

POLYCAPROLACTONE-POLY (ETHYLENE GLYCOL) BLOCK COPOLYMER III DRUG RELEASE BEHAVIOR

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ABSTRACT

The drug release behavior of degradable polymer—polycaprolactone-poly(ethylene glycol)block copolymer(PCE) in vitro was investigated by using 5-Fluoro-uracil (5-Fu) as a model drug under a condition of pH 7.4 at 37°C. It is found that the release rate of 5-Fu from PCE increased with increasing polyether content of the copolymer. The results show that the increasing polyether content of the copolymer caused increasing hydrophilicity and decreasing crystallinity of the PCE copolymer. Thus, the drug release behavior and the degradable property of the PCE can be controlled by adjusting the composition of the copolymer.

INTRODUCTION

Polymeric materials are well used as drug carrier in Drug Delivery System (DDS). In the case of general polymer used, following use the drug carrier must be taken out of the patient body since it can not be degraded in vivo. Biodegradable polymer can auto-degrade in vivo. The obvious advantage is that it eliminates the needs of removing drug device following use. It is also hopeful to realize a constant drug release^[1,2]. So biodegradable polymer is an ideal polymer material to be used as drug carrier for long-term implant drug device.

Polycaprolactone (PCL) has a good drug permeability. It is also one of the aliphatic polyesters with hydrolyzable ester bond. The biodegradation rate of PCL is very slow due to the crystallinity of PCL which makes it difficultly to be hydrolyzed^[3]. Aimed at improving and controlling the

degradability of the PCL, a lot of copolymers such as random or block copolymers of caprolactone-co-lactide^[4], poly (caprolactone)-b-poly (lactide)^[5,6] etc. have been studied.

We have reported a biodegradable polymer-poly (caprolactone) - poly (ethylene glycol) block copolymer (PCE). The crystallinity of PCE has been reduced by introducing polyether component^[7,8]. The objective of this work is to study the effect of content and molecular weight of polyether on the drug release behavior of the PCE copolymer by using 5-fluoro-uracil as a model drug.

EXPERIMENTAL

Materials

ϵ -Caprolactone: from Aldrich Chemical Company it was purified by drying with calcium hydride for 24hrs and distilled at 70°C/125Pa.

Poly (ethylene glycol): M.W. of 1000, 6000, 10,000 respectively, furnished by the Tianjin Eastern Health Material Factory.

Synthesis and purification

A mixture of ϵ -caprolactone (CL) and PEG, with the tetra-*n*-butyl titanate (Ti (OBu)₄) as catalyst was reacted under an argon atmosphere at 160°C for 10hrs. The PCE crude products were purified by reprecipitation from chloroform solution with petroleum ether and by extraction with cold ethanol, then it was dried in vacuum at room temperature^[7,8].

Water sorption

The water sorption of the copolymer was determined by the method reported previously^[9]:

$$\text{Water sorption (\%)} = \frac{W_1 - W_2}{W_2} \times 100\%$$

where W_1 is the weight of the copolymer after water sorption, and W_2 is the weight of the dried copolymer.

Determining the composition of the copolymer

The component ratios of the PCE copolymer were determined by ¹H-NMR spectrometry using a JOEL JNM-FX100 spectrometer with *d*-chloroform as solvent at room temperature.

Crystallinity of the copolymer

Crystallinity of the copolymer was measured by X-ray diffraction using

Rigaku Dmax-3B X-ray diffractometer and by Differential Scanning Calorimeter model Perkin-Elmer DSC-7 at a heating rate of 5°C/min.

In vitro degradation of PCE copolymer

Two hundred mg of PCE copolymer films (thickness about 0.15mm) were placed into flasks filled with 150ml of a pH 7.2 phosphate buffer solution at $37 \pm 1^\circ\text{C}$. After certain time intervals, the film samples were removed from the flask and were rinsed with distilled water. Then the samples were dried in vacuum and over phosphorus pentaoxide to constant weight. The degradation degree in vitro (percentage) was identified by the viscosity decreasing ($\Delta [\eta]$) of the copolymer as below:

$$\Delta [\eta] (\%) = \frac{[\eta]_0 - [\eta]_t}{[\eta]_0} \times 100\%$$

where $[\eta]_0$ and $[\eta]_t$ are inherent viscosity of the samples before and after degradation, respectively. The inherent viscosity was determined at 30°C , and calculated from η_r by the "One point method"^[10].

In vivo degradation of PCE copolymer

Two hundred mg of PCE copolymer tablets (thickness about 3.0mm) were implanted in the back of rats. After certain time intervals, the tablet samples were taken out from the back of rats and were cleaned with distilled water. Other post treatment of the tablet samples in vivo is the same as that in vitro degradation.

Determining drug release property

5-Fluoro-uracil has been used as model drug. A mixture of 20mg of 5-Fu and 200mg of PCE copolymer was charged into poly (tetrafluoroethylene) mould and then heated at 70°C to obtain tablet sample with a size of 10mm diameter and 3mm thickness. The tablet samples were placed into flasks filled with 120ml of pH 7.4 buffer medium and the drug release test was carried out at $37 \pm 1^\circ\text{C}$. After certain time intervals, the medium was vibrated and sampled and the concentration of 5-Fu was detected by 751G model UV Spectrometer at 266nm. The drug release rate was calculated as below:

$$D (\%) = \frac{C_t \times 120}{W_0} \times 100\%$$

where W_0 is the original 5-Fu weight, and C_t is 5-Fu concentration at t time.

RESULTS AND DISCUSSION

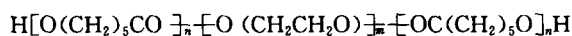
Dependence of drug release rate on the composition of PCE

Poly (caprolactone) -poly (ethylene glycol) block copolymer (PCE) is a biodegradable polymer. To determine its drug release behavior, a series of PCE copolymers (Formula 1) with different component ratios of PCL to poly (ethylene glycol) (PEG) were synthesized. Fig. 1 showed the 5-Fu release behavior of the PCE copolymers with different component ratios of CL to EG. The 5-Fu releasing periods changed from 1 day to 5 weeks in the samples with decreasing PEG portions from 60 to 20 in PCE copolymer. When homo-PCL was used as a carrier, 5-Fu release term was prolonged several months. At the same time, the dependence of water sorption on the composition of PCE copolymers was observed (Fig. 2). It was shown that the hydrophilicity of the PCE copolymer increased obviously with increasing content of the PEG. It should promote the diffusion and dissolution of 5-Fu drug. Fig. 2 also showed that the crystallinity of the copolymer decreased with the addition of PEG segment into PCL. It means that the amorphous regions, which allow penetration of water into the polymer, are extended. The amount and molecular weight of the PEG segment in the copolymer have a pronounced effect on the hydrophilicity and crystallinity of PCE (Fig. 2 and Table 1); this, in turn, controls the drug release rate. Fig. 3 indicated the delivery drug behavior of the PCE with PEG segments of different molecular weight and PCL segments fixed.

Table 1 Dependence of crystallization heat of PCE copolymer on molecular weight of PEG

No.	Segment molecular weight		ΔH (J/g)*
	PCL	PEG	
PCE-12	20,000	1,000	64.40
PCE-3	20,000	6,000	56.34
PCE-7	20,000	10,000	53.34

* measured by DSC



PCL

PEG

PCL

Formula 1 Polycaprolactone-Poly(ethylene glycol)
block copolymer(PCE)

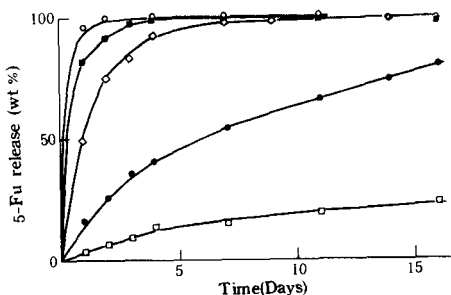


Fig. 1 Drug release behavior of PCE copolymer using 5-Fu as model drug [at pH 7.4 and 37°C]

PCE composition (molar ratio of CL/EG):

-□- 100/0; -●- 80/20; -◇- 70/30; -■- 60/40; -○- 40/60.

M. W. of PEG: 6000

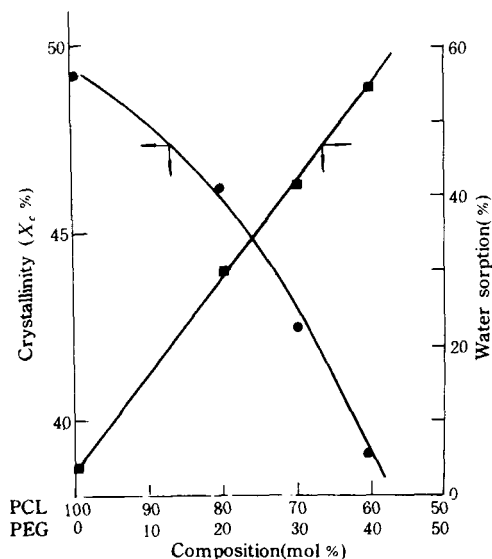


Fig. 2 Dependence of the crystallinity and water sorption on the composition of PCE copolymer

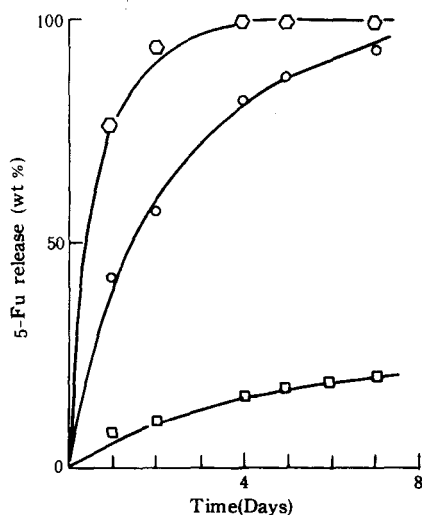


Fig. 3 Dependence of 5-Fu release rate on molecular weight of PEG component (at pH 7.4 and 37°C) M. W. of PCL segment: 20,000, M. W. of PEG: □ 1,000; ○ 6,000; ◇ 10,000

Effect of degradability of PCE on drug release behavior

The degradation of the PCE was reported previously^[8]. Fig. 1 indicates the release drug rates for some of the PCE (the portion of PEG is above 30) are very fast, so the hydrolytic degradation of the carrier has less effect on drug release behavior. The periods of release drug for using PCL and PCE-20 (molar ratio of CL/EG is 80/20) as a carrier are quite long, while at the same time hydrolytic degradation of the carrier occurs. Fig. 4 shows that the

relationship between the degradation and composition of the polymer. Referring to the results of drug release of PCE, it is found that the inherent viscosity reservation dergee of PCE-20 is about 80% in its release drug period (5 weeks), but that of PCL remains 95% in 2 months. The hydrolytic degradation of the carrier efficiently decreases the diffusion resistance of the 5-Fu. This is very important property for the carrier of drug, because it can compensate the decreasing of the drug release rate with reducing the drug content in the polymer. Fig. 5 shows the plot of 5-Fu release rate from the carrier as a function of crystallinity of PCE copolymer. It is revealed that release rates of 5-Fu change widely and can be controlled by adjusting the crystallinity of PCE copolymer. Based on this result, a 5-Fu and PCE blend with constant drug release rate has been prepared (Fig. 6).

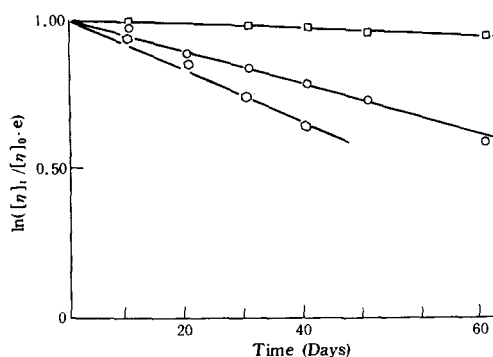


Fig. 4 Dependence of degradability on composition of PCE copolymer (at pH 6.5 and 37°C)
Composition (Molar ratio of CL/EG):
□- 100/0; ○- 80/20; △- 60/40

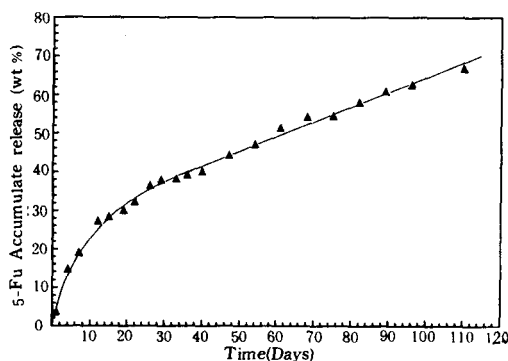


Fig. 6 The release drug behavior of PCE with constant rate (at pH 7.4 and 37°)

The degradability of PCE copolymer

Biodegradable polymer, which can auto-degrade in vivo, is especially suitable to be used as a carrier for controlling drug release. The degradability of PCE copolymer is characterized respectively by hydrolytic reaction in vitro and in vivo.

According to the hydrolysis dynamic equation of common esters^[3]:

$$[\eta] = [\eta]_0 \exp(-\alpha K t)$$

where α is the exponent in the Mark-Houwink equation of $[\eta] = KM^\alpha$, K is a constant dependent on temperature, and t is degradation time. So the changing degree of inherent viscosity can be written as:

$$\frac{[\eta]}{[\eta]_0} = \exp(-\alpha K t)$$

or

$$\ln\left(\frac{[\eta]}{[\eta]_0} \times e\right) = 1 - \alpha Kt$$

The plot of degradation time to the changing degree of inherent viscosity is shown in Fig. 4. From Fig. 4, $T_{1/2}$ and constant of αK can be obtained. $T_{1/2}$ is defined as a term in that the copolymer reducing its $[\eta]_0$ to half. The relationship among $T_{1/2}$ and constant of K as well as crystallinity of the PCE copolymer was shown in Fig. 7. It can be seen that the degradation rate of the PCE copolymer increased with reducing crystallinity of PCE copolymer. The degradation rate of the PCE copolymer can be adjusted by controlling the crystallinity of the copolymer, that is controlled by changing the content or molecular weight of the PEG component.

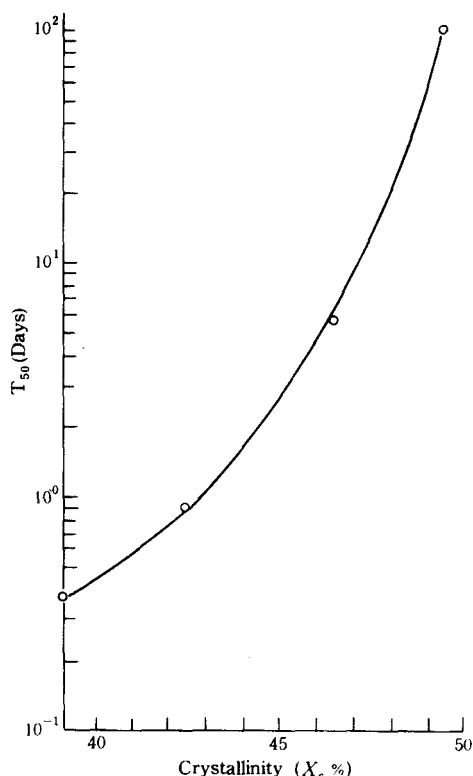


Fig. 5 Dependence of 5-Fu release rate on crystallinity of PCE copolymer (at pH 7.4 and 37°C)
M. W. of PEG: 6000

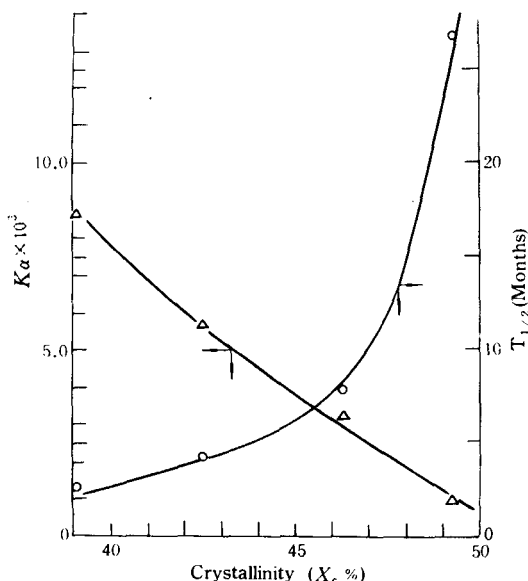


Fig. 7 Dependences of degradation rate ($T_{1/2}$) and constant of $K\alpha$ on crystallinity of PCE copolymer (at pH 6.5, 37°C)

It is shown in Table 2 that degradation rate of the PCE copolymer is closely related with the composition of the copolymer, either in vitro or in vivo. In addition, the degradation rate of PCE in vivo is much faster than in

vitro, the greater the PEG content is, the greater acceleration is. Because of the introduced PEG segment the crystallinity of PCE copolymer is reduced effectively (Fig. 2). Thus hydrolytic degradation and biodegradation of PCE are taken place easier than that of PCL. As Fig. 7 indicated, the lower the crystallinity of PCE is, the less $T_{1/2}$ is, and the degradation rate of PCE is faster. These results show that PCE copolymer can be used as a good biodegradable polymer.

Table 2 Degradation behavior of PCE copolymer in vitro and in vivo

Molar ratio of PCE (PCL/PEG)	Degradation environmental	$\Delta[\eta]\% = \frac{[\eta]_0 - [\eta]_t}{[\eta]_0} \times 100\%$
100/0	in vitro *	6.3
	in vivo **	16.7
80/20	in vitro	7.6
	in vivo	22.8
60/40	in vitro	10.8
	in vivo	44.5

* in vitro; Samples were dipped in pH 7.2 buffer at 37°C for 30 days

** in vivo; Samples were implanted in the back of rats for 28 days

Keywords:

Polycaprolactone; Poly(ethylene glycol); Block copolymer; Crystallinity; Degradability; 5-Fluoro-uracil; Drug release property

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