# Synthesis of PDON-*b*-PEG-*b*-PDON Block Copolymers and Drug Delivery System Thereof

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**ABSTRACT:** ABA-type block copolymers of poly(1,4-dioxan-2-one) (PDON) with poly(ethylene glycol) (PEG) were synthesized and characterized. From the results of differential scanning calorimetry and wide-angle X-ray diffraction, it was observed that the PDON blocks show similar crystallization behavior with homopolymer while the PEG blocks demonstrate lower melting temperature and crystallinity than PEG homopolymer. Their dynamic contact angles ($\theta_a$) decreased with the increase of PEG fraction in copolymers, indicating the hydrophilicity of PDON-*b*-PEG-*b*-PDON (PDPEPD) copolymers was improved gradually. The potential application of PDPEPD copolymers in the drug delivery system has been investigated. The release rate of Levonorgestrel (LNG) increased with the strengthening of hydrophilicity of copolymer samples. The burst effect of release of LNG is small in copolymers with short PDON blocks. When DON mole fraction in copolymers is high enough, no burst effect can be observed. In an experimental period of about 25 days, the release rate of LNG kept almost constant.
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**Key words:** 1,4-dioxan-2-one; poly(ethylene glycol); ABA block copolymer; drug delivery system

## INTRODUCTION

Numerous studies have been devoted to the synthesis, characterization, and processing of biodegradable polymers such as poly(glycolic acid) (PGA), poly(lactic acid) (PLA),[1] poly(1,4-dioxan-2-one) (PDON),[2] and poly($\epsilon$-caprolactone) (PCL), and many biomaterials for biomedical applications were developed in recent decades.[3–5] Various biodegradable polymers have been used as drug carriers to tailor drug dose and period in the body. Copolymers have been extensively investigated due to their improved properties and processibilities compared with homopolymers. Besides random copolymers, block copolymers like PLA-*b*-PCL showed interesting properties.[6,7] Poly(ethylene glycol) (PEG) presents outstanding physicochemical and biological properties, including hydrophilicity, solubility in water and in organic solvents, lack of toxicity, and absence of antigenicity and immunogenicity, which allow PEG to be used for many biomedical and biotechnological applications.[8,9] The hydroxyl end group can react with many compounds. Block copolymers such as PLA-*b*-PEG and PCL-*b*-PEG had been synthesized, and studies on their properties and drug delivery behavior to certain medicine have also been reported.[10–14] It was realized that the water permeation in polyester is affected by the hydrophilic components of the polymers. The

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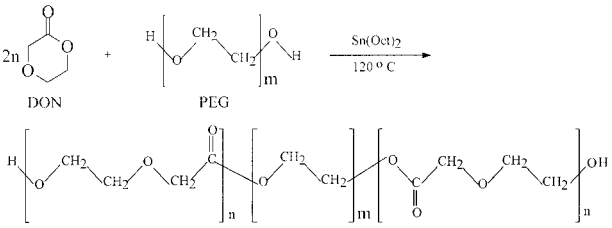


PDON-*b*-PEG-*b*-PDON

**Scheme 1**

copolymerization of polyester with PEG provided the possibility of varying hydrophilic/hydrophobic segment ratios, and offered a very attractive method to modulate the properties of the homopolymer. PDON is a hydrophobic polyester, and could be used in the body safely, degrading to nontoxic compounds.[15] Its flexibility and tensile strength is better than PLA.[15] It has been commercially used as surgical sutures.[16] However, few studies on the application of polymers of DON in the drug delivery system (DDS) have been reported. This article presents preparation of the block copolymers PDON-*b*-PEG-*b*-PDON and the release behavior of DDS consisting of copolymers and Levonorgestrel (LNG).

## EXPERIMENTAL

### Materials

$Sn(Oct)_2$ (Pfaltz & Bauer, Inc.) was used as received. The stock solution of $Sn(Oct)_2$ in cyclohexane (0.3849 mol/L) was used as polymerization catalyst. Cyclohexane was freshly distilled over sodium. PEG (Tianjin Tiantai Fine Chemicals Co. Lt.) with a molecular weight of 6820 g/mol and a hydroxyl end group functionality of 2.09 was allowed to stand at 110°C for 24 h 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 1,4-Dioxan-2-one

1,4-Dioxan-2-one (DON) was synthesized and purified according to the same procedures as in our previous article,[17] and distilled over $CaH_2$ just before polymerization.

### General Procedure for Block Copolymerization of DON with PEG

The calculated amount of dried PEG was charged into a flame-dried glass tube. The system was connected with a vacuum line dried at 110°C for 30 min and purged with nitrogen. Under nitrogen atmosphere the proper amounts of DON and $Sn(Oct)_2$ stock solution were charged into the tube with a flame-dried syringe. The tube was purged with nitrogen four times. After sealing *in vacuo,* it was heated and kept at 120°C for 10 h. The copolymer was dissolved in $CHCl_3$, then precipitated in methanol. It was further purified by immersing into deionized water, as a solvent for PEG, for several days to remove the homopoly-

**Table I Copolymerization of DON with PEG**

| Sample | PEG (g) | DON (g) | $f_{DON}$[a] (%) | $F_{DON}$[b] (%) | Yield (wt %) | $W_1$[c] (g) | $M_{n,F}$[d] | $[\eta]$[e] (dL/g) |
|---|---|---|---|---|---|---|---|---|
| PDPEPD1 | 0.1429 | 3.000 | 90.1 | 88.7 | 72.73 | 2.2846 | 64000 | 0.405 |
| PDPEPD2 | 0.1957 | 1.875 | 80.5 | 81.4 | 73.98 | 1.5254 | 26600 | 0.356 |
| PDPEPD3 | 0.0487 | 0.500 | 81.6 | 78.7 | 66.54 | 0.3651 | 25700 | — |
| PDPEPD4 | 0.4860 | 2.875 | 71.9 | 69.2 | 70.24 | 2.3404 | 15300 | — |
| PDPEPD5 | 0.4850 | 2.813 | 71.4 | 65.3 | 50.20 | 1.6530 | 13100 | 0.343 |
| PDPEPD6 | 0.5018 | 1.750 | 60.1 | 57.9 | 67.43 | 1.5001 | 8300 | 0.280 |
| PDPEPD7 | 0.1467 | 0.500 | 59.5 | 52.5 | 63.92 | 0.4134 | 7700 | 0.243 |
| PDPEPD8 | 0.2955 | 0.500 | 42.2 | 34.4 | 55.10 | 0.4383 | 3600 | — |
| PDPEPD9 | 0.5861 | 0.500 | 26.9 | 22.1 | 49.32 | 0.5357 | 2000 | — |

[a] Mole fraction of DON in the feed, $f_{DON}$ = [DON]/([DON] + [EO]) × 100%, EO (ethylene oxide) is the repeat unit of PEG.
[b] Mole fraction of DON in the copolymer, $F_{DON}$ = $d$[DON]/($d$[DON] + $d$[EO]) × 100%, determined by $^1$H-NMR spectroscopy.
[c] Weight of copolymer after immersed 4 days in water.
[d] Molecular weight of each PDON block estimated by $^1$H-NMR spectroscopy.
[e] In $C_2H_2Cl_4$ at 30 ± 0.05°C.

**Table II DSC Data for PDON-*b*-PEG-*b*-DON Copolymers**

| Sample | | PDON[a] | PDPEPD2 | PDPEPD5 | PDPEPD6 | PDPEPD7 | PDPEPD8 | PEG |
|---|---|---|---|---|---|---|---|---|
| $T_m$ (°C) | PDON | 111.0 | 108.8 | 111.6 | 109.0 | 106.6 | 108.8 | — |
| | PEG | — | — | 44.0 | 38.9 | 39.5 | 48.1 | 64.8 |
| $\Delta H^b$ (J/g) | PDON | 91.41 | 89.45 | 85.55 | 97.04 | 105.1 | 104.4 | — |
| | PEG | — | — | 9.55 | 24.03 | 23.55 | 62.48 | 174 |

[a] Intrinsic viscosity of PDON [$\eta$] = 0.379 dL/g.
[b] The enthalpy of PDON segments (or PEG segments) in copolymers divided by the total weight of PDON segments (or PEG segments) in copolymers.

mers of the PEG. The copolymer was dried *in vacuo* at ambient to constant weight.

### Preparation of PDON-*b*-PEG-*b*-PDON Matrix Loading Levonorgestrel and Release Experiment

PDON-*b*-PEG-*b*-PDON copolymers and Levonorgestrel with proper weight ratio were dissolved in dichloromethane, then the solvent was evaporated naturally, and dried under vacuum to constant weight. The mixtures of copolymer and LNG were pressed into circular cylinders under a pressure of 19.6 kPa. The cylinders were immersed in 15% ethanol/water mixture solvent. They were kept in a shaking bath at constant temperature of 37°C. The immersion solvent was refreshed regularly, and in the meantime their UV absorbency at 248 nm were recorded.

### Characterization

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 solvent. 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 the solvent. The number of hydroxyl end groups of PEG was calculated as 2.09 by a titration method,[18] with the molecular weight of 6820 g/mol. $^1$H-NMR of PEG ($CDCl_3$, TMS, ppm): 3.66 (s). The mol fraction of DON in the block copolymer, $F_{DON}$, was determined from the integration ratio of the methylene triplet of the PDON segment at $\delta$ 4.4 ppm and the methylene siglet of the PEG segment at $\delta$ 3.66 ppm. Fourier transform

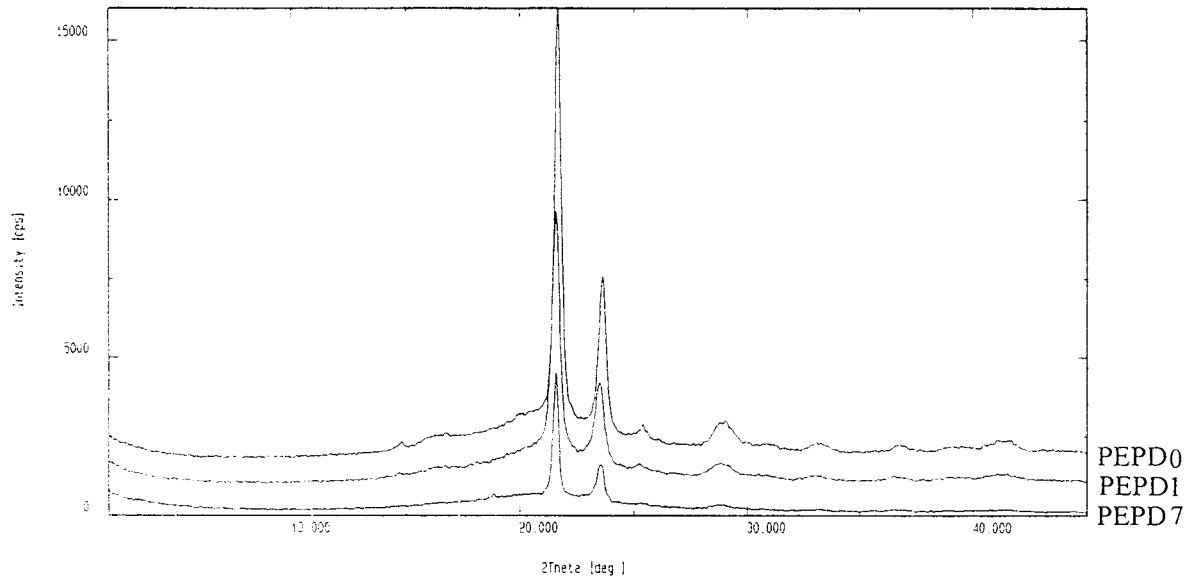


**Figure 1** WAXD spectra of PDPEPD copolymers.

**Table III WAXD Data of PDON-*b*-PEG-*b*-PDON Copolymers with Different $F_{DON}$**

| Sample | PDPEPD0 | PDPEPD1 | PDPEPD7 |
|---|---|---|---|
| $F_{DON}$ | 0.982 | 0.902 | 0.525 |
| $2\theta$ (°) | 21.60 | 21.60 | 21.62 |
| | 23.76 | 23.54 | 23.68 |

infrared (FTIR) spectra were measured using a Nicolet Magna-IR 750 spectrometer with KBr pellets. Intrinsic viscosities of copolymers were determined with a Ubbelohde viscometer at 30 $\pm$ 0.05°C, using tetrachloroethane as the solvent. Differential scanning calorimetry (DSC) thermograms were recorded on a DuPont DSC-1090 Differential Scanning Calorimeter with a heating rate of 10°C/min. Wide-angle X-ray diffraction (WAXD) was performed with Ragua X-ray diffraction instrument equipped with a Cu K$\alpha$1 ($\lambda$ = 0.1542 nm) source. Dynamic contact angles (DCA) were obtained on a DCA-322 Dynamic Contact Angle Analyzer at 37°C with film on glass plate.

## RESULTS AND DISCUSSIONS

### Syntheses of PDON-*b*-PEG-*b*-PDON Block Copolymers

With Sn(Oct)$_2$ as catalyst, PDPEPD block copolymers with various DON contents were synthesized via ring-opening polymerization by changing the feed proportion of DON and PEG. Scheme 1 shows the structure of the resulting block copolymers determined by FTIR and $^1$H-NMR. Their compositions are listed in Table I. The mol fractions of DON, $f_{DON}$, were varied from 0.901 to 0.269. With increase of the PEG feed, the molecular weight of the PDON segments in the copolymers decrease. As PEG with $\alpha,\omega$-dihydroxy end groups was used for the polymerization with DON, theoretically two hydroxyl end groups of PEG would initiate DON to polymerize, and ABA-type copolymers could be obtained. Some articles[10,12,20] had proposed an initiation mechanism for block copolymerization of LA with PEG. This mechanism can be extended to the present block copolymerization of DON with PEG. In the monomer, DON, conversion ranged from 50% (wt) to 73% (wt), which is similar to the homopolymerization of DON using the Sn(OCt)$_2$ catalyst. When the $f_{DON}$ increased, the weight percentage of PEG abstracted by water slightly increased from 0.1% (wt) to 5.5% (wt).

### Thermal Analysis and Crystallinity of Copolymers

The DSC thermograms for melting point, $T_m$, were recorded with the samples cooled naturally to ambient after heating to 120°C. DSC results, indicating the phase separation of PEG and PDON blocks, are listed in Table II. The $T_m$ of PDON segments in copolymers changed slightly compared with the one for the PDON homopolymer. From Table II it can be seen clearly that the $T_m$ of PEG blocks in copolymers changed greatly compared with PEG homopolymers. In copolymers, $T_m$ of the PEG blocks are lower than that of the PEG homopolymers, and when DON mol fractions, $F_{DON}$s, are higher than 0.814, the $T_m$ of PEG blocks cannot be detected. Obviously, PDON blocks in the copolymers impeded the crystallization of PEG blocks. From the enthalpy data it can be seen that the crystallinity of the PEG blocks decreased as its weight percentage decreased in the copolymer. On the other hand, the crystallinity of PDON blocks gets higher when its proportion in the copolymer is lower. This might be due to the acceleration effect of flexible chains of the PEG blocks to the PDON blocks, which leads to a small domain of PEG and difficult to crystallize or just form thinner crystallites with lower $T_m$.

Figure 1 shows WAXD spectra of PDPEPD copolymers: the data are listed in Table III. From the thermal analysis it is known that only PDON blocks in copolymers with DON fraction higher than 65.3% are crystallizable, and PEG blocks are amorphous. It can be concluded from the WAXD spectra that the two sharp diffraction of PDPEPD copolymers with $F_{DON}$ from 54.3 to 98.2% belong

**Table IV DCA Data for PDON-*b*-PEG-*b*-PDON Copolymers with Different Components, $F_{DON}$**

| $F_{DON}$ | 1.000 | 0.902 | 0.814 | 0.793 | 0.653 | 0.579 | 0.543 |
|---|---|---|---|---|---|---|---|
| $\theta_a$ (°) | 57.21 | 44.92 | 42.00 | 41.36 | 39.18 | 39.83 | 39.08 |
| $\theta_r$ (°) | 20.60 | 24.69 | 22.66 | 28.15 | 26.65 | 25.40 | — |

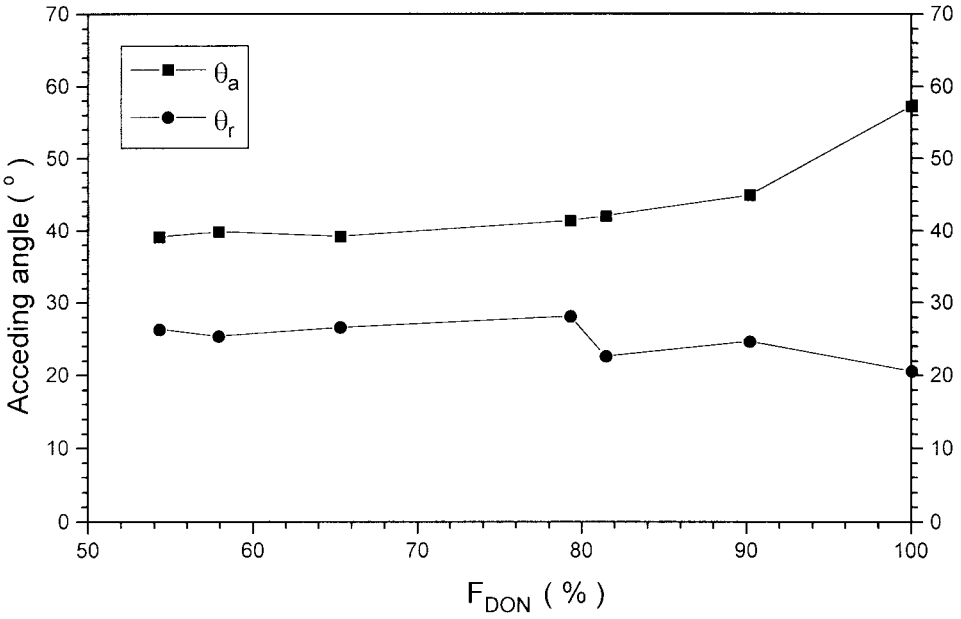


**Figure 2** DCA varying as a function of copolymer composition.

to the crystallites of PDON blocks. The sharp diffraction of the copolymers with three compositions have nearly the same degree value, i.e., the values of $2\theta$ are around 21.60° and 23.70°. The intensities of the two peaks of the copolymers decrease slightly with the decrease of DON mol fraction in copolymers. The sharp diffraction of crystalline PEG, $2\theta$, are at 19.4° and 23.6°[19]; however, the $2\theta$ at 19.4° cannot be detected, indicating that PEG blocks in these copolymers are in the noncrystalline phase, which is in agreement with the conclusion from thermal analysis, i.e., when DON fractions, $F_{DON}$s, are higher, PEG blocks are amorphous. It can be seen from Figure 1 that the copolymers with higher $F_{DON}$ give sharper peaks, indicating that with the increase of the length of PDON blocks the crystallinity of PDON blocks and the regulation of the PDON crystal improved. The value of $2\theta$ is nearly the same in these copolymers, indicating that the crystallites of PDON blocks in all these copolymers are similar.

## Hydrophilicity of PDPEPD Copolymers

Hydrophilicity of PDPEPD copolymers was determined by dynamic contact angle, and the data of acceding angle $\theta_a$ and receding angle $\theta_r$ are compiled in Table IV. Figure 2 clearly shows that the $\theta_a$ of the copolymer increases with the increase of the DON mol fraction, $F_{DON}$, in the copolymer. In other words, the hydrophilicity of copolymers became stronger when the PEG content in copolymers increased due to the better hydrophilicity of PEG.

## Water Absorption of Copolymers

The data on water absorption of PDPEPD copolymers listed in Table V clearly indicate that the water absorption of PDPEPD copolymers increases with the increase of PEG content in copolymers.

**Table V Water Absorption of PDON-*b*-PEG-*b*-PDON Copolymers with Different Components**

| $F_{DON}$ (%) | 88.7 | 81.4 | 79.3 | 69.2 | 57.9 |
|---|---|---|---|---|---|
| $W_w$[a] | 0.0276 | 0.0257 | 0.0334 | 0.0098 | 0.0150 |
| $W_d$[b] | 0.0227 | 0.0176 | 0.0225 | 0.0060 | 0.0082 |
| Water absorption (wt %) | 27.0 | 46.0 | 48.4 | 63.0 | 83.0 |

[a] Weight of wet sample.
[b] Weight of dry sample.

**Table VI LNG Contents in PDPEPD Matrices**

| Sample | $F_{DON}$ | LNG (%) | $W$ (g) | LNG (mg) |
|---|---|---|---|---|
| PDON | 1.000 | 19.48 | 0.0188 | 3.662 |
| PDPEPD1 | 0.887 | 19.85 | 0.0155 | 3.077 |
| PDPEPD2 | 0.814 | 20.24 | 0.0161 | 3.259 |
| PDPEPD4 | 0.690 | 19.73 | 0.0162 | 3.196 |
| PDPEPD6 | 0.579 | 19.95 | 0.0159 | 3.172 |

### Release of LNG from PDON-*b*-PEG-*b*-PDON Block Copolymers Matrices

The DDS compositions of block copolymer matrices and the drug Levonorgestrel (LNG) are listed in Table VI.

The amount of LNG released per day was determined according to the absorbency intensity of immersion solution at 248 nm measured in UV spectrometer.

Figures 3 and 4 are the release profiles of LNG from PDPEPD copolymers matrices. The samples of PDPEPD with higher PEG content are liable to scatter in immersion solvent, so only the samples of PDPEPD with $F_{DON} > 0.579$ were used in the release experiments.

Figure 3 clearly shows that the increase of PEG composition in the copolymers accelerated the release rate of LNG. There is nearly no burst effect in matrices of PDPEPD1 and PDPEPD2. From the discussions above it can be concluded that the PEG blocks improved the hydrophilicity of copolymers, 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 became larger when PEG fraction in copolymers further increased.

In 25 days the relation of accumulative release of LNG from PDPEPD1 or PDPEPD2 with time gives an almost straight line, indicating that the release of LNG in 25 days is of zero order and the release rate is nearly constant. In PDPEPD4 and PDPEPD6 matrices the PEG contents are higher than in PDPEPD1 and PDPEPD2. In the initial stage of release in PDPEPD4 and PDPEPD6, water permeated into the matrices quickly, and the LNG dispersed out from the matrices at higher speeds with the result of large burst effects. After 10 days or so the LNG around the surface was nearly depleted, and with the water permeation into deeper positions of matrices the LNG in the inner parts of the matrices began to disperse out, and the release rate decreased.

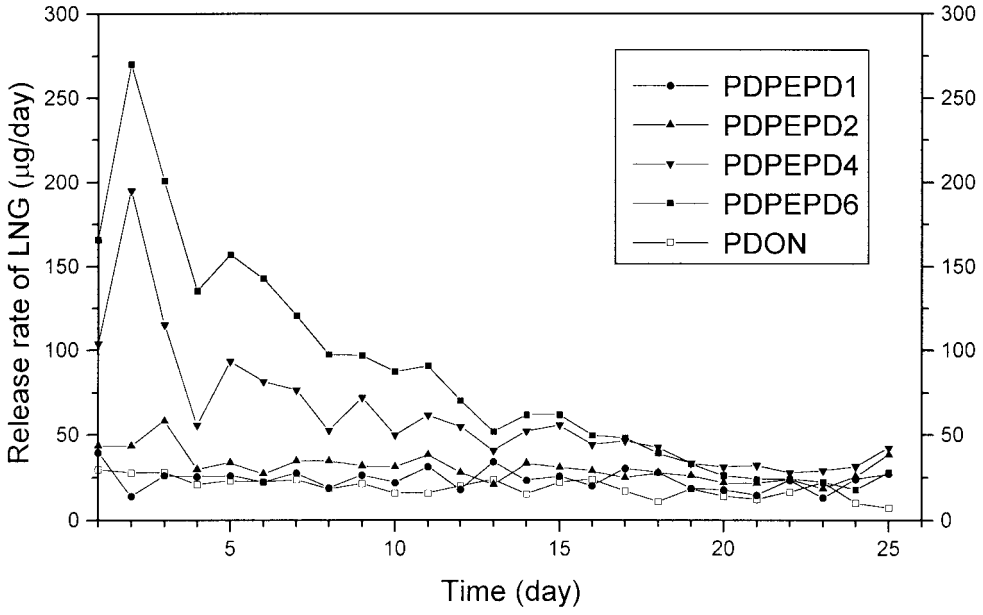


**Figure 3** Release rate of LNG from PDPEPD matrices.

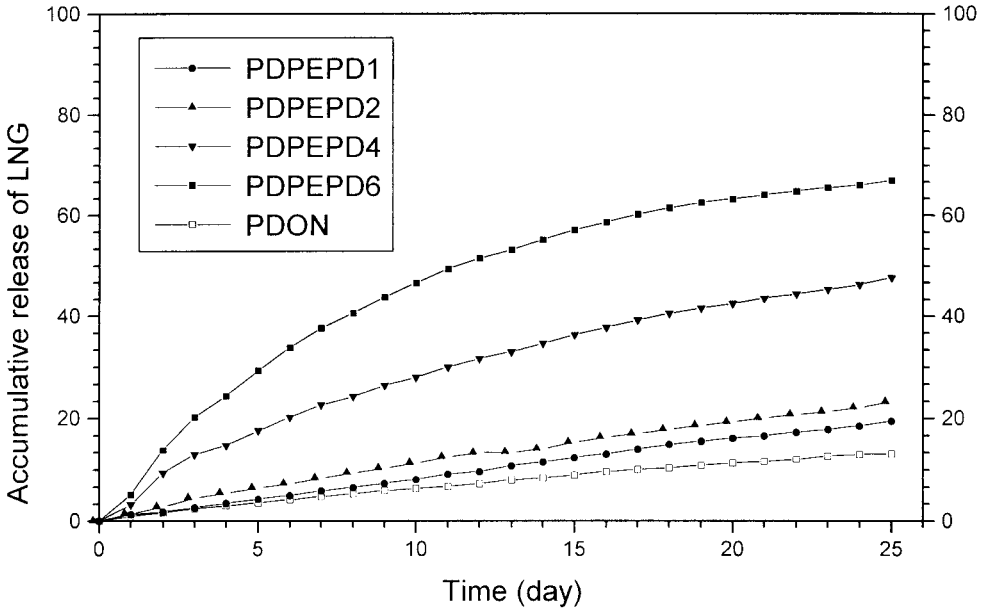


**Figure 4** Correlation between accumulative release of LNG from PDPEPD matrices and time.

The release of LNG in PDPEPD is mainly diffusion controlled in the initial experimental period as the accumulative release linearly increased with square root of time; i.e., obey the Higuchi equation. However, the role of degradation of PDON blocks is not negligible and increasingly important after 10 days. It has been observed that viscosity of PDPEPD1 decreased from 0.531 dL/g to 0.46 dL/g and 0.394 dL/g after release tests for 11 days and 25 days, respectively. The weight loss was observed to be 6.4% (wt) for PDPEPD1 after 25 days release test.

## CONCLUSION

PDON-*b*-PEG-*b*-PDON (PDPEPD) copolymers with different DON content were synthesized and the DDS of PDPEPD/LNG was prepared by the dissolution/vaporization method. The release of LNG from the matrices has an obvious correlation with the components of the copolymers. It was found that the hydrophilicity of the sample is the most important factor. The release rate of LNG from the matrices increased with the increase of hydrophilicity. The burst effect of release of LNG from the PDPEPD matrices is small, or even disappeared when the DON mol fraction in copolymers is higher than 0.690, and in 25 days the release rate is almost constant; i.e., obeying the model of zero order dynamics such as for PDPEPD1 and PDPEPD2 matrices. By controlling the compositions of PDPEPD copolymers the DDS of PDPEPD/LNG can realize constant release in a short period (25 days).

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