (MW. of PEG : 7500 and conc. of PEG : 20 wt.%)

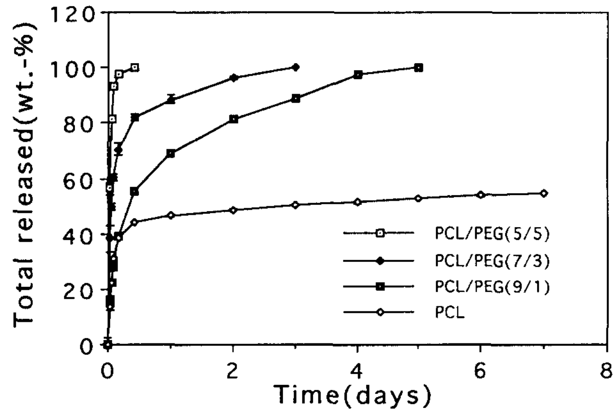

Fig. 2. Release of 5-FU from the PCL/PEG IPNs against weight fraction of PEG (MW. of PEG : 7500, drug loading : 5 wt.% and conc. of PEG : 20 wt.%)

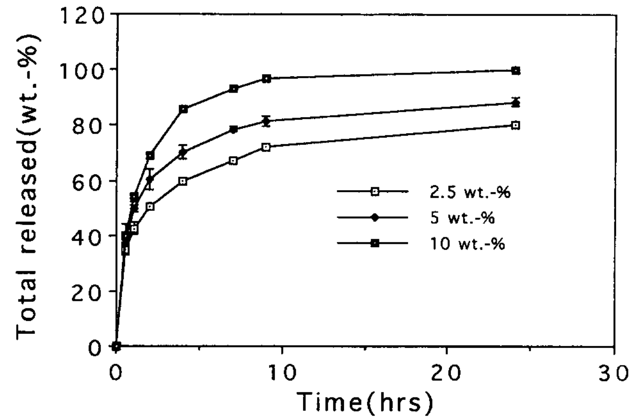

Fig. 3. Release of 5-FU from the PCL/PEG(7/3) IPNs with different drug loading (MW. of PEG : 7500 and conc. of PEG : 20 wt.%)

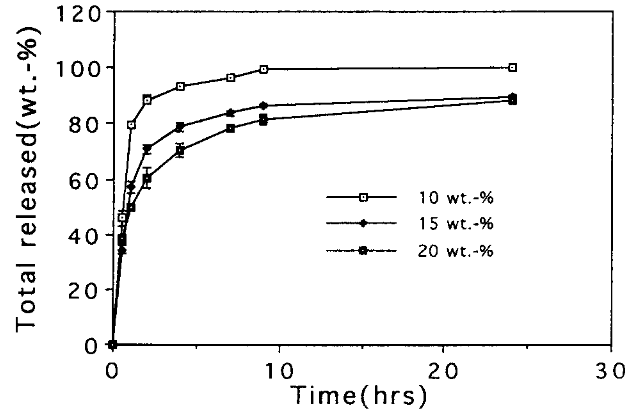

Fig. 4. Release of 5-FU from the PCL/PEG(7/3) IPNs against conc. of PEG macromer (drug loading: 5 wt.% and MW.of PEG : 7500)

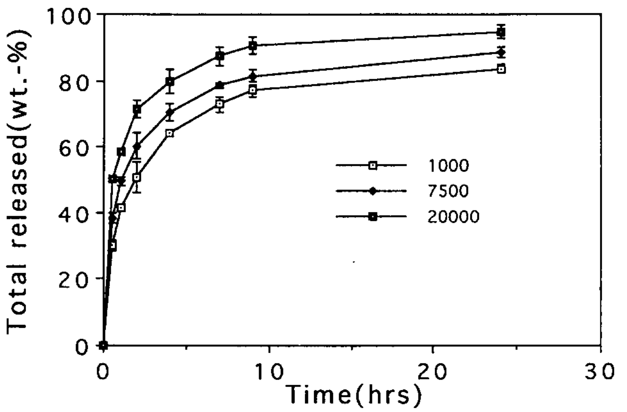

Fig. 5. Release of 5-FU from the PCL/PEG(7/3) IPNs against MW. of PEG macromer (drug loading: 5 wt.% and conc. of PEG : 20 wt.%)

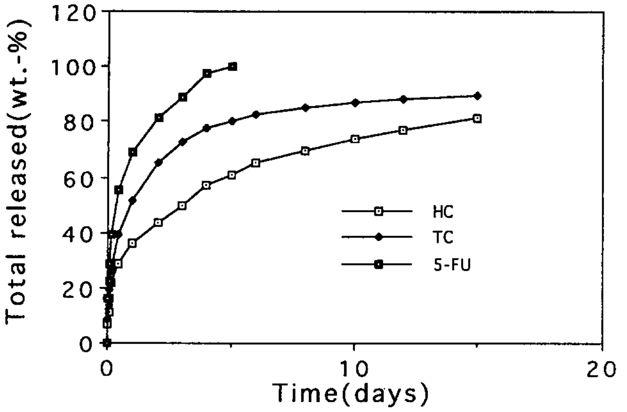

Fig. 6. Release of drug from the PCL/PEG(9/1) IPNs with different water solubility of drugs (MW. of PEG : 7500, conc. of PEG : 20 wt.% and drug loading: 5 wt.%)

the release of the drug. These observed phenomena could be explained in relation to the degree of swelling of the PCL/PEG IPNs matrices as shown in the Fig. 1. The penetration of water molecules within the IPNs became easier with the increase of hydrophilicity of PEG in the IPNs.

Fig. 3 shows total release of 5-FU from the PCL/PEG (7/3 : W/W) IPNs with different drug loadings. These results indicated that the larger the drug loading, the faster released. More than 93% of the initial 5-FU was released from 10% drug loading within 7 h, whereas only 67% from 2.5% drug loading was released for the same period of time. This feature might be assigned to the diffusion mechanism of drug from the IPNs matrices without occurrence of interactions between 5-FU and PCL/PEG IPNs.

Fig. 4 shows total release of 5-FU from the PCL/PEG (7/3 : W/W) IPNs against concentration of PEG macromer in the IPNs preparation. These results indicated that the lower concentration of PEG macromer in the IPNs preparation leads to a fast drug release than higher concentration of PEG macromer. This was attributed to formation of the higher cross-link density of the PEG gel by the higher concentration than lower one.

Fig. 5 shows total release of 5-FU from the PCL/PEG (7/3 : W/W) IPNs against molecular weight(M.W.) of PEG macromer. As shown in the Fig. 5, the higher M.W. of PEG macromer, the faster released. This was attributed to the increase of water content with the increase of M.W. of PEG macromer. As a matter of fact, the water contents of the PEG networks prepared by PEG macromers with molecular weights 1,500, 7, 500 and 20,000 were 55.9, 77.5, and 88.6 wt%, respectively.

Fig. 6 shows total release of drugs from the PCL/PEG (9/1 : W/W) with different water solubility of drugs (HC : 0.28 mg/ml, 5-FU : 12.5 mg/ml and TC : 100 mg/ml). These results indicated that the more drugs were released with increased water solubility of drugs

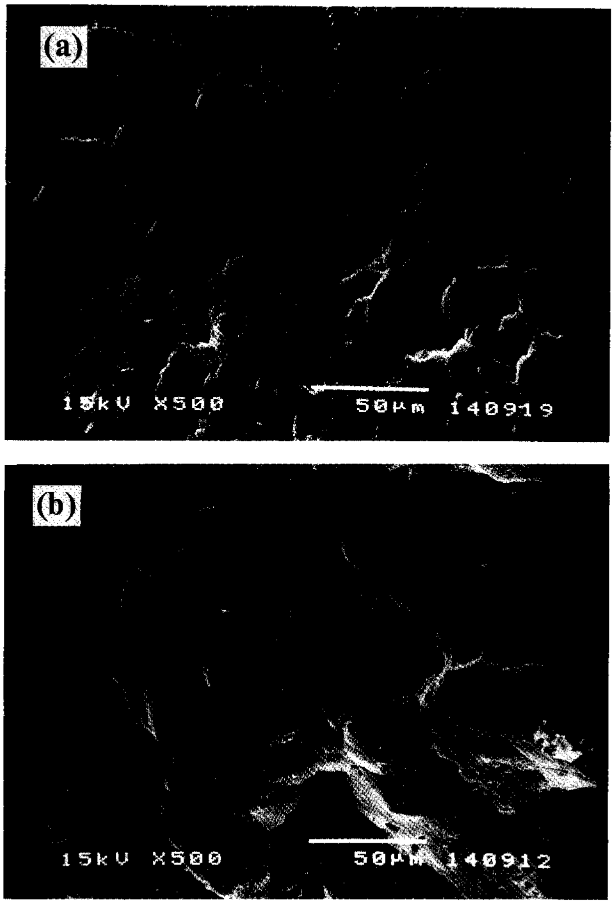

Fig. 7. Scanning electron microscopy of PCL/PEG(7/3) IPNs before (a) and after (b) in vitro drug release (3 days)

between HC and 5-FU for the same period of time. But, interestingly, TC were more slowly released than 5-FU although the solubility of TC in water was higher than that of 5-FU. These results reflected occurrence of acid-base interaction of the base drug with the chain end carboxyl groups of PCL (Mauduit *et al.*, 1993).

Fig. 7 shows SEM photographs of PCL/PEG(7/3 : W /W) IPNs before (a) and after (b) in vitro drug release. As shown in the Fig. 7, the morphology of the IPNs between before and after in vitro drug release appeared quite different. The morphology of the IPNs after 3 days of drug release was rather porous. This porosity well accounted for the drug release in the aqueous medium. It is likely that the porosity was formed during the drug release. Also, this feature might be regarded that drugs were released from the diffusion mechanism as already explained in the drug loading effect on the release.

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