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STUDIES ON PROPERTIES AND DRUG DELIVERY SYSTEMS OF PTMC-*b*-PEG-*b*-PTMC BLOCK COPOLYMERS

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Key Words: Poly(trimethylene carbonate), Poly(ethylene glycol), ABA Type Block Copolymers, Drug Delivery System

ABSTRACT

ABA type block copolymers of poly(trimethylene carbonate) with poly(ethylene glycol) were synthesized and characterized. The dynamic contact angle of **PTMC**-*b*-PGG-*b*-**PTMC**(**PTPEPT**) block copolymer film was determined. It revealed that the acceding angle (θ_a), decreased with the increase of **PEG** content in copolymers, indicating that the **PEG** fractions lead to higher hydrophilicity of **PTPEPT** copolymers. The potential application of **PTPEPT** copolymers for drug delivery systems was investigated. The measurement of drug delivery using **PTPEPT** as matrices showed that the release rate of Levonorgestrel (**LNG**) increased with the increase of hydrophilicity of copolymer samples. No obvious burst effect of release of **LNG** could be observed in the **LNG/PTPEPT** systems especially when the **PTMC** block became longer. In a short period, about 25 days, the release rate of **LNG** remained almost constant.

INTRODUCTION

Biodegradable polymers have drawn much attention due to their bright application prospect in the biomedical field. For instance, multifilament and monofilament sutures made of poly(lactide) (**PLA**) or poly(1,4-dioxan-2-one) (**PDON**) have been used clinically for a long time [1]. Over the last two decades numerous synthetic biodegradable polymers like **PLA**, poly(ε-caprolactone) (**PCL**), polyanhydride were used as drug carriers to control drug release rate and dose in the body [2, 3]. Eventually, they can degrade into untoxic products which could be absorbed or excreted instead of being taken out through surgery. However, most of them such as **PLA**, **PCL** and **PDON** are hydrophobic polymers. Poly(ethylene glycol) (**PEG**) shows excellent physic-chemical and biological properties such as biocompatibility, hydrophilicity, solubility in water and in organic solvents, lack of toxicity, antigenicity and immunogenicity [4, 5]. Its good hydrophilicity makes it easily removed from the body by metabolism. Thus, **PEG** has been used as additives in food and drug. The hydroxyl end group can readily react with a variety compounds. It is seen that the water permeation through polyester is related with the hydrophilic compositions of polymers. Block copolymers such as **PEG-*b*-PLA-*b*-PEG** [6-8], **PEG-*b*-PCL-*b*-PEG** [9, 10], and **PEG-*b*-PDON-*b*-PEG** [11] have been synthesized and the studies of their drug delivery behavior have also been reported. The copolymerization of polyester with **PEG** offered the possibility of varying hydrophilic/hydrophobic segment ratios, and constitutes a very attractive means to tailor the basic properties of each homopolymer. **PTMC** is a hydrophobic polymer. It is found that **PTMC** can degrade into untoxic small molecules to be excreted [12]. **PTMC** has good flexibility, however, its degradation is extremely slow for the following reasons: (i) the degradation of **PTMC** cannot produce carboxylic group like **PLA** and **PDON**, i.e., no self-catalyzing effect for **PTMC** degradation; (ii) hydrophobicity of **PTMC** retards water permeation. **TMC** is usually used as comonomer with LA or CL in preparation of copolymers to improve flexibility of sutures [13, 14]. Little attention was paid to the studies on the application of **PTMC** in drug delivery system (**DDS**). Pitt reported that the diffusion coefficient of progesterone in **PTMC** is comparable to the value in **PCL** because of non-crystallinity of **PTMC** [15]. We have reported previously the synthesis and properties of **PTMC-*b*-PEG-*b*-PTMC** block copolymers [16]. This paper presents the relation between physical properties and drug delivery behavior of DDS consisting of **PTMC-*b*-PEG-*b*-PTMC** block copolymers and Levonorgestrel.

EXPERIMENTAL

Materials

1,3-Propandiol (Beijing Chemical Factory), diethyl carbonate (J. T. Baker Chemicals B. V., GC 99%), stannous octoate ($Sn(Oct)_2$, PFALTZ & BAUER, Inc.) were used as received. Cyclohexane (Beijing Chemical Factory) was freshly distilled over sodium. The stock solution of $Sn(Oct)_2$ in cyclochexane (0.3849 mol/L) was used as catalyst of all polymerization. **PEG** (Tianjin Tiantai Fine Chemicals Co. Lt.) was first allowed to stand at 110°C for 24 hours, then further dried under reduced pressure just before use. Levonorgestrel (**LNG**, Beijing Third Pharmaceutical Factory) was used as received. All other solvents and reagents were domestic products and used as received.

Synthesis of 1,3-Dioxan-2-one (Trimethylenecarbonate, TMC) Monomer

TMC was synthesized according to a modified literature procedures [17]. 105 mL (111.3 g, 1.46 mol) of 1,3-propandiol, 400 mL (389.6 g, 3.30 mol) of diethyl carbonate, and 20 g of K_2CO_3 was added to a 1000 mL one-necked, round-bottomed flask fitted with a condenser . The flask was heated to 120°C in an oil bath. The solution was kept stirring for 3 hours while CH_3CH_2OH was distilled out. The residual mixture was filtered and the filtrate was concentrated, giving the crude product. The crude product was distilled under reduced pressure of 133.3 Pa in the presence of CaH_2 and a few drops of $Sn(Oct)_2$. The distillate at 120°C was collected. It solidified to white crystal while dropping in a collecting flask. This product was recrystallized three times in THF/ether mixed solvent (8:4, v/v). After drying in vacuum for 24 hours it was kept in drying desiccate, giving m.p. 45.5 - 46.5°C (literature. m.p.: 45°C [18]). Yield: 36%. ^1H NMR ($CDCl_3$, **TMS**, ppm): 4.47 (t, 4H), 2.16 (quint., 2H).

General Procedure for Block Copolymerization of TMCwith PEG

Calculated amounts of **PEG** and **TMC** were charged into a flame-dried glass tube. The system was connected with a vacuum line dried at 110°C for 30 minutes and purged with nitrogen. Under nitrogen a proper amount of $Sn(Oct)_2$ stock solution was charged into the tube with a flame-dried syringe. After it was sealed in vacuum, it was then heated and kept at 120°C for 10 hours. The copolymer was dissolved in $CHCl_3$, then precipitated in methanol. It was further purified by immersing into deionized water, the solvent of **PEG**, and then THF, the solvent of **PTMC**, for several days, respectively, in order to remove the

homopolymers of **PEG** and **PTMC**. The copolymer was dried in vacuum at ambient temperature to constant weight.

Preparation of PTMC-*b*-PEG-*b*-PTMC/Levonorgestrel DDS and Determination of LNG Release Rate

Calculated **PTMC-*b*-PEG-*b*-PTMC** copolymers and Levonorgestrel (**LNG**) were dissolved in dichloromethane, then the solvent evaporated naturally and dried under vacuum to a constant weight. The copolymer and **LNG** mixtures were pressed into circular cylinders under 1.96 KPa pressure. The cylinders were immersed in 15 wt% ethanol/water mixture solvent which is the good solvent for **LNG**. They were kept in a shaking bath at 37°C. The immersion solvents were refreshed regularly, and in the meantime the amount of **LNG** released per day was determined by their UV absorbance at 248 nm.

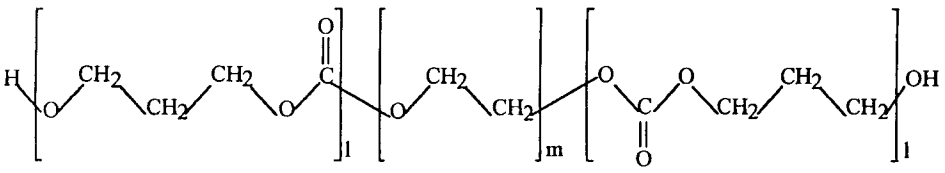
Characterizations

The 400 MHz ^{1}H NMR spectra were recorded on a Bruker ARX400 spectrometer at room temperature. Tetramethylsilane (**TMS**) served as internal reference for all ^{1}H NMR measurements and $CDCl_3$ was used as a solvent. The mole fraction of **TMC** in block copolymer, F_{TMC}, was determined from the integration ratio of the methylene triplet of **PTMC** segment at δ 4.24 ppm and the methylene singlet of **PEG** segment at δ 3.66 ppm. Fourier transform infrared (FT-IR) spectra were measured using a Nicolet Magna-IR 750 spectrometer with KBr pellets. Intrinsic viscosity of copolymers were determined with a Ubbelohde viscometer at 30±0.05°C using tetrachloroethane as a solvent. Differential scanning calorimetry (DSC) thermo-grams were recorded on a Shimadzu DSC-50 Differential Scanning Calorimeter with a heating rate of 10°C/min. Dynamic contact angles (DCA) were obtained on a DCA-322 Dynamic Contact Angle Analyzer at 37°C with film on a glass plate. Molecular weight of **PEG** was determined to be 6820 by vapor pressure osmometry (VPO) performed on a KNAUER Vapor Pressure Osmometer at 37°C with chloroform as a solvent. The number of hydroxyl end groups of **PEG** was calculated as 2.09 by titration method [19] with the molecular weight of 6820. ^{1}H NMR of **PEG** ($CDCl_3$, **TMS**, ppm): 3.64 (s).

RESULTS AND DISCUSSION

Syntheses of PTMC-*b*-PEG-*b*-PTMC(PTPEPT) Block Copolymers

With **PEG**, using $Sn(Oct)_2$ as catalyst, **PTPEPT** block copolymers were synthesized via ring opening polymerization of **TMC**. Block copolymers with



PTMC-*b*-PEG-*b*-PTMC m=155

SCHEME 1

various **TMC** contents could be controlled by changing the feed proportion of **TMC** and **PEG**. Scheme 1 is the structure of resulting block copolymers determined by FT-IR and ^{1}H NMR. Their compositions are listed in Table 1. It can be seen that the mole fractions of **TMC**, f_{TMC}, were varying from 0.951 to 0.400. With an increase of **PEG** feed, the molecular weights of **PTMC** segments in copolymers, as well as molecular weight of resulting copolymer, decrease. As the hydroxy group show very high reactivity towards stannous catalyst [6, 7] and the two hydroxy end groups of **PEG** should possess equivalent reactivity, the ABA block copolymers is considered to be formed at present polymerization.

Thermal Properties of Copolymers

The DSC thermographs for glass transition temperatures, T_gs, of copolymers were recorded with the samples cooled rapidly by immersing in liquid nitrogen immediately after heated to 150°C in order to obtain amorphous samples, and the thermographs for melting point, T_m, were recorded with the samples cooled naturally to ambient temperature after heated to 120°C. The experimental data were listed in Table 1. The T_g value of **PTMC** blocks was detected at -15.3°C, T_g of **PEG** blocks, however, was not detected in the experiments. From Table 1 it can be seen that the T_g of **PTMC** blocks in copolymers change regularly with the composition of **PTMC** blocks. The T_ms of **PEG** blocks in PTPEPT6 samples is 34°C, it is much lower than that of **PEG** homopolymer (T_m=65°C). As for other copolymers the T_m of **PEG** blocks can not be detected. Obviously, **PTMC** blocks obstructed the crystallization of **PEG** blocks.

It is well known that the release rates of drug from non-crystalline as well as lower T_g polymeric matrix are higher than that from crystalline and higher T_g matrix. The **PTPEPT** block copolymers with non-crystalline **PEG** blocks and low

TABLE 1. Composition and Molecular Weight of **PTMC-*b*-PEG-*b*-PTMC** Copolymer[a]

No.	PEG (g)	TMC (g)	f_{TMC}[b] %	F_{TMC}[c] %	$\overline{M}_{n,F}$[d] 10^3	Yield[f] (%)	$[\eta]$[g] (dL/g)	T_g[h] (℃)
PTMC	0.000	2.499	100.0	100.0	315.3[e]	92.9	4.33	-15.3
PTPEPT1	0.044	2.000	95.1	96.8	240.6	82.8	0.666	-20.5
PTPEPT2	0.143	2.994	90.0	93.4	112.1	71.1	0.587	-23.8
PTPEPT3	0.202	1.880	80.1	84.7	43.6	40.7	0.572	-26.2
PTPEPT4	0.486	2.810	71.4	79.0	29.8	70.2	0.499	-29.5
PTPEPT5	0.502	1.749	60.0	74.0	22.5	62.6	0.416	-28.2
PTPEPT6	0.838	1.296	40.0	63.5	13.2	63.0	0.355	-29.7

[a] [TMC]/[$Sn(Oct)_2$]=2000. [b] Mole fraction of TMC in the feed, f_{TMC} = [TMC]/([TMC]+[EO]) × 100%, EO is the repeat unit of PEG.

[c] Mole fraction of TMC in the copolymer, F_{TMC} = d[TMC]/(d[TMC]+d[EO]) × 100%, determined by ^1H NMR spectroscopy. [d] Molecular weight of each PTMC block estimated by ^1H NMR spectroscopy. [e] Determined by $[\eta]=KM^{\alpha}$, K=1.986 × 10^{-4}, α=0.789 [15].

[f] Calculated according to W_0/(Weight of PEG+Weight of TMC) × 100%. [g] In $CHCl_3$ at 30±0.05 ℃. [h] Determined by DSC.

T_g of **PTMC** blocks used in this work will favor the release of drug from DDS of **PTPEPT/LNG**.

Hydrophilicity of PTPEPT Copolymers

The analysis of the dynamic contact angle will provide the information of hydrophilicity of copolymers. The data of acceding angle θ_a and receding angle θ_r of **PTPEPT** are compiled in Table 2. It clearly shows that the θ_a of copolymer decreases with the increase of **TMC** mole fraction, F_{TMC}, in copolymer. In other words, the hydrophilicity of copolymers became high while the **PEG** content in copolymers increased due to the strong hydrophilicity of **PEG** blocks.

Release of LNG from DDS consisting of PTMC-*b*-PEG-*b*-PTMC Block Copolymers Matrices and LNG

The composition of DDS consisting of copolymer matrices and Levonorgestrel (**LNG**) were listed in Table 3.

TABLE 2. DCA Data of **PTMC-*b*-PEG-*b*-PTMC** Copolymers

No.	PTMC	PTPEPT1	PTPEPT2	PTPEPT3	PTPEPT4	PTPEPT5	PTPEPT6
θ_a(°)	83.66	74.05	68.33	61.86	48.96	45.50	27.15
θ_r(°)	28.62	24.97	—	—	—	—	—

TABLE 3. **LNG** Contents in **PEPTPE** Copolymer Matrices

	F_{TMC}	**LNG** (%)	Weight of copolymer (g)	**LNG** (mg)
PTPEPT2	0.934	16.98	0.0164	3.354
PTPEPT4	0.790	16.74	0.0158	3.177
PTPEPT6	0.635	16.81	0.0235	4.749

The amount of **LNG** released per day was determined by the UV absorbance of immersion solution at 248 nm with an UV spectrometer.

As the samples of **PTPEPT** with higher **PEG** content are liable to scatter in immersion solvent, so only the samples of **PTPEPT** with F_{TMC}>0.635 were used in the release experiments. Figures 1 and 2 are the release profile of **LNG** from **PTPEPT** copolymers matrices.

Figure 1 clearly shows that introduction of **PEG** into copolymers accelerated the release of **LNG**. It can be concluded that **PEG** blocks in copolymers improve the hydrophilicity of polymers, as well as their water absorption. The increase of the rate of water permeation into the matrices can enhance the dispersion of **LNG** in the matrices. However, the burst effect will become larger with the increase of **PEG** in copolymers. There is nearly no burst effect in **DDS** of **PTPEPT2** and **PTPEPT4**.

In 25 days, the relation of accumulative release of **LNG** from **PTPEPT2** or **PTPEPT4** with time gives almost a straight line (cf. Figure 2), indicating that the release of **LNG** in 25 days is in zero order, that is the release rate is nearly constant. The big initial burst effect would happened when the drug mainly distributed on the surface of **DDS** or the matrix polymer can be dissolved in medium quickly. This is not the case for **PTPEPT6/DDS**. For **PTPEPT6** system, the **LNG** can be mixed homogeneously in matrix. In the beginning of release, the burst effect is not high.

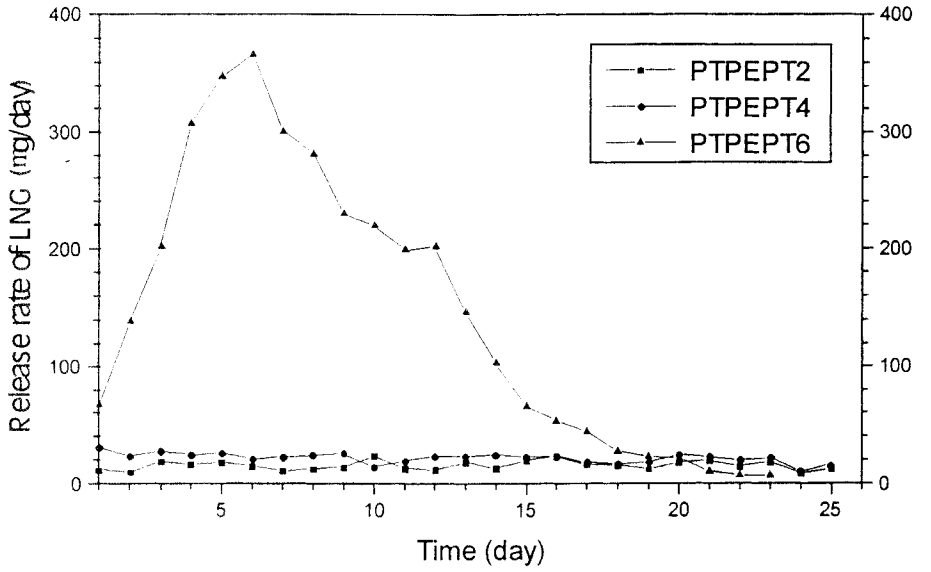


Figure 1. Correlation between Release Rate of **LNG** and Time.

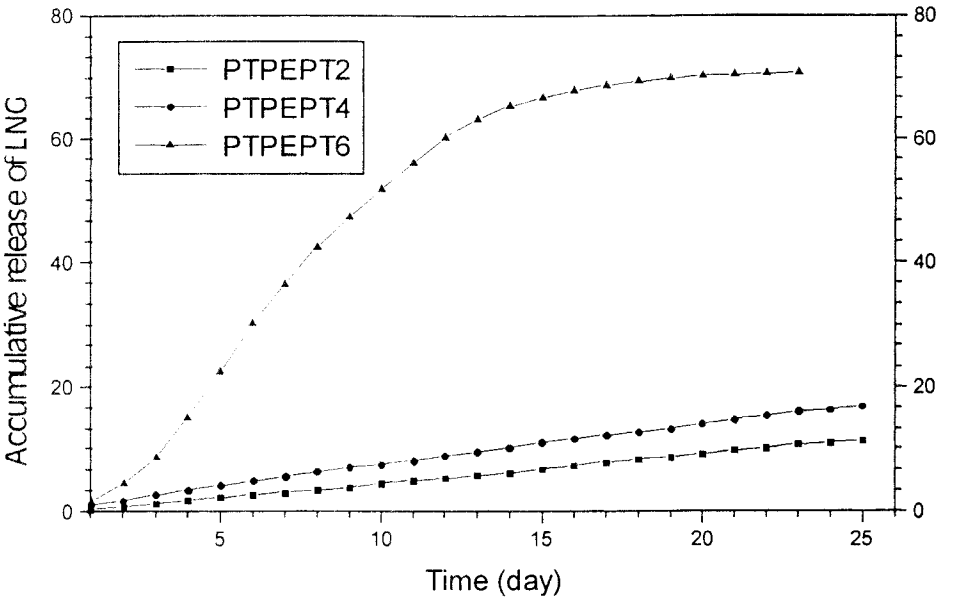


Figure 2. Correlation between cumulative release of **LNG** and time.

As the **PEG** content is higher than two other samples, the **PTPEPT6** possess higher hydrophilicity and water permeated into the matrices, leading to swelling when it was immersed in solvent. This made **LNG** dispersed out from the matrices at higher speeds to show large burst effects. Until 10 days or so the **LNG** in the surface was nearly depleted, and with the water permeated into deeper positions of matrices the **LNG** in inner of matrices began to disperse out via longer distance. The release rate decreased in the meantime.

CONCLUSION

PTMC-*b*-PEG-*b*-PTMC(PTPEPT) block copolymers with different **TMC** content have been prepared and their **DDS** with **LNG** was prepared by dissolution/vaporization method. The release of **LNG** from the matrices is obviously dependent of the components of copolymers. As the hydrophilicity of the sample is the most important effect, the **PTPEPT** copolymers with high **PEG** composition gives high release rate of **LNG** from the matrices. The burst effect of release of **LNG** from **PTPEPT** matrices is very small when **TMC** mole fraction in copolymers is equal to or higher than 0.790. In 25 days the release rates for **PTPEPT2** and **PTPEPT4** matrices are almost constant, i.e. following zero order release dynamics. By controlling the compositions of the **PTPEPT** matrices, the constant release of **LNG** can be realized in a short period.

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